THE 1952 YEAR BOOK *of* ENDOCRINOLOGY

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PUBLISHER'S NOTE

The dates appearing under the title of this Year Book indicate that journals received within that period have been reviewed by the editor in selecting the articles abstracted herein.

INTRODUCTION

There seems to be a general impression that clinical endocrinology leans heavily upon laboratory procedures. True, intelligent use of the laboratory can aid greatly in endocrine diagnosis and can provide valuable base lines to serve as checks on the efficacy of treatment. Yet, with few exceptions, definitive endocrine diagnosis can be made from evidence supplied by a carefully taken history and a thorough physical examination. Indeed, many an endocrine disorder can be recognized and labeled exactly upon inspection alone.

A valuable exercise, particularly for those who believe that only the medical knowledge of the last few years is worthy of study, is to unearth some of the classics of endocrinology and to discover from their pages that practically all the major endocrine disorders were well described on clinical bases alone long before the advent, and certainly before the present popularity, of laboratory tests. As a case in point, reference might be made to Lisser's section, "Diseases of the Endocrine System," in Blumer's *Bedside Diagnosis,* written a quarter of a century ago (Philadelphia: W. B. Saunders Company, 1928; Vol. 3). It is true that ovarian agenesis was not identified as such before procedures for assaying pituitary gonadotrophin were available and that recognition of the disorders of the parathyroid glands awaited accurate determinations of blood calcium, phosphorus and alkaline phosphatase levels. With a few exceptions such as these, the major endocrine disorders were well recognized in the prelaboratory era. This discussion does not argue a return to "the good old days"; instead, it is a plea for the selective use, rather than abuse, of the laboratory.

Before any test can be evaluated, its sensitivity and specificity must be known. The mere fact that the results are reported in milligrams or milliequivalents (often to the third decimal place!) does not prove sensitivity or specificity. The nonspecificity of most tests usually becomes apparent with experience in their use. This is particularly true of tests of thyroid and adrenal cortical activity.

Historically, the oldest laboratory test for evaluation of

thyroid status is that of the basal metabolic rate or, more accurately, the rate of uptake of oxygen, expressed as per cent above or below a theoretical normal (derived from studies of residents of Boston and Rochester, Minn.). It seems hardly necessary to restate the well known clinical observation that the BMR is often rapid in the absence of hyperthyroidism (anxiety, pheochromocytoma, perforated ear drum, parkinsonism, lymphoma and many other disorders), low in the absence of hypothyroidism (nonspecific hypometabolism, nephrosis and so on), normal in undoubted hypothyroidism and, less often, normal in true thyrotoxicosis. Because of this nonspecificity, the BMR has been supplemented, and in some areas supplanted, by other laboratory procedures: serum cholesterol level, blood protein-bound iodine content and radioiodine uptake.

The serum cholesterol level is almost invariably elevated in primary thyroidal myxedema; if it is not, one should suspect hypopituitarism masquerading as myxedema. Although hypercholesteremia is a reliable index of myxedema, it rarely occurs in mild hypothyroidism, and, conversely, hypocholesteremia is not a dependable sign of hyperthyroidism. When first introduced, the test for serum hormonal iodine was hailed as the solution to all the problems of laboratory diagnosis of thyroid status. Accumulated data have shown that hyperthyroidism is almost always accompanied by a high protein-bound iodine level. Unfortunately, high readings are also found in patients who have taken iodine-containing medications or x-ray contrast mediums, and the false high levels so produced may persist for long periods. The type of mild hypothyroidism so frequently seen in office practice, the diagnosis of which can be verified by an objective response to thyroid substance, is rarely characterized by a low blood protein-bound iodine level. Low levels may be artificially induced by prolonged administration of mercurial diuretics—another instance of the influence of extrathyroidal factors. Radioiodine uptake is almost universally accelerated in patients with Graves' disease. But a similar rapid uptake is found in colloid goiter, when the thyroid is actually underfunctioning. In short, radioiodine uptake demonstrates only the avidity of the thyroid gland for iodine and by itself cannot be accepted as decisive when thyroid function is in question. Fortunately, the state of thyroid

function can usually be determined on clinical grounds alone, and it is unlikely that all of these tests will give erroneous results at the same time. Practically the only danger then lies in being misled by the results of a single, nonspecific test which contradicts all inferences derived from the patient's history and physical signs.

Interest in adrenal cortical function in various disorders has flourished in the past few years. Despite the mountain of work accomplished, I think it fair to say that at present there are no satisfactory tests for evaluation of adrenal function, unless it is grossly deficient, as in Addison's disease, or prodigiously enhanced, as in the most florid cases of Cushing's syndrome. Even in these extreme instances, all of the present tests may fail to demonstrate definitely decreased or increased adrenal cortical activity. The physician does well to transfer cautiously the conclusions derived from unusually accurate research laboratories to the assays available to most practicing doctors. Many of the tests now used as indexes of adrenal cortical function are insufficiently grounded, both theoretically and clinically. Here, as in many other fields, it is likely that theory has outstripped fact.

Tests of adrenal cortical function seem even less specific than tests of thyroid function. One of the best is the insulin tolerance test, particularly in the detection of primary hypocorticism or hypophyseal insufficiency, in which insulin sensitivity is usually greatly increased. The procedure is dangerous in these disorders, however, because the victims lack the necessary mechanism to raise the blood sugar level, and death from profound hypoglycemia may result. When Addison's disease or hypopituitarism is suspected, it is prudent to use only half the ordinary dose of insulin (0.05 unit instead of 0.1 unit/kg. body weight). In addition, a physician should be stationed at the bedside with a prepared syringe of hypertonic glucose solution close at hand. This is an all-or-none test: in adrenal lack, the blood sugar content falls more than 50% and does not rebound; any intermediate degree of adrenal response cannot be quantitated. This procedure is also nonspecific, since extreme insulin sensitivity also occurs in profound anorexia nervosa.

The once valuable salt deprivation test of Wilder is now only of historical interest; because of its hazards, it has been

replaced by the innocuous water excretion test. The latter, like the insulin tolerance test, gives an all-or-none response and is useless for determining anything less than total lack of adrenal cortical function. It, too, suffers from great nonspecificity. The results of the water excretion test are positive (addisonian) in any debilitating disease, particularly hepatic or renal disorders, the very conditions which are most difficult to differentiate from Addison's disease.

It was hoped that the circulating eosinophil count would serve as a good index of adrenal cortical function, but this hope, too, has been dashed. Corticotrophin has been used to quantitate adrenal cortical function, and certainly a drop of 60% or more in the number of circulating eosinophils after intravenous administration of corticotrophin excludes Addison's disease. Recent data (see the section on Adrenal Cortex) indicate that falls of this magnitude occur spontaneously during the morning hours, so the test probably should be conducted in the afternoon. Use of epinephrine to stimulate the "pituitary-adrenal axis," thereby reducing the number of circulating eosinophils, has been discarded, since it has been shown that epinephrine directly lowers the eosinophil count in adrenalectomized men. A refinement of this "Thorn test" calls for administration of corticotrophin intravenously over an eight hour period. A decrease in eosinophils and an increase of 3.0 mg. or more in 17-ketosteroid excretion constitute a normal response. Since 17-ketosteroid levels as determined in commercial laboratories often fluctuate by this amount or more, the procedure must be considered appropriate only for research institutions.

Urinary 17-ketosteroid excretion is often used as an index of adrenal cortical function, particularly in women. Like the tests of thyroid function, 17-ketosteroid determinations are often affected by nonspecific factors. Excretion is greatly reduced in malnutrition, anorexia nervosa, myxedema, nephritis and hepatic diseases, to name the most obvious. It is by no means established that the lowered excretion rate in these conditions reflects the decreased function of the adrenal cortex.

Recently, I was asked to venture an opinion about the presence or absence of Addison's disease in a woman who had cachexia and vomiting. Her physician had considered the possibility of Addison's disease and asked for a determination of

17-ketosteroid excretion. The laboratory reported 30 mg. a day, which he doubted. He had the test repeated and was informed that the correct answer was 0 mg. Since neither amount seemed correct, he had the test run again. The third report was 3.0 mg. a day. By this time, he wished he had never ordered the test. Clinical examination ruled out Addison's disease, and the patient responded well to psychiatric care appropriate for anorexia nervosa.

I offer this as an ordinary example of laboratory errors as they occur in practice; it should not be interpreted as a criticism of the proper use of the laboratory. Actually, there are many pitfalls in the determination of 17-ketosteroid values. The collection may be incomplete, the specimen may be labeled with the wrong name, extraction may be inadequate or hydrolysis imperfect, the filter from a previous determination may have been left in the colorimeter, the reading may be faulty, decimal errors may be made in the calculation, and so on. How much more tricky, then, is the determination of 11-oxysteroid values. At present, there are no clinically available methods for the accurate quantitation of urinary corticosteroids. Recent development in chromatography should rectify this fault in short order, and we may soon be able to look on the crude technics as measurement of 17-ketosteroids and 11-oxysteroids as relics of the Dark Ages. Methods presently limited to use in research laboratories should soon be simplified to the point where we shall be able to determine exact steroid patterns in blood and urine. It may well be that Cushing's syndrome will soon be called hyperhydrocortisonosis and quantitated mathematically by the levels of hydrocortisone in the blood and urine. Until that day, I think we might well listen to Don Camillo, who warns that ". . . . numbers are what have put men out of kilter. Having discovered numbers, they've proceeded to deify them."

A large portion of this volume was prepared while I was on sabbatical leave in Europe. It gives me great pleasure to express my appreciation to the many clinicians and physiologists whom I met there and who were good enough to extend some of the wisdom of the older European schools to a representative of the younger American discipline. I wish particularly to thank Professor F. Verzár of Basel, in whose laboratory I would gladly have spent more time, Dr. Albeaux-

Fernet and Dr. André Lichtwitz of Paris, and Dr. Russell Fraser and the staff of the Postgraduate Medical School at Hammersmith, London.

Finally, I gratefully acknowledge the stenographic help of Mrs. Kathleen Davy, the editorial labors of Miss Mary Morrow, and the continued courtesies and co-operation of the Year Book Publishers.

—Gilbert S. Gordan.

THE PITUITARY GLAND

Adenohypophysis

Although the anterior pituitary gland has long been termed "the master gland" by physiologists and theorists, its role in clinical medicine is distinctly subordinate to that of the adrenals, thyroid and gonads. Indeed, much of the sovereignty once accorded to the anterior pituitary gland by theorists has been transferred to the hypothalamus, so that the latter is now in danger of becoming the catch-all for poorly understood syndromes. It is to be hoped that the many careful studies now in progress will clarify the actual relation of the hypothalamus to the endocrine system.

Attempts to master the master gland by administration of hormones of the target organs have become increasingly popular and successful. This is one of the many possible mechanisms by which large doses of estrogens or androgens may produce transient remission of far-advanced carcinoma of the breast. The work of Moon and others has shown that preparations of the anterior pituitary rich in the growth factor stimulate neoplasia in the rat. Extension of this work to neoplastic disease in man is technically difficult, because activity of the normal pituitary gland cannot be suppressed by very large doses of x-ray, and the gland's secure position in the human skull makes hypophysectomy a most formidable procedure. Consequently, the operation has been carried out only in cases of far-advanced malignancy in which good results are, perhaps, too much to hope for.

The central nervous system manifestations of hypopituitarism have come in for renewed attention. Possibly this shift of focus is to be attributed to the dramatic mental and emotional changes often produced by the administration of cortisone or corticotrophin. The importance of this system throughout clinical endocrinology can hardly be overstated.

The symptomatology of anterior pituitary disorders can be remarkably protean. This peculiarity of the adenohypophysis may be attributed to the relatively large number of hormones which it is thought to produce, or to the variability of end-organ reactivity to these hormones. The latter explanation seems the more important, for how otherwise can one explain the clinical appearance of preadolescent eunuchoidism associated not only with unimpaired growth but with excessive height and eunuchoid proportions in certain patients with craniopharyngiomas? Theory aside, hypopituitarism may masquerade as myxedema, Addison's disease, eunuchoidism, or anorexia nervosa or other emotional or mental disorder. This consideration is not only important in diagnosis, but also in appropriate therapy, which must be individualized most minutely in the treatment of these brittle patients.—Ed.

Disappearance of Diabetes during Estrogen Therapy in Acromegaly. E. Perry McCullagh, John C. Beck and C. A. Schaffenburg[1] (New England Med. Center, Boston) report on a patient with acromegaly and diabetes, an association noted in 17% of 153 cases of acromegaly. The value of estrogens in suppressing pituitary growth hormones is known, but this is

(1) Cleveland Clin. Quart. 19:121-126, July, 1952.

the first reported instance of complete reversal of diabetes.

Woman, 45, was hospitalized because of hypertension, prolapsed uterus and acromegalic thickening of features, hands and feet for at least eight years. Headaches, hirsutism and amenorrhea were present. BMR was +51%, glucose tolerance abnormal (Fig. 1) and x-rays showed great enlargement of the sella turcica. Stilbesterol, 2 mg. daily, was discontinued after one month because of nausea. Ethinyl estradiol, 1 mg. daily for three months, was associated with disappearance of headache, decrease in coarseness of features and improved glucose tolerance. When it was discontinued for two months all signs reappeared; hand volume increased from 485 to

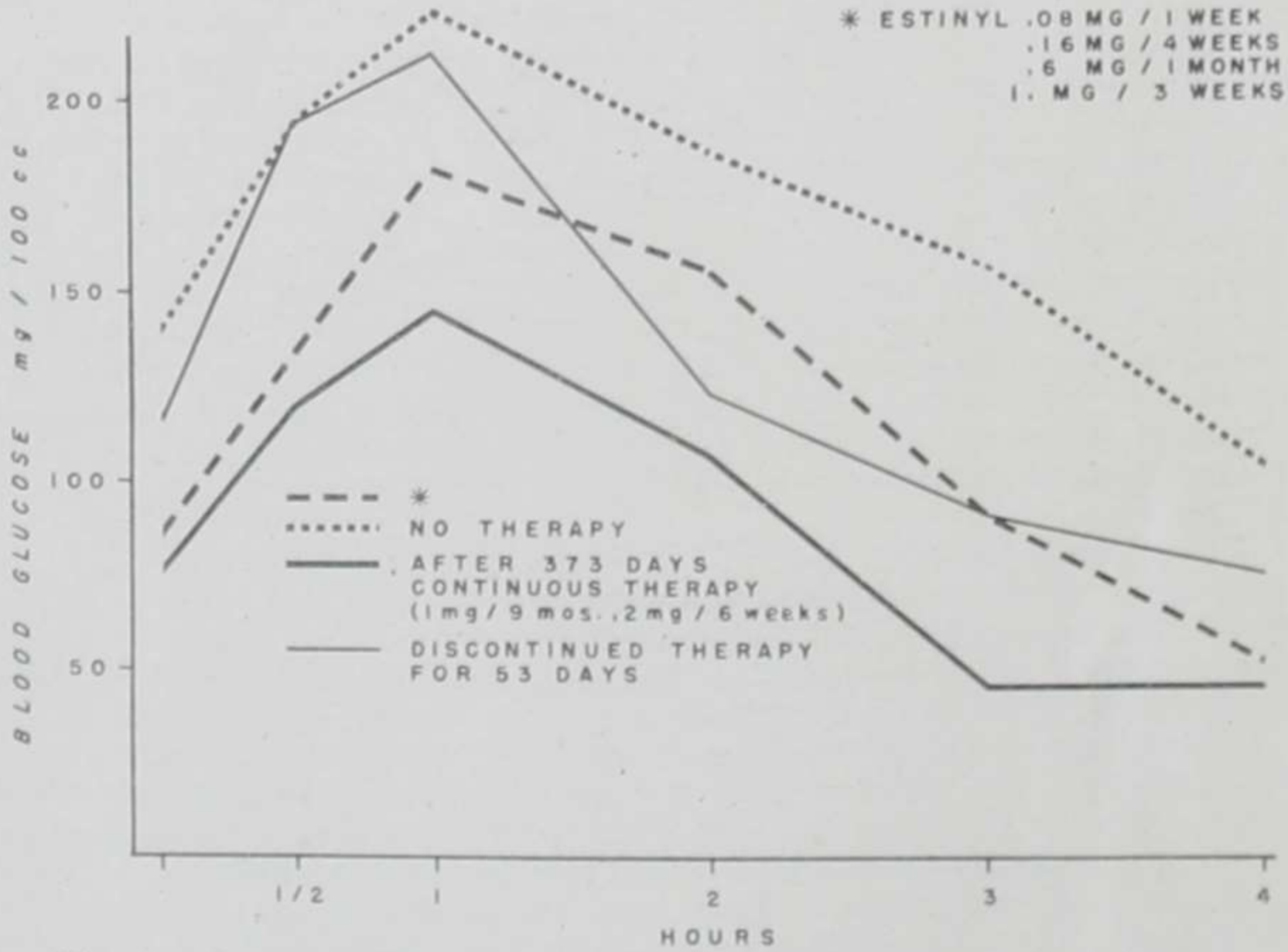

Fig. 1.—Alterations in glucose tolerance with therapy. (Courtesy of McCullagh, E. P., *et al.*: Cleveland Clin. Quart. 19:121-126, July, 1952.)

550 cc. Resumption of the estradiol for nine months produced great improvement. Discontinuation was followed by a mild ictus and progressive bitemporal hemianopia, for which 2,000 r of x-ray was directed at the pituitary without effect. Estrogens again caused improvement.

[Estrogens can degranulate eosinophil cells of the pituitary, suppress growth and probably inhibit other functions of the anterior lobe. When used by themselves in the treatment of acromegaly, even in very large doses, estrogens usually do not produce such striking effects as this. In acromegaly in general, if the visual fields are impaired, operative intervention is indicated; otherwise, large doses of x-ray (3,600 tissue r or more) may be given, followed by appropriate estrogen or androgen therapy. The "sex hormones" can be counted on to relieve the secondary hypogonadism which so frequently accompanies acromegaly; they may

also have theoretical value in suppressing excessive activity of the eosinophils. It is to be noted that the dose of estrogen required to produce the excellent effect reported here (1 mg. ethinyl estradiol daily) is extremely large, for the ordinary dose in the menopause is only 0.02-0.05 mg. daily. —Ed.]

Differentiation of Growth Hormone from Pituitary Factor Which Produces Diabetes. Extensive experimentation has shown that the pituitary contains a potent diabetogenic agent, or combination of agents, which rapidly produces severe insulin-resistant diabetes when administered to susceptible animals and produces permanent diabetes with pancreatic damage after prolonged administration. Acceptance of growth hormone as the pituitary diabetogenic factor stems largely from the belief that the purified growth hormone preparations which produce the effect, including those which are crystalline and electrophoretically homogeneous, are indeed chemically and biologically pure. M. S. Raben and V. W. Westermeyer[2] (Boston) prepared crude growth hormone by extracting "pituitary powder" with acetic acid and removing thyrotrophin, luteotrophin, gonadotrophin and corticotrophin by precipitation and adsorption. This growth hormone was further purified by treatment with alcohol in the cold. The purified preparation thus obtained was found by assay in the hypophysectomized rat to be about equal in growth-promoting activity to the preparations of Li and of Wilhelmi and to the Armour preparation.

After this growth hormone preparation failed to produce glycosuria in three adult dogs when injected in doses up to 10 mg./kg./day, the preparation was compared for diabetogenic activity with the Armour growth hormone. A dog was given two courses of 50 mg./day of the Armour preparation, alternated with three courses of the authors' preparation. Although glycosuria appeared after the third injection of the former, it did not develop with doses as high as 200 mg./day of the latter. However, the authors' preparation before purification produced glycosuria. The growth hormone prepared by this method is probably not entirely freed of the diabetogenic principle, for large doses, although not producing glycosuria, seemed to delay disappearance of established glycosuria. Separation of the growth hormone from the factor which pro-

(2) Proc. Soc. Exper. Biol. & Med. 80:83-86, May, 1952.

duces diabetes was nearly complete, however, and indicated the separate identity of these substances.

Effects of Single Intravenous Injections of Pituitary Growth Hormone to Normal Adult Men were studied by A. Carballeira, H. Elrick, K. R. Mackenzie and J. S. L. Browne[3] (McGill Univ.). After a suitable fast, five normal men were given 320 cc. amino acid solution over a brief period; this infusion was repeated two days later with concurrent administration of growth hormone, 1, 2 or 3 mg./kg. In the control experiments the blood amino acid nitrogen values rose to a maximum immediately after cessation of the amino acid infusion, returned to fasting levels within three to five hours and remained approximately at this level, the terminal values after six hours falling slightly in two cases. With growth hormone, maximal values were reached at the same time but were consistently less than the controls by an average of 32%. The values returned to fasting levels within one to three hours as compared with three to five hours in the controls and subsequently fell below the fasting values. Blood nonprotein nitrogen minus amino acid nitrogen values were not increased in the growth hormone experiments. Total amino acid nitrogen excretion over a period preceding and including the experiment was an average of 24% less under influence of growth hormone.

The amino acid nitrogen changes in blood and urine without increase in nonprotein nitrogen probably mean a significant retention of the administered amino acids somewhere in the body—presumably the intracellular and/or extracellular space. The blood glucose levels during the first part of the experiment were consistently elevated under the influence of growth hormone (without, however, causing glycosuria), whereas in the controls a depression of the fasting level usually resulted at this time.

Other changes noted were an increase in the ketonemia of the fasting state in three subjects so studied and an increased urinary excretion of sodium-retaining material in the two subjects so tested. No consistent effects were noted on blood and urine phosphorus, serum alkaline phosphatase or blood eosinophils.

The failure of others to demonstrate positive effects in

(3) Proc. Soc. Exper. Biol. & Med. 81:15-20, October, 1952.

man with large doses of growth hormone may be due to the fact that it was given subcutaneously or intramuscularly. The hormone may be rapidly inactivated by subcutaneous and muscle tissue. Another possible explanation is the rapid formation of antibodies with repeated doses.

[Many previous attempts to show that the pituitary growth hormone is effective in man have been disappointing. Because such gross methods as estimations of linear growth or retention of protoplasmic constituents (balance studies) had failed to demonstrate anabolic activity of this substance in man, the authors devised this ingenious technic. Their studies appear to show an anabolic effect, as measured by a retention of amino acids. Clinically, pituitary preparations are still useless for the production of growth; this is a great misfortune for dwarfed girls. For boys, adequate growth can usually be stimulated by the administration of methyltestosterone. Attempts to induce similar growth in girls are usually limited by the virilizing effect of the compound. Methylandrostenediol has been somewhat better, but even this steroid is too androgenic for most girls, in contrast to its action in older women. A ray of hope is afforded by the recent statement of Raben, Westermeyer and Leaf (J. Clin. Invest. 31:655, 1952) that pituitary growth hormone prepared by the Astwood process is anabolic in man.—Ed.]

Articular and Other Limb Changes in Acromegaly: Clinical and Pathologic Study of 25 Cases is presented by J. H. Kellgren, J. Ball and G. K. Tutton[4] (Manchester Univ.). Criteria for diagnosis were enlargement of the hands and feet, together with coarsening of the features. All patients had some clinical or radiologic evidence of a disturbance in the region of the pituitary fossa. The series included 16 females, and ages ranged from 13 to 67. The two youngest, a boy 13 and a woman 24, were over 6 ft. tall and might be considered giants. Nine patients had never had significant pains in the limbs or back.

There appear to be two clinical types of acromegalic arthropathy. In one, massive bony outgrowths and deformity of the bone ends lead to gross limitation of movement in many joints (Fig. 2). The other, more common, condition is characterized by pains in the limbs and back with soft tissue enlargement of the joints, excessive and abnormal mobility, synovial thickening and recurrent effusions. The characteristic radiologic finding is an increased joint space, with remodeling of the bone ends (Fig. 3). This picture is unlike that of osteoarthritis or rheumatoid arthritis and is best described as acromegalic joint disease. Macroscopic joint changes are shown in Figures 4 and 5. There may be hyperplasia and

(4) Quart. J. Med. 21:405-424, October, 1952.

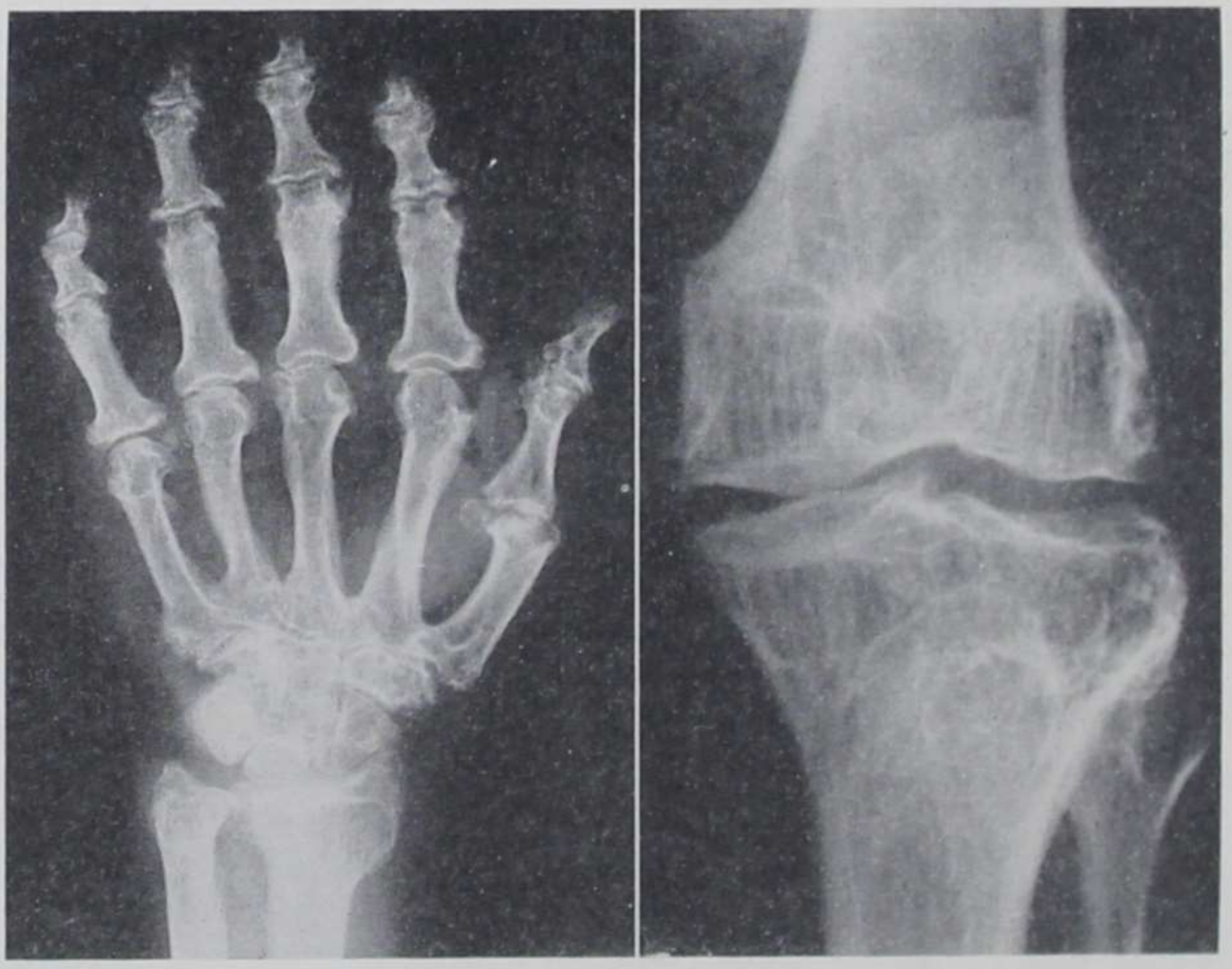

Fig. 2 (left).—Typical hypertrophic changes and bony outgrowths around joints.
Fig. 3 (right).—X-ray of knee showing wide shafts and squared, shortened condyles with greatly altered trabecular pattern. Despite these severe changes, a wide joint space is present.
(Courtesy of Kellgren, J. H., *et al.*: Quart. J. Med. 21:405-424, October, 1952.)

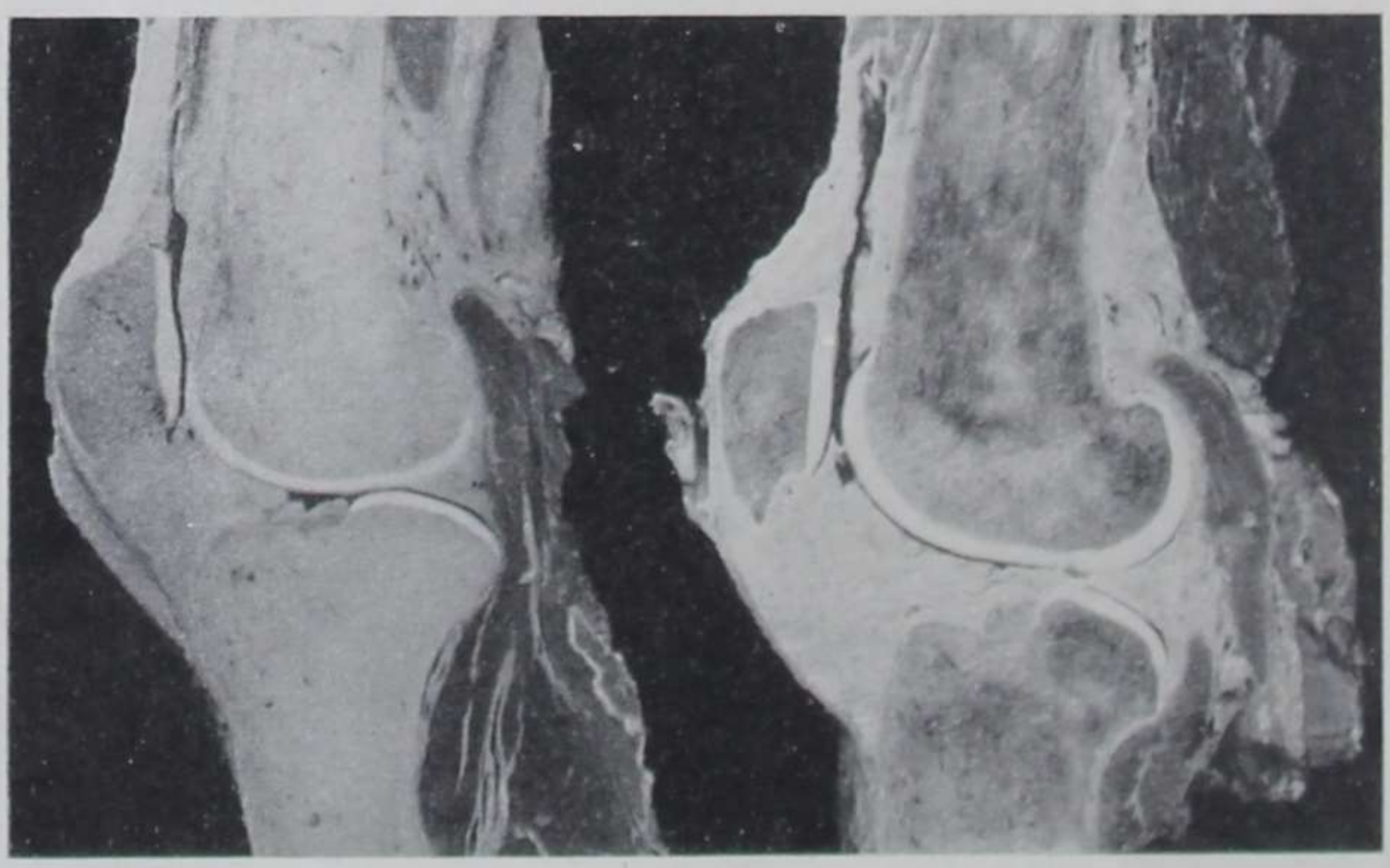

Fig. 4 (left).—Section of normal knee joint.
Fig. 5 (right).—Section of knee joint showing enlarged femoral condyle, thickened articular cartilage and enlargement of ligaments, meniscus and infrapatellar fat pad.
(Courtesy of Kellgren, J. H., *et al.*: Quart. J. Med. 21:405-424, October, 1952.)

softening of the articular cartilage. When this occurs in the deeper layers of the pressure zones, it leads to formation of peculiar ulcers with undermined edges. Softening of the ligaments and other limb structures may cause the extremities to acquire a curious rubbery consistency. These changes give rise to pain and instability.

Hyaluronidase metabolism was studied because of this noninflammatory alteration in the physical state of collagenized tissue. Saline-hyaluronidase wheals remained in the skin of the acromegalic patient for 5.2-21 (mean 10.5) minutes as compared with 0.7-5.0 (mean 2.2) minutes in a group of normal subjects. This relative ineffectiveness of hyaluronidase in acromegalic skin might result from the presence of an excess of an antihyaluronidase, but it seems more likely that it results from some alteration in the connective tissues themselves.

Bilateral median nerve lesions were noted in three patients, and in one of these compression of the nerves in the carpal tunnel was relieved by decompression.

Malignant Eosinophilic Hypophyseal Adenoma and Primary Cancer of Liver are described by J. Ormos and B. Z. Mónus[5] (Univ. of Szeged).

Woman, 49, had had acromegaly, manifested by enlargement of hands, feet, nose and chin, since she was 20. Progress of acral enlargement had ceased four years later, after a course of x-ray therapy, but amenorrhea had persisted. One year before her death cardiac complaints had appeared. At that time blood pressure varied between 120/75 and 180/110. Urinalysis disclosed no abnormalities. Glucose tolerance curve was: 85, 104, 112, 111, 83 and 96 mg.%. She died suddenly in an attack of syncope. The clinical diagnosis was acromegaly, pituitary tumor, partial atrioventricular block and Adams-Stokes syndrome. Autopsy revealed a malignant eosinophilic adenoma of the pituitary gland and a hepatic tumor with a microscopic picture closely resembling a hypernephroma. Changes of the endocrine glands indicated hypopituitarism, possibly resulting from cystic degeneration of the pituitary tumor. Early in the course of the disease, clinical signs of hyperpituitarism were manifested by acromegaly.

The hepatic tumor was considered a primary carcinoma of the liver. The abundance of growth hormone during the early stage of the disease is considered important in the development of tumor in the liver.

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(5) Schweiz. Ztschr. allg. Path. 15:29-44, 1952.

Acromegaly Associated with Pheochromocytoma. Although acromegaly has been reported to be associated with diabetes, thyrotoxicosis, galactorrhea and other endocrine disturbances, Kurt Iversen[6] (University Hosp., Copenhagen) reports the unique association of acromegaly with pheochromocytoma.

Man, 44, noted reduced visual acuity in 1930. X-ray examination showed an enlarged sella, and he had partial removal of an adenoma of the anterior pituitary by Cushing in Boston. Visual symptoms and acromegalic features progressed despite three courses of x-radiation.

In 1949, after 16 days of thyroid powder, 400 units [sic] daily, he was seized with a violent pulsation in the abdomen and chest; synchronously with the heartbeat he had severe pain in the arms and legs, a throbbing headache, a feeling of suffocation and audible labored respirations. The attack lasted only a few minutes, but recurred 400 times in the next five months. The attacks observed in the hospital appeared typical, so despite negative results of histamine, TEA and benzodioxane tests, an operation was done and a goose-egg-sized pheochromocytoma removed uneventfully. Six months later he had had no further attacks.

[The two preceding reports suggest a relationship between pituitary growth activity and neoplastic growth. Moon and co-workers (Cancer Res. 10:364-370, June, 1950) found hyperplasia of the adrenal medulla in rats treated for a long time with pituitary growth extract.—Ed.]

Two Cases of Panhyperpituitarism with associated acromegaly and Cushing's syndrome in patients from whom a hypophyseal tumor had been removed some years earlier are reported in detail by Gilbert-Dreyfus, M. Zara and J.-L. Frank[7] because of their striking similarity.

Case 1.—Woman, 31, was puny in infancy, but had no illnesses except measles. Her parents were cousins; the mother died when the patient was 2, but the father, 60, is well. A brother and sister are also healthy. Menstruation began at 13 and was irregular; during the summer it occurred every month, but in the winter it ceased for three or four months. Hormone therapy of an undetermined character regulated it to some extent after 1945. She had been married for 10 years but had never become pregnant. Between 1942 and 1945, a progressive structural change took place, characterized by: signs of acromegaly (thickening and enlargement of extremities, thickening of features, enlargement of nose and chin, and macroglossia), which are still present; obesity, which increased the weight by 40 lb.; accentuation of hirsutism, which reached its present status (beard, mustache and sideburns; excess growth on chest, abdomen, thighs and legs); generalized virilism (broadening of shoulders, pronounced atrophy of breasts and lowering of tone of voice), and,

(6) Acta med. scandinav. 142:1-5, 1952.
(7) Ann. endocrinol. 12:1052-1056, 1951.

finally, enlargement of the thyroid gland and bilateral exophthalmos. Roentgenograms indicated presence of a pituitary tumor. Operation was done in February 1948. Histologically, the specimen was an adenoma, predominantly acidophilic. Removal of the tumor brought no change in the general condition. Thyroid enlargement became more pronounced. Puncture revealed a hematic thyroid cyst, from which 60 cc. liquid was removed; two months later an additional 70 cc. was removed.

A complete humoral analysis was made in November 1950. 17-

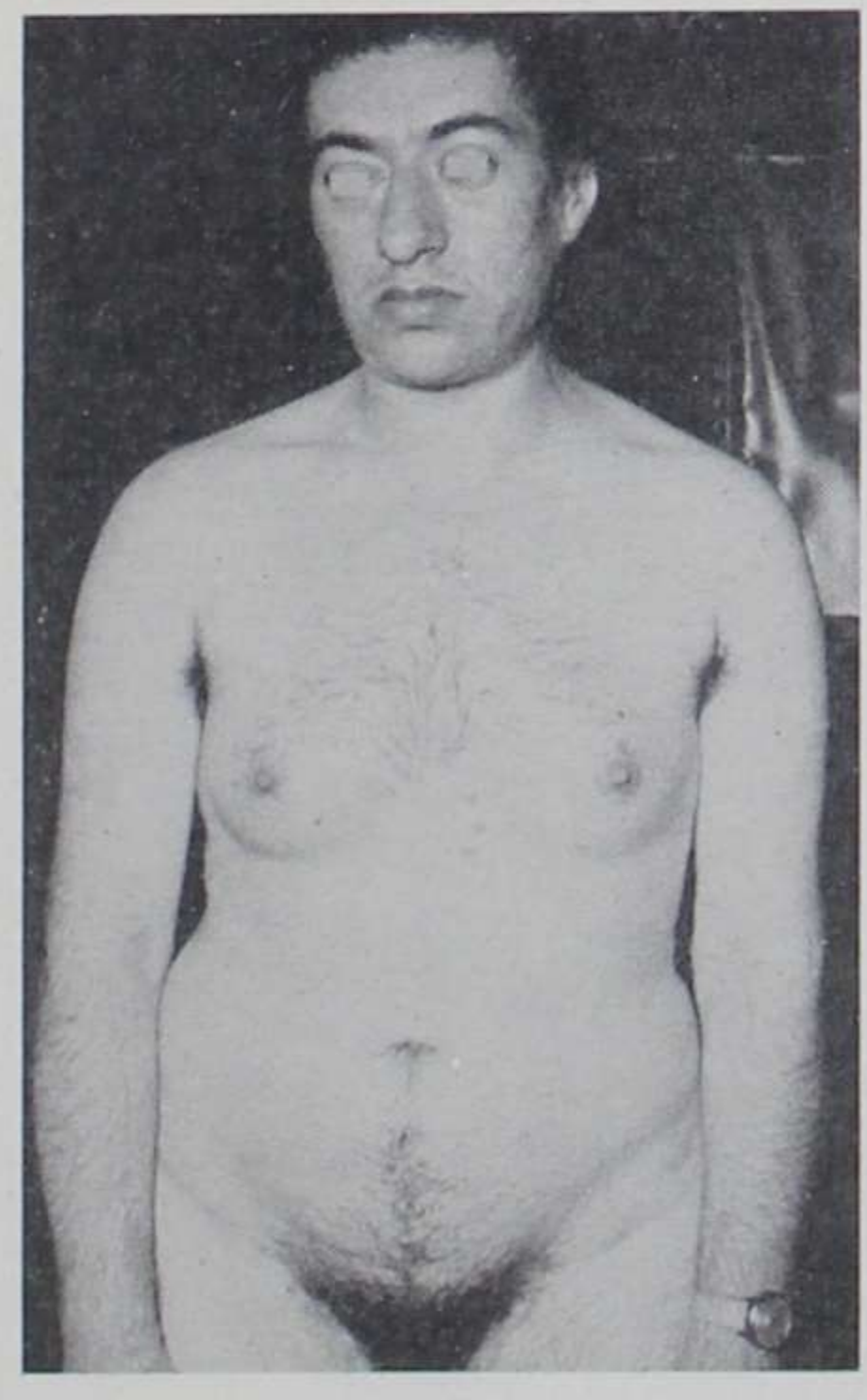

Fig. 6.—Appearance of patient in Case 1. (Courtesy of Gilbert-Dreyfus, *et al.*: Ann. endocrinol. 12:1052-1056, 1951.)

Ketosteroid excretion, which was 20 mg. before operation and 6 mg. immediately afterward, had increased steadily. Vaginal smears showed a curve of the hypofolliculin type, and an endometrial biopsy on the 22d day of the cycle showed a mucosa of the folliculin-lutein type. Oral glucose tolerance tests on two occasions revealed the following values (mg./100 cc.):

79	129	91	111	91	30
72	142	30	122		94

I^{131} uptake was normal, as were the ocular fundi. Skull films showed an enormous sella turcica. Finally, pneumoretroperitoneum failed to show the adrenals, either on plain films or on tomographs taken on the right and left at 5 and 6 cm.

Case 2.—Woman, 30, had healthy parents, two brothers and a sister. Menstruation began at 13 and was regular with a 3 day flow every 28 days until age 19, when the intervals became greater and amenorrhea supervened. At the same time (1940-43), structural changes occurred. The extremities, which had been short but extremely wide, were greatly enlarged; the nose, chin and cheek bones became hypertrophied; macroglossia and facial hirsutism (sideburns and chin growth) appeared, and the pubic growth assumed a masculine character. Weight was 143 lb. and height 64½ in. The patient did not have clearly characteristic headaches, but suffered from polydipsia and polyuria; she had rather pronounced asthenia and galactorrhea in 1943, when a large hypophyseal tumor was removed. At that time arterial tension was 110/70, and the ocular fundi were normal. The tumor cells were substantially uniform and slightly acidophilic, with fairly numerous nuclear irregularities, suggesting an epithelioma.

Headache and polydipsia disappeared after operation, but menstruation did not recur, and obesity, especially about the trunk, increased, as did hirsutism. In 1944, when the patient was deported, she weighed 165 lb. During deportation, she contracted typhus; in 1945, when she was repatriated, weight had dropped to 92½ lb. Obesity returned rapidly thereafter and by October 1946, when she sought advice because of amenorrhea and overweight, she weighed 187 lb. On admission to the hospital in April 1950, she had, in addition to the typical stigmas of acromegaly, a remarkable degree of hirsutism on the arms and the lower part of the back. Her face was marred by acne and her voice was heavy. Arterial tension and ocular fundi were normal. Biologic tests disclosed no tendency to progression of the disease. Vaginal smears showed a curve of definite hypofolliculin type and endometrial biopsy showed aplasia of the mucosa. Glucose tolerance test gave the following values: 93 mg./100 cc., 143, 143 and 96. Finally, a skull x-ray showed deformation of the sella turcica, and pneumoretroperitoneum showed only the right adrenal gland, which was normal.

Both women were Jewish, Polish in origin, and in both symptoms began to appear at about age 20. Development of the syndrome was progressive, first manifesting itself by signs of acromegaly and of virilism affecting the form, voice and hair but not the clitoris, then by menstrual disturbances consisting of winter amenorrhea in one and total amenorrhea in the other and, finally, by obesity of an android type, which was conspicuous in one and relative in the other. The only points of difference were atrophy of the breasts in one patient and hypertrophy of the breasts with accompanying galactorrhea in the other; also a normal thyroid in one patient and a large hematic thyroid cyst in the other.

One patient presented an obvious picture of panhyper-

pituitarism in which the peripheral action of various agents could be seen: acromegaly caused by the growth hormone; obesity and virilization, by corticotrophin; the hematic thyroid cyst, by thyrotrophin, and the menstrual disturbances, by the gonadotrophins also. The picture presented by the other patient was less pronounced but showed the effects of general overstimulation by growth, corticotrophic, lactogenic and perhaps gonadotrophic hormones, with only the thyroid being unaffected. Neither patient had hypertension. The disturbances were related to a hypophyseal tumor which in each case was extirpated. But, unlike the result obtained in persons with primary lesions of the adrenal glands, the arresting of adrenal cortical stimulation was not followed by regression of the obesity and virilization attributable to adrenal hyperfunction. Efforts to find an existent adrenal anomaly have been unsuccessful; consequently, the symptoms presented by the patients, who are otherwise in good health, must be considered evidences of a panhyperpituitarism which is now extinct.

Roentgen Therapy in Pituitary Adenomas: With Special Consideration of Chromophobe Type. H. M. Aitken and E. A. Pohle[8] (Univ. of Wisconsin) analyzed 36 cases observed between 1936 and 1951. The patients were aged 21-71 (average, 43) and 19 were men. Histologic proof of tumor was obtained from biopsy or postmortem specimens in 14 cases. There were seven chromophobe adenomas, five malignant adenomas, one craniopharyngioma and one adamantinoma. Diagnosis in the other 22 cases was based on clinical and/or x-ray evidence. There were 12 chromophobe adenomas, 8 eosinophilic and 1 basophilic adenoma and 1 of undetermined type. Impaired vision and headache were the commonest complaints. These, with mental or personality changes, weakness, enlargement of the face or extremities, somnolence or obesity, should immediately suggest pituitary tumor. Physical signs resulted from pressure of the tumor on adjacent structures and/or disturbance in endocrine function. Roentgen signs included enlargement and/or erosion of the sella turcica, presence of a suprasellar mass and the typical bone changes of acromegaly.

Of the 14 patients with proved tumors, 2 with adenocarcinomas and the 1 with adamantinoma died within the post-

(8) Wisconsin M. J. 51:666-671, July, 1952.

operative period and received no x-ray therapy. The other 11 were treated with a combination of surgery and x-rays. X-ray therapy for 3-12 months before operation was given to four, of whom three (two with cystic tumors and one with adenocarcinoma) subsequently died. The fourth had a cystic adenoma and was much improved after operation. These cases emphasize that failure to improve within two to four months after adequate x-ray therapy is probably an indication for surgery. Six patients with chromophobe adenomas and one with adenocarcinoma received postoperative irradiation. All but one improved during five month to four year follow-up periods. The sixth patient improved temporarily and later became psychotic.

X-ray treatment only was given to 17 patients, 1 of whom had Cushing's disease. Of the other 16, 8 had chromophobe and 8 acidophilic adenomas. Only four of the latter who had adequate follow-up obtained good results, whereas six with chromophobe tumors were definitely improved. Apparently the concept of the high radioresistance of all chromophobe adenomas should be revised; satisfactory response may be expected if sufficiently high doses are administered.

[In earlier studies, the reported failure of roentgen therapy to control pituitary tumors, particularly eosinophil adenomas, was probably the result of inadequate dosage. Now that the use of multiple small ports makes it possible to give large doses of x-ray to the pituitary without exposing large areas of skin, better results may be expected.—Ed.]

Tumors of the Pituitary Body and Its Environs. By examination of 50 autopsy specimens of complex cysts and tumors in the pituitary region E. S. J. King[9] (Univ. of Melbourne) was able to demonstrate step-by-step formation of the various structures found in these growths. These complex neoplasms are regarded as variations of simpler structures which in turn closely resemble, and could easily originate from, adult tissues already in the area. For example, in a simple cyst the squamous epithelium may become pseudostratified or stratified, possibly with keratin formation. The squamous epithelium may then form a basal type epithelium with calcifiable secretion. Lymphocytic accumulation and cartilage formation occurs. This relation of complex neoplasms to simpler ones makes it unnecessary to postulate cell rests or totipotent cells.

(9) Australian & New Zealand M. J. 21:201-211, February, 1952.

[Readers interested in the theory of "cell rests" will find much to interest them in the complete article, for the author has assembled and ingeniously arranged an amazing collection of photomicrographic evidence to support his point of view.—Ed.]

Hypopituitarism with Pituitary Tumors: Cortisone in Treatment of Stupor Associated with Hypopituitarism. J. E. Caughey, Anthony James and E. K. Macleod[1] (Otago Med. School) report on four patients with hypopituitarism due to intrasellar tumors in whom stupor developed after surgery.

Man, 44, had lethargy for five years and bitemporal hemianopsia for two months. The day after removal of a craniopharyngioma he was restless, then stuporous. A second and third operation to rule out a subdural clot produced no change. He was comatose for five weeks, then steadily improved without special treatment.

Another patient recovered after daily treatment with testosterone, DCA (100 mg.), salt and desiccated thyroid (0.1 Gm.). A third patient responded to cortisone and neo-synephrine® with a notable improvement in 48 hours after two re-explorations for clot had failed to relieve stupor. Cortisone produced recovery in 28 hours in a fourth patient. After recovery, all four had amnesia for the period of stupor. In no case was there sweating, vomiting, hypoglycemia or a state comparable to an addisonian crisis.

Treatment of Hypopituitary Coma. H. L. Sheehan and V. K. Summers[2] (Univ. of Liverpool) report nine cases of pituitary coma in eight patients, all suffering from postpartum pituitary necrosis (Sheehan's syndrome) for 6-21 years. This coma of unknown mechanism develops after years of hypopituitarism. It may follow a trivial infection or operation. Despite the uniform picture of coma, some patients have hypoglycemia, others low plasma sodium and chloride levels and others severe hypothermia which can be easily overlooked since a special thermometer is necessary to obtain readings as low as 77 F. Two patients died and two recovered without treatment. Treatment should be directed to the particular disturbance. Glucose intravenously was helpful in patients with hypoglycemia. A warm tub bath promptly revived patients with hypothermia. Cortisone, 125 mg. of the intramuscular suspension, injected intravenously every half hour in two patients, gave no benefit. Saline, DCA and testosterone produced no recognizable improvement.

[Coma or stupor in patients with hypopituitarism may result from

(1) Brit. M. J. 1:1216-1219, June 7, 1952.
(2) Ibid., pp. 1214-1215.

hypoglycemia, Addison's crisis or intracranial damage. A diagnostic test, by intravenous administration of hypertonic glucose solution, will exclude hypoglycemia. The response to previously available adrenal cortical agents was too slow for this purpose and therefore of little diagnostic value. Rapidly acting steroids prepared in solutions for intravenous use can now be given for immediate effect; these are hydrocortisone and desoxycorticosterone glucoside.—Ed.]

Effects of Surgical Hypophysectomy in Man with Malignant Melanoma is reported by Michael B. Shimkin, Edwin B. Boldrey, Keith H. Kelly, Howard R. Bierman, Paul Ortega and Howard C. Naffziger[3] (Univ. of California).

Man, 32, with malignant melanoma from a left supraclavicular node diagnosed histologically and with multiple discrete shadows throughout both lung fields seen on x-ray, had surgical hypophysectomy and exogenous steroid therapy for two weeks thereafter. With hormonal medication withdrawn, a syndrome of progressive hypopituitarism was noted, with apathy, sluggishness, somnolence, diminished reflexes, a fall of BMR from —3 to —33% and progressive dryness of the skin without loss of turgor. The complexion was sallow with a suggestion of periorbital puffiness. Axillary and pubic hair, beard growth and axillary secretions remained unchanged; there was no clinical change in the thyroid or prostate, and no significant change in fluid balance or specific gravity of the urine. Biochemical observations conformed with clinical evidence of the hypopituitary state: serum protein-bound iodine dropped from 6.7 to 3.6 μg./100 ml. by the third week; fasting blood glucose content dropped from 75 to 45 mg./100 ml. by the fifth week; urinary 17-ketosteroid (total neutral steroid fraction) excretion dropped to 3 mg./24 hours by the fourth week, and serum sodium and chloride levels decreased during the fifth week. Serum phosphorus and calcium contents remained at borderline low levels. Blood cholesterol and protein contents, red blood cell count, hemoglobin content and glucose tolerance were unaffected. Insulin sensitivity increased. The number of circulating lymphocytes increased. Chest x-rays showed progressive growth of the metastatic lesions. Six weeks after hypophysectomy, he suddenly grew worse and, after a steady downhill course, died on the 67th postoperative day.

Autopsy revealed epithelial atrophy of the testes, adrenals and thyroid and generalized hyperplasia of lymph nodes. The pituitary fossa contained about two dozen pituitary cells which were predominantly degranulated chromophobes with rare acidophils and basophils; the posterior pituitary lobe had been completely removed.

The absence of some of the findings associated with panhypopituitarism is attributable to the relatively short period of observation. Clinical manifestations of panhypopituitarism in man appear within one month and histologic manifestations within two months of hypophysectomy.

[This study demonstrates that the clinical and chemical abnormalities

(3) J. Clin. Endocrinol. 12:439-453, April, 1952.

long thought to be associated with hypopituitarism are indeed the result of pituitary deficit. In addition, the results indicate the time necessary for their development. It is interesting that the clinical appearance of this patient corresponded to the type of hypopituitarism known as pituitary myxedema and that the patient did not live long enough to become cachectic.

The lack of effect on the patient's neoplastic disease does not prove that hypophysectomy is useless for melanosarcoma. To determine this point, the operation should probably be tried earlier in the course of the illness, while there is still some chance that the neoplastic growth may be under hormonal influence.—Ed.]

Therapeutic Effect of Subsequent Pregnancy in Simmonds' Disease is reported by R. Murdoch and A. D. T. Govan[4] (Glasgow).

Woman, 40, was first seen at age 33, 16 months after birth of her fourth child. Delivery had been complicated by prolonged labor and severe postpartum hemorrhage. From that time there were amenorrhea and failure to lactate. She had also failed to lactate after birth of the second child, which was also complicated by severe hemorrhage. Soon after birth of the fourth child she noted weakness, dyspnea, loss of hair, cold intolerance, weight loss and lack of libido. She had pale skin, absence of pubic and axillary hair, genital atrophy with senile-appearing labia and narrow vaginal introitus. Laboratory tests showed moderate anemia, BMR + 4%, 17-ketosteroid excretion of 1.5 mg./24 hours and pronounced insulin sensitivity.

Simmonds' disease was diagnosed, and she was treated for a short time with gonadotrophic hormones with variable results. She did not return for further examinations until five years later, when she was pregnant. She then gave a history of gradual general improvement with onset of menses two to three times a year, reappearance of hair and loss of cold intolerance. Laboratory tests showed 17-ketosteroid output of 18 mg., moderate anemia, BMR + 6% and moderate insulin hypersensitivity. Labor was induced and she was delivered of a normal infant. Puerperium was normal except for failure to lactate. Examination six months later revealed her to be essentially normal, with sparse pubic and axillary hair and normal libido. Menses were somewhat irregular and external genitalia were entirely normal. A year later she was pregnant but had a spontaneous abortion. She had regular menses every eight weeks thereafter and was entirely well.

[I have always been skeptical about the possibility of pregnancy in patients with Simmonds' disease, inasmuch as the absence of the hormones which are essential for reproduction is one of the most characteristic features of the disease. One might speculate that this patient, the mother of four children, had anorexia nervosa rather than true Simmonds' disease. Pronounced insulin sensitivity and low 17-ketosteroid values are not unknown in the cachectic stage of anorexia nervosa. Chances are, however, that this was a case of true Simmonds' disease for, whereas anorexia nervosa is rare in married women, Simmonds' disease most commonly follows severe postpartum hemorrhage. This remarkably well documented case does seem to prove the authors' contention.—Ed.]

(4) J. Obst. & Gynaec. Brit. Emp. 58:18-21, February, 1951.

Anemia of Hypopituitarism. V. K. Summers[5] (Liverpool) made a hematologic evaluation of 10 patients with hypopituitarism. In six, the anemia was macrocytic and hypochromic. A myxedematous appearance and achlorhydria were present in all cases. Thyroid therapy failed to improve the anemia although the macrocytosis was relieved. In four, the anemia was normocytic and hypochromic. Testosterone was given four patients with a small sustained rise in both red blood cell count and hemoglobin in one instance. Iron was of no value. Liver was not used because the bone marrow showed no evidence of megaloblastic change. ACTH or cortisone was administered to four patients, with prompt response in one. The duration of treatment was too short to allow conclusions to be drawn, but cortisone may be useful for the anemia of hypopituitarism.

[In my experience, the anemia of hypopituitarism has responded best to administration of methyltestosterone. The complete lack of response in two of the four patients studied indicates that methyltestosterone cannot be relied on to counteract anemia in all cases. A trial of cortisone seems reasonable, in view of the fact that polycythemia is a frequent concomitant of Cushing's disease. Because this syndrome is not common, reports of small series of patients, even of single cases, are needed to supply sufficient data to settle the point.—Ed.]

Practical Aspects of Insufficiency of Anterior Pituitary Gland in Adult, collated from the literature, are presented by Roy F. Perkins (Alhambra, Calif.) and Edward H. Rynearson[6] (Mayo Clinic). Acute lesions of the anterior pituitary are nearly always due to necrosis, with subsequent scarring and fibrosis; usually (in 79 of 132 recorded autopsies) they follow severe circulatory collapse in an obstetric patient (Sheehan's syndrome). Hemorrhage into the anterior pituitary is rare and usually results from bleeding into a degenerating adenoma. Subacute lesions include giant cell granulomas, actinomycosis and chronic abscesses. Chronic progressive fibroses of uncertain origin, probably representing the late healed stage of acute or subacute lesions, cysts and tumors, account for many cases. In 76 of 82 cases of severe pituitary insufficiency, autopsy revealed profound atrophy of all endocrine glands, severe atrophy of most of the viscera and, in females, superinvolution of the uterus, vagina and vulva.

The clinical picture varies with the degree of pituitary destruction and is patterned according to deficiency of hormones from the "peripheral" endocrine glands. The clinical

(5) Brit. M. J., 1:787-790, Apr. 12, 1952.
(6) J. Clin. Endocrinol. 12:574-603, May, 1952.

picture may suggest myxedema or Addison's disease, or physical signs may be few. Typically, there is complete loss of sexual function, usually including loss of libido. Axillary hair is lost within a few months and pubic hair within about two years of onset. The eyebrows (particularly the outer part) thin and become depigmented. The hair on the head thins in about half the patients. The skin is described as slightly scaly, dry, smooth and soft, waxy, sallow or lemon-tinged and does not tan on exposure to the sun. The almost pathognomonic facies is slightly puffy, particularly below the eyes, with a

Fig. 7.—Two patients with pituitary insufficiency. Center patient, in whom Simmonds' cachexia was erroneously diagnosed, has anorexia nervosa. (Courtesy of Perkins, R. F., and Rynearson, E. H.: J. Clin. Endocrinol. 12:574-603, May, 1952.)

weakness and lack of animation suggestive of myopathy or of a person asleep. Premature senility has been noted in only 10% of patients. The heart is usually small and the blood pressure labile. Sensitivity to cold, physical weakness, lack of ambition and interest and mental torpor increase. Speech is usually slow and soft. Acute necrosis of the anterior pituitary should always be suspected in the woman who, after a delivery complicated by circulatory collapse, is a "different person," fails to lactate, shows rapid involution of the breasts, loss of pigment in the areolae and slow regrowth of shaved pubic hair.

Pituitary insufficiency may be confused with nephrosis,

severe anemia (sometimes seen in pituitary insufficiency), primary thyroidal myxedema, hyperinsulinism, psychosis, Addison's disease (pigmentation suggestive of Addison's disease may be found in pituitary insufficiency) and, most often, anorexia nervosa, which often exactly duplicates clinical and laboratory findings of pituitary insufficiency. Emaciation, common in anorexia nervosa, has been found in only 13-27% of patients with pituitary insufficiency and then was often terminal event. A critical review of the literature indicates that the patient most reported as an example of Simmonds' cachexia really had anorexia nervosa (Fig. 7). Contrary to pituitary insufficiency, classic anorexia nervosa is found in the nullipara, usually under 30, with a history of acute or chronic psychic maladjustment; she is severely emaciated, shows increased body hair and is mentally and physically alert. Laboratory procedures, useful in differential diagnosis, assess the functional state of various "target organs" (thyroid, adrenals, gonads) and of urinary gonadotrophins. The danger of the insulin tolerance test or of thyroid therapy in patients with primary or secondary adrenal cortical insufficiency is emphasized.

Long term therapy with anterior pituitary extracts is impractical; end organ replacement therapy is recommended and involves, primarily, treatment of adrenal cortical, thyroidal and gonadal insufficiency. In adrenal cortical insufficiency, cortisone should be given before thyroid is used. The bleeding cycle in the female may be reproduced with estrogens, with or without progesterone. Virtually all men and many women with pituitary insufficiency are greatly improved by the anabolic properties of methyltestosterone; women should be advised of possible androgenic effects. There is evidence that sex hormone therapy may reactivate chromophobe adenomas. Appropriate end organ replacement therapy has been reported to have enabled pregnancy in a woman with complete pituitary insufficiency and genital atrophy which followed a previous parturition.

Variability of Endocrine Dysfunction in Postpartum Hypopituitarism was evident in six patients reported on by M. H. Oelbaum[7] (Manchester). Although the symptoms and signs of this disease can be explained by damage to the anterior

(7) Brit. M. J. 2:110-113, July 19, 1952.

pituitary and subsequent secondary failure of the thyroid, adrenal cortex and ovary, analysis of biochemical findings indicated a possibly striking dissociation in the degree of functional impairment of these glands (table). In one mild case (Case 2) there was only a deficiency of gonadotrophin excretion with apparently normal thyroid and adrenocortical function. In another mild case (Case 3), gonadotrophin output and thyroid function were normal, but adrenocortical activity, as evidenced by low 17-ketosteroid excretion, positive result of the Kepler test (but high factor) and borderline insulin tolerance, was slightly reduced.

Although results of biochemical and metabolic tests may be positive only in severe forms of the disease, partial anterior pituitary failure can be detected by careful attention to the clinical picture. There must be a definite history of hemor-

VARIATION IN DEGREE OF DAMAGE TO HORMONE PRODUCTION

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Gonadotrophin ..	+++	+++	0	+++	+++	0
Thyrotrophin ..	+++	0	0	++	++	++
Adrenocorticotrophin ..	++	0	+	+++	+++	++

0 = no damage; ++ = moderate damage;
+ = mild damage; +++ = severe damage.

rhage and collapse at time of delivery with subsequent failure of lactation and amenorrhea. Other features common to all cases include asthenia, intolerance to cold, and diminition of libido. The smooth and glistening skin has a waxy pallor out of all proportion to the degree of anemia. The eyebrows are usually thinned, and axillary and pubic hair is nearly or entirely lacking. The areolae are usually depigmented and the external genitalia atrophic. Arthritis of the knees is common. The severity of the disease is apparently not entirely related to its duration but is probably more affected by the amount of hemorrhage and degree of collapse at delivery.

[Because the clinical manifestations of hypopituitarism are so variable, therapy must be tailored to fit the individual patient. When hypogonadism and cachexia predominate, methyltestosterone may be the most effective form of treatment, while in some cases adrenal cortical substitution therapy alone may suffice. Treatment of the secondary hypothyroidism must be undertaken cautiously, since administration of thyroid substance alone may throw some of these patients into severe and even fatal adrenal insufficiency.—Ed.]

Adrenal Cortical Dysfunction Leading to Crisis in Simmonds' Disease. Simmonds' disease consists of a syndrome of multiple endocrine dysfunctions associated with a severe pathologic lesion of the pituitary. Cachexia, when it occurs, is probably due to an associated hypothalamic lesion; only a minority of patients show weight loss. It should be possible to make the correct diagnosis in most cases of moderately advanced disease, particularly when there is a typical history of postpartum hemorrhage, but in the early stages, if there is no history to help, differentiation from disease affecting only one endocrine organ may be difficult. It is nevertheless important to establish the correct diagnosis early, since there is danger not only of giving inadequate treatment but, in the case of excessive thyroid therapy, of precipitating a severe and perhaps fatal crisis. John O. Laws[8] presents two cases in which this occurred.

Case 1.—Woman had had severe postpartum hemorrhage in 1932. In 1936 she showed myxedema, dry skin, hair loss, brittle nails and a BMR of —35%. She was given desiccated thyroid and improved at first, but because of a gradual deterioration the dose was raised to 10 gr. daily. By December 1941 she had deteriorated greatly and had hypotension, asthenia and complete hair loss. Thyroid as well as adrenocortical deficiency was diagnosed. She improved greatly on combined adrenocortical and thyroid therapy but through error was maintained only on thyroid after discharge and again deteriorated. Addisonian crises recurred and she died. Autopsy showed atrophy of the pituitary, adrenal cortices, thyroid and ovaries.

The second patient similarly showed typical myxedema and responded well to thyroid therapy at first, only slowly developing a "refractory" state. Attention was directed to the steady progress of the alteration in endocrine function in each case by occurrence of a crisis, induced apparently by some minor stress.

[Patients with hypopituitarism, like patients with Addison's disease, should be supplied with vials of cortisone tablets. Even patients who do not require cortisone for maintenance therapy must be taught to recognize and look for early symptoms of Addison's crisis. Unless the patient is vomiting so badly that cortisone cannot be retained, many incipient crises may be successfully nipped in the bud and the hazards and expense of a profound crisis averted.—Eds.]

Studies of Electrolyte Metabolism in Two Patients with Pituitary Insufficiency are reported by Christine Waterhouse, E. Henry Keutmann and Leonard D. Fenninger[9] (Univ. of

(8) Guy's Hosp. Rep. 101:280-292, 1952.
(9) J. Clin. Endocrinol. 12:798-920, July, 1952.

Rochester). Low serum electrolyte concentrations—with contracted plasma volume, depressed glomerular filtration and circulatory collapse—are common in salt deficiency; they have been reported, without obvious intravascular dehydration, in far advanced tuberculosis, tuberculous meningitis, hepatic cirrhosis and cardiac decompensation. Only with control of the underlying disease was the serum electrolyte concentration restored to normal.

Case 1.—Man, 51, who had had myxedema at age 35, was hospitalized in practically a hibernating state, with dry, cold skin and no body hair. Blood pressure was 92/75 mm. Hg; he had anemia, and BMR was —50%. X-rays showed a normal skull. He was studied in the metabolic unit for 40 days.

Case 2.—Man, 65, had had symptoms of hypothyroidism and the climacteric for 10 years. Four years before hospitalization, evidence of increased intracranial pressure was noted and a pituitary chromophobe adenoma was removed. Postoperative recovery was poor. He was finally hospitalized in coma. Blood pressure was 150/100; he was unresponsive, and the skin was fine, dry and devoid of hair. The heart was enlarged and there was moderate edema of the extremities. Metabolic unit studies were made over a 120 day period.

Included were nitrogen, sodium, chloride, potassium, phosphorus, and calcium balance studies. Three biopsies in one and four in the other patient were made of the gastrocnemius or deltoid muscles. Since complications were numerous, the exact sequence of events was not always evident, but certain characteristics of the electrolyte aberrations were striking and definite.

Both patients had low serum electrolyte concentrations over long periods, even without a deficit of total body sodium and chloride. Excessive extracellular fluid retention and edema readily occurred despite persistently low concentrations of serum sodium and chloride. When sodium and chloride retention was produced by high salt intake, desoxycorticosterone acetate or testosterone propionate, plasma sodium and chloride contents were increased but the extracellular fluid expanded still further. Evidence of excessive sodium and deficient potassium within the cells was obtained by both metabolic balance and muscle biopsy data. Increased nitrogen excretion during administration of thyroid substance was not accompanied by potassium and phosphorus loss in quantities usually associated with destruction of protoplasm.

The low plasma electrolyte concentrations suggested that

intra- and extracellular osmotic pressures were less than normal. Generally changes in osmotic pressure will cause alterations in volume of the three fluid compartments of the body. Although changes of these forces within the vascular system and in the resistance furnished by the tissues are responsible for the movements between the vascular bed and interstitial spaces, the variables responsible for the shift of water between the extracellular compartment and the interior of the cell are less well understood. Intracellular osmotic pressure is thought to be adjusted to that of the interstitial fluid by shifts of water. In many conditions, however, the metabolic status of the cells may be largely responsible for osmotic pressure and the extracellular fluid adjusted accordingly.

Pitressin® has been found to increase excretion of sodium and retention of water in some patients with liver disease. An antidiuretic hormone (ADH) has been reported in the blood when solute concentrations therein were low. Although such an agent could explain the inability of these patients to excrete excessive extracellular fluid, the process initiating the low solute concentration would still be obscure. If it is posterior pituitary ADH, then that ADH must disturb the composition of all body cells. In this connection, autopsy in one case showed probable total destruction of the posterior pituitary lobe, although the supraopticohypophyseal system may have been intact and capable of secreting ADH.

Although deficiencies of thyroid and androgenic activity were present in both, failure of one to maintain higher serum osmotic pressure while receiving testosterone propionate and thyroid substance suggests that the fundamental abnormality responsible for the low osmotic pressure still existed. The discrepancy between nitrogen balance and phosphorus and potassium balances during thyroid therapy may have resulted from protein within the cells not associated with normal amounts of phosphorus and potassium. This is additional evidence for a primary intracellular metabolic change which could result in low intracellular osmotic pressure and secondary reduction of extracellular electrolyte concentration.

Gradual restitution of both intra- and extracellular phases occurred as the disease process was controlled in one patient. This may have been associated with the positive caloric, nitrogen and potassium balances. Nitrogen and potassium balances

may have been potentiated by the androgen therapy. Failure of the other patient to attain normal electrolyte concentrations during the period of observation may have been due to inadequate therapy or less than optimal caloric intake during therapy.

[The lowest serum sodium levels I have encountered have been in patients with pituitary insufficiency of the pituitary-myxedema type. In this case it is particularly interesting that thyroid substance caused excretion of nitrogen but that the loss of potassium and phosphorus was too slight to suggest the breakdown of protein tissue. Perhaps the concept of tissue protein stores must be revived.—Ed.]

Pituitary Necrosis in Routine Necropsies. Subtotal necrosis of the anterior pituitary, as it is observed after childbirth, is

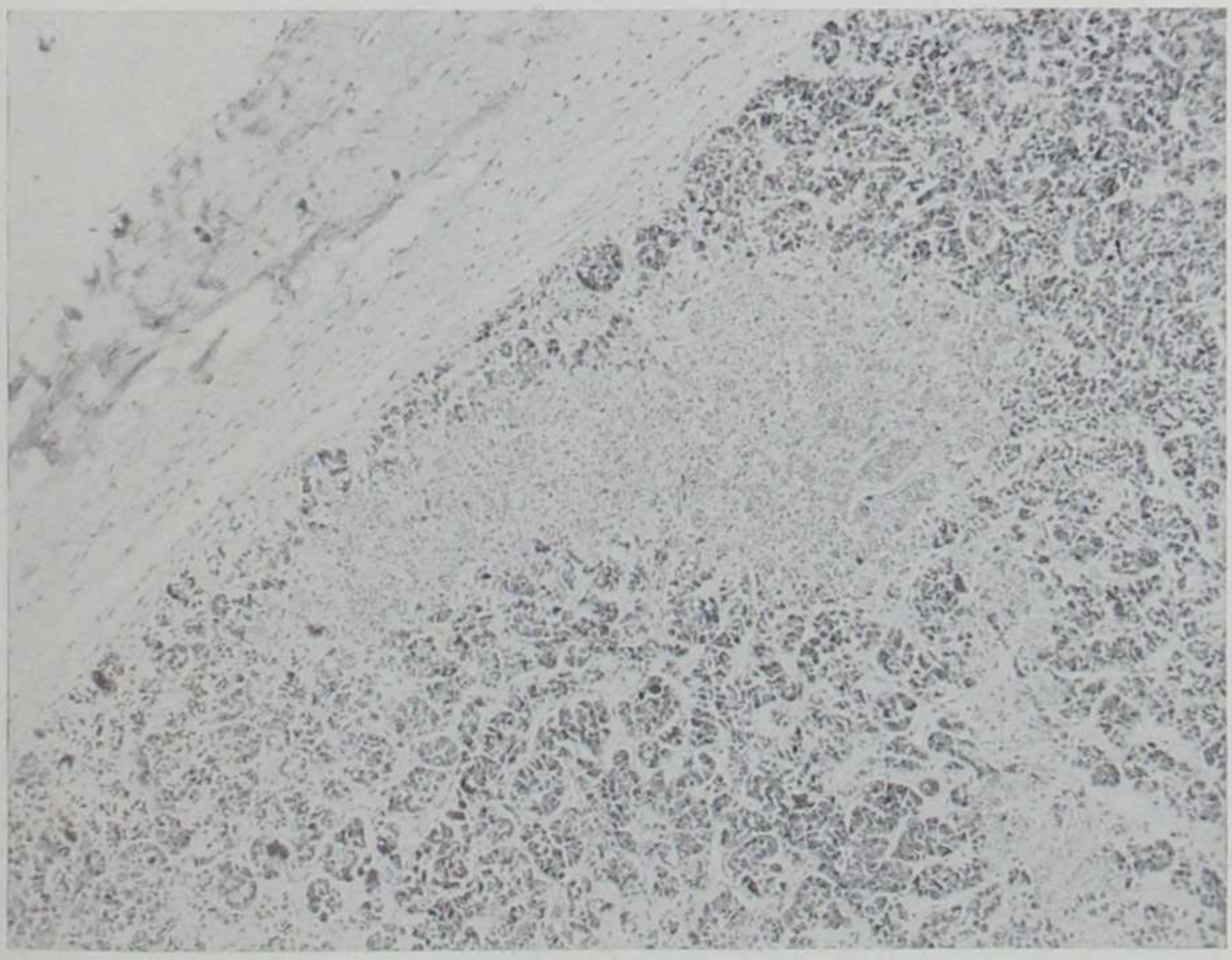

Fig. 8.—Typical subcapsular necrosis in man, 51, with abdominal carcinomatosis. Thin, somewhat interrupted layer of well preserved tissue lies between region of necrosis and capsule. In right lower corner, necrosis extends deeper into tissue. Hematoxylin-eosin; reduced from × 77. (Courtesy of Plaut, A.: Am. J. Path. 28:883-899, Sept.-Oct., 1952.)

ascribed to anoxemia associated with severe hemorrhage and shock. Since similar irreversible circulatory disturbances are common before death, Alfred Plaut[1] (V.A. Admin. Hosp., Topeka, Kan.) searched for pituitary necrosis at 149 autopsies. It was found 12 times by routine sections and once by serial

(1) Am. J. Path. 28:883-899, Sept.-Oct., 1952.

sections. The suspicion that such necrotic areas could represent postmortem changes is unlikely. Leukocytes were absent in one third of the lesions. The capillaries in the necrotic areas were well preserved and, with one exception, the larger blood vessels showed no narrowing, thrombosis, emboli or occlusion. The necrotic foci were situated near one of the connective tissue structures, usually the capsule (Fig. 8). A thin layer of well preserved cells generally was interposed between the connective tissue structure and the necrotic area. The largest necrotic focus measured 5 mm. in diameter. Many were smaller than 1 mm.

There were 11 pituitaries with necrosis in 60 men under age 55, but only 2 in 94 men over 55. Hypertension had been an outstanding finding in 11 patients and 4 of them had necrosis, 2 after sympathectomy. Although in some patients shock and circulatory failure were noted during the last days of life, necrotic areas were present in two patients who died suddenly and unexpectedly. No correlation with clinical disease was otherwise evident. A review of the illustrations of previous reports of pituitary necrosis which attribute the disorder to emboli and infarction failed to confirm this claim. It appears that most of the necrotic lesions in the pituitary previously described as embolic or thrombotic are not of such origin and are indistinguishable from those of the present series. The subtotal postpartum necrosis of the anterior pituitary described by Sheehan represents an exaggeration of a process that takes place often during the last days of life, in nonpregnant women and in males, without a close relationship to the disease from which the patient is dying.

Nervous Anorexia. Since anorexia nervosa was first described by William Gull in 1888 (Fig. 9), there have been many reports on patients who starve themselves to death because of lack of appetite. Helge Hertz[2] (Rigshosp., Copenhagen) reviews 50 cases diagnosed as anorexia nervosa from 1932 to 1949. Follow-up revealed that in five instances the diagnosis was wrong, because cancer, infection or osteomalacia was discovered subsequently. Only 2 of the other 45 cases occurred in males. In 13 cases, diseases or disturbances of the digestive tract probably led to a fear of eating, since food increased the discomfort. Other possible contributing causes included goiter,

(2) Acta med. scandinav. (supp. 266) 142:523-527, 1952.

encephalitis and concussion; in 17 cases a reasonable psychologic mechanism was apparent.

A search for endocrine disorder by x-ray study of the sella turcica in 16 cases, visual field study in 18 and sugar tolerance tests in 5 was unrewarding. Urinary assays for estrogenic and androgenic substances in 12 revealed low values in 8. Amenorrhea was present in 24. Other investigators have reported this disturbance in cases of emaciation due to starva-

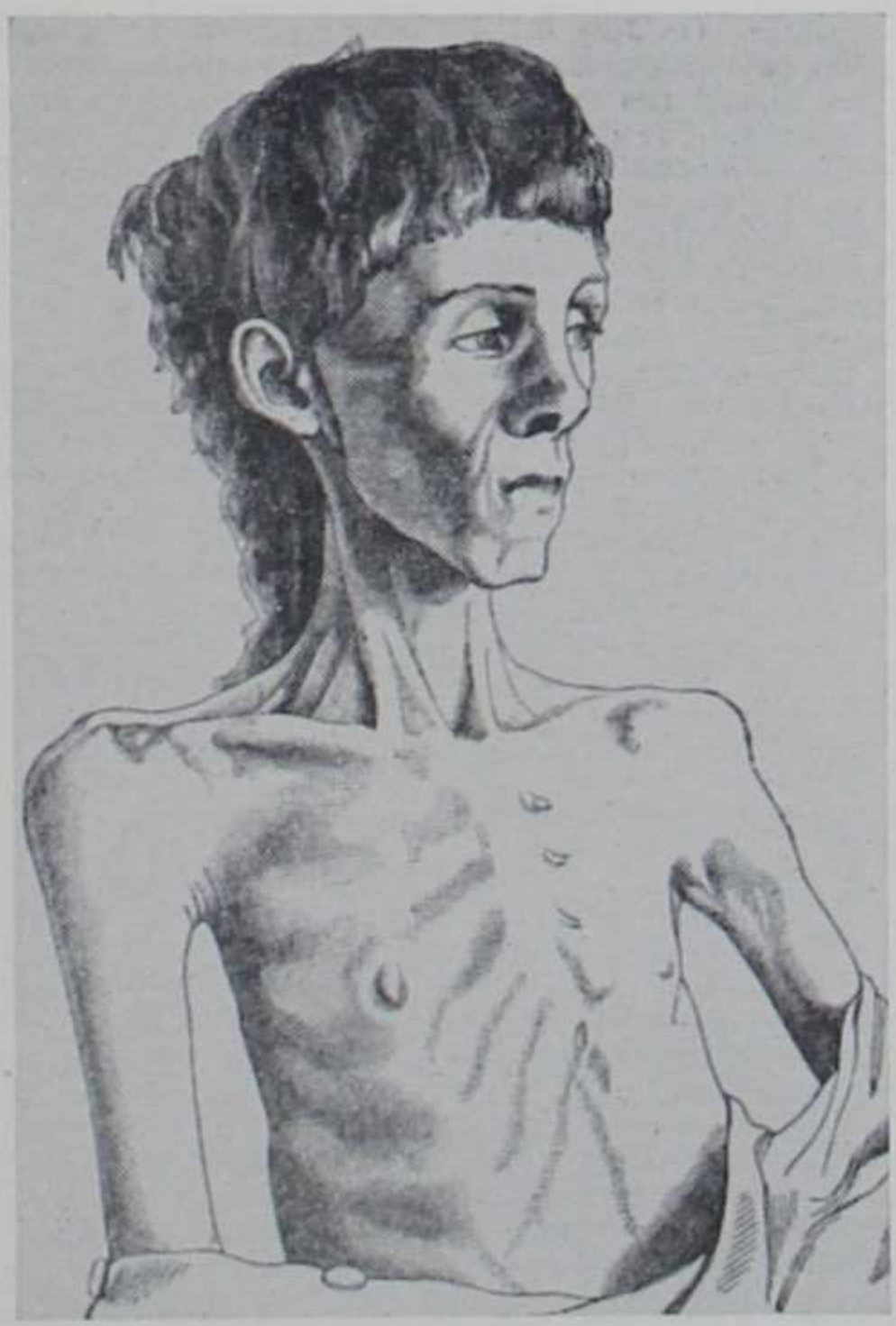

Fig. 9.—Anorexia nervosa. Wood engraving from report by William Gull in Lancet, 1888. (Courtesy of Hertz, H.: Acta med. scandinav. (supp. 266) 142:523-527, 1952.)

tion. Hypotension was present in 14 patients and a low BMR in 8 of 32 tested. According to others, both conditions may be secondary to emaciation. One patient had polyuria of 10 L. daily, uncontrolled by posterior pituitary extract. Electrocardiograms revealed findings suggestive of thiamine deficiency in only one patient.

Treatment with insulin, small meals and psychotherapy resulted in improvement in 21 of 38 patients followed. In the 14-25 year age group, in which psychologic traumas were most

obvious, 14 of 17 patients improved. Older patients with no psychologic trauma did not improve.

Present knowledge of conditioned reflex control of gastric motility, knowledge that appetite stops on starvation and advances in psychotherapy should lead to improvement in the understanding and psychologic treatment of this disease.

[Anorexia nervosa can be a serious disorder; in extreme cases it may even lead to death. Skilled psychiatric treatment is usually desirable. The condition may closely resemble Simmonds' disease, even to the point that, in the cachectic stage, excretion of pituitary gonadotrophins and 17-ketosteroids may be identical in these two conditions. The principal diagnostic features in differentiating these disorders lie in the fact that in anorexia nervosa local signs of pituitary tumor, such as bitemporal hemianopsia and enlargement of the sella turcica, are lacking and that anorexia nervosa occurs almost exclusively in unmarried, teen age girls. Insulin therapy is not without danger; extreme insulin sensitivity may exist in anorexia nervosa, just as it does in hypopituitarism.—Ed.]

Neurohypophysis and Water Metabolism

A vast accumulation of data in recent years has suggested that the posterior pituitary antidiuretic hormone may play a role in fluid accumulation in such diseases as cirrhosis of the liver, congestive failure and nephrosis. Recently, the specificity of the tests used to quantitate presence of antidiuretic substance has been questioned, and the whole problem must be considered wide open.

Which hormones are natural antagonists to antidiuretic substance has not been established. In certain diseases in which destruction of the posterior lobe of the pituitary leads to diabetes insipidus, the responsible neoplasm or granuloma may progress to include the anterior lobe, whereupon diabetes insipidus usually disappears. The studies of Leaf and others (J. Clin. Invest. 31:914-927, October, 1952) indicate that when the whole pituitary is destroyed and the symptoms of diabetes insipidus are abolished, the persistence of the physiologic defect can still be detected by the patient's inability to produce a hypertonic urine during severe dehydration. Furthermore, polyuria returns when the excretory solute load is increased by the administration of salt and urea. In such instances the term "panhypopituitarism" seems justified.—Ed.

Regulation of Water Excretion by Neurohypophysis is discussed by H. B. van Dyke[3] (Columbia Univ.). The antidiuretic hormone (ADH), according to H. W. Smith, acts on the distal renal tubule where 10-15% of glomerular filtrate is normally actively reabsorbed, as contrasted with passive reabsorption in the proximal tubule. In diabetes insipidus, this large amount is not entirely excreted, as complete deficiency of the hormone probably never occurs. The essential feature of the action of ADH is to increase the rate of reabsorption of water by the kidney. Although striking increases in electrolyte excretion may occur while the hormone is exert-

(3) Bull. New York Acad. Med. 29:24-33, January, 1953.

ing an antidiuretic effect, an increased excretion of electrolytes is not necessarily present, especially after doses in the physiologic range. The effects of the hormone on electrolyte excretion probably depend on a number of factors such as electrolyte stores of the body, electrolyte in the diet and rate of secretion of adrenal cortical steroids.

In true diabetes insipidus, the polyuria is primary; the associated polydipsia serves to keep the organism in water balance. Intravenous infusion of 2.5% saline or injection of nicotine will stop diuresis in hysterical polydipsia and thus differentiate these conditions. Transient liberation of ADH can be provoked by pain or excitement, dehydration, large doses of electrolyte (NaCl) and by drugs. Hypersecretion of ADH for prolonged periods because of disease has not been convincingly demonstrated. The evidence that hypersecretion occurs in cirrhosis with ascites, adrenal insufficiency, toxemias of pregnancy and a number of other diseases is based on the presumed recognition of excessive amounts of ADH in the urine or blood of patients. Usually the assays have been performed by subcutaneous or intraperitoneal injection in hydrated normal rats. This is not a specific test for ADH. Much more satisfactory is the production of transient antidiuresis after intravenous injection of the test material in hydrated normal dogs or dogs with diabetes insipidus. In one study in which this method of assay was used in patients with cirrhosis of the liver, the urinary ADH titer was only slightly higher in the ascitic than in the nonascitic patients.

Hyperthyroidism Associated with Diabetes Insipidus: Relief of Both Diseases after Treatment with Radioactive Iodine is reported by Charles W. Rieber and Solomon Silver[4] (New York City).

Man, 32, stated that for as long as he could remember, and certainly for the past eight years, he had suffered from great thirst and had passed large amounts of water-clear urine. On several occasions the urinary output was about "10 qt. in 24 hours." For the past two years he had become aware of heat intolerance, excessive perspiration, palpitation, nervousness, asthenia and a progressive weight loss of 20 lb.

Physical examination revealed a nervous, tense man with rapid, explosive speech and a slight bilateral lid lag. The mucous membranes of the mouth and pharynx were dry. The thyroid gland was moderately and diffusely enlarged. No bruit was present over the

(4) Ann. Int. Med. 37:379-383, August, 1952.

thyroid. Lungs, heart and abdomen were normal. Blood pressure was 150/60-30 mm. Hg; the pulse was of the Corrigan type. There was a fine tremor of the outstretched fingers. Laboratory findings other than urinary data were essentially normal. The daily output of urine averaged 11 L., passed in 14 voidings; specific gravity varied between 1.001 and 1.005. Tests for albumin and sugar gave negative results. After 1 cc. pitressin® was given subcutaneously, urinary output dropped to 3,400 cc. in 24 hours. Results of other studies made during water deprivation, water excess and intravenous injection of hypertonic NaCl, as well as the glomerular infiltration rate, were typical of true diabetes insipidus. The BMR was +72% and the protein-bound iodine was 23.1 μg./100 cc. The patient excreted 18% of an oral tracer dose of 100 μc. radioactive iodine in 24 hours in 8,000 cc. urine, a finding consistent with hyperthyroidism. He was given 5 mc. I^{131} orally and discharged. Five and one-half weeks later he was improved; he had gained 7 lb. and was less nervous. The BMR was +11% eight weeks after therapy. There were progressive diminution in thyroid function and improvement in diabetes insipidus thereafter, until nine months after treatment the BMR was +4% and the 24 hour urine output 1,900 cc. in six voidings, with specific gravities between 1.008 and 1.016.

The pathogenesis of diabetes insipidus has been the subject of much speculation and experiment since the earliest description. For some time the disease was thought to be a manifestation of increased posterior pituitary function. Farini first suggested that decreased function of the posterior lobe was essential for production of polyuria, a concept supported by the remarkable control of polyuria by subcutaneous or intranasal administration of posterior pituitary extract. In 1918, the idea was advanced by von Hann and confirmed by Rowntree that an intact anterior lobe was necessary for development of diabetes insipidus. Later, attention was called to the importance of lesions in the diencephalon. The present concept of diabetes insipidus is that it is the result of decreased function of the posterior pituitary lobe due to lesions of that lobe or of the tracts leading to it from the midbrain; an intact anterior pituitary lobe and a functioning thyroid gland are probably necessary for full development of the syndrome.

The association of true diabetes insipidus and hyperthyroidism is rare and has many interesting aspects, because both the thyroid and the pituitary-diencephalic area are involved in the present concepts of water metabolism and renal secretion. The present case is the first in which modern diagnostic methods were applied to both diseases. Control of

hyperthyroidism by I^{131} is well established. The simultaneous control of diabetes insipidus confirms experimental data that in some way the effects of thyroid secretion on water metabolism are related to clinical diabetes insipidus.

In view of the ease with which myxedema can now be induced in euthyroid subjects by administration of I^{131}, this treatment should be considered in severe diabetes insipidus, provided myxedema would prove less troublesome than polyuria.

[This report suggests strongly that, as has been suggested earlier, thyroid hormone is a natural antagonist of antidiuretic hormone. I admit that I would have been skeptical of the diagnosis of diabetes insipidus in this case had the documentation not been so exact. Psychogenic polydipsia produces identical symptoms and is much more common than diabetes insipidus, but the authors excluded this condition by the Carter-Robbins test, i.e., the response to intravenous administration of a hypertonic solution of sodium chloride. This neat study demonstrates that, even in these statistic-minded days, careful observation of a single patient may yield valuable information.—Ed.]

Four Cases of Diabetes Insipidus and Pulmonary Disease. John D. Spillane[5] (United Cardiff Hosp.) describes four patients with both diabetes insipidus and diffuse pulmonary disease, the posterior pituitary gland and lungs presumably having been injured by a common process.

One man, 35, had a typical onset of sarcoidosis with uveoparotid fever and facial palsy; later hilar adenopathy, coarse pulmonary fibrosis and diabetes insipidus developed. Two patients had diabetes insipidus associated with a diffuse fine reticular x-ray pattern of the lungs ("honeycomb lungs") thought to be typical of xanthomatosis. Ten similar cases are reported in the literature. No cutaneous xanthomas or skeletal lesions were found. One patient had mental deterioration, and the possibility of tuberous sclerosis was considered. Autopsy in one case revealed eosinophilic granulomas of the lungs with cystic degeneration and granulomatous replacement of the hypothalamus, which probably caused the diabetes insipidus since the pituitary was normal.

Idiopathic Diabetes Insipidus with Normal Pregnancy. A woman treated for six months of pregnancy with pitressin® is reported on by A. J. Tannenbaum, M. H. Bertling and J. G. Burwell, Jr.[6] (Greensboro, N. C.).

Woman, 26, had polyuria, polydipsia, weakness and weight loss

(5) Thorax 7:134-147, June, 1952.
(6) Am. J. Obst. and Gynec. 63:472-473, February, 1952.

for three months. Urine output was 5 gal. in 24 hours, with specific gravity 1.002. Skull x-ray was normal and the history was not significant. Her symptoms were all relieved by 1 cc. of pitressin® tannate in oil every 12 hours.

A year later she became pregnant and continued on the usual pitressin® dosage. The pitressin® requirement gradually fell as pregnancy advanced, and at the sixth month it was discontinued without difficulty. During this period, blood pressure averaged 122/78 and she gained 13 lb. At term she was delivered uneventfully of a normal baby but, 48 hours later, polyuria, polydipsia and weakness began. Pitressin® therapy was reinstituted and she was again asymptomatic.

The authors concluded that the fetal posterior pituitary secretion had been sufficient to care for the mother's requirements from the sixth month on. They point out that pitressin® has a marked antidiuretic effect and some pressor action with minimal uterine stimulation, whereas pitocin,® the other posterior lobe extract, has 150 times the oxytocic effect of pituitary powder but has little antidiuretic or pressor action.

[If after the sixth month of gestation the fetal posterior pituitary produced enough antidiuretic substance to cope with the mother's diabetes insipidus, one might expect that the newborn child would have a syndrome caused by excess posterior pituitary activity. Actually, such a syndrome has been postulated by S. L. Simpson and called "diabetes tenuifluus." Since this baby was normal, perhaps the placenta, which seems to be capable of producing every other hormone, should be considered as a possible source of posterior pituitary hormone.

It is interesting that the doses of vasopressin necessary to control the mother's diabetes insipidus in the first five months of pregnancy did not overly stimulate the uterus and produce abortion.—Ed.]

THE THYROID GLAND

The antithyroid drugs have been available for 10 years, but whether they provide definitive therapy for hyperthyroidism is still controversial. Advocates of such therapy point out that operation and surgical complications are thereby avoided. Opponents point to the higher relapse rate when the drugs are finally withdrawn and the increasing incidence of untoward dangerous and fatal drug reactions. The two alternatives to drug therapy, namely, surgery and radioactivity, can hardly be mentioned together. The use of radioiodine must still be considered experimental and probably should not be applied in young patients. The proper utilization of surgical procedures depends entirely on the training and skill of the surgeon. In practice, I prefer to prepare patients with Graves' disease for thyroidectomy with antithyroid drugs, e.g., propylthiouracil followed by iodine, or iodothiouracil. My preference for surgical therapy is undoubtedly influenced by the availability within my area of highly skilled, well trained goiter surgeons. Otherwise, I might be more amenable to drug therapy.

The fact that thyroid status must be determined clinically requires frequent reiteration. In a recent and timely letter to the editor of the

Journal of the American Medical Association (149:504, May 31, 1952), Doctor S. J. Glass and associates pointed out the many pitfalls in the laboratory diagnosis of thyrotoxicosis. They called attention to false results in protein-bound iodine values and uptake of radioiodine, which are to be expected in patients who have been taking thyroid substance, antithyroid drugs or iodine-containing medications, including the contrast mediums used for cholecystography, urography and myelography. It seems hardly necessary to mention the many sources of error in basal metabolism determinations. So, in the estimation of thyroid status, as in all medicine, the physician must "stand on his clinical feet" and be ready to discard any laboratory data which are inconsistent.—Ed.

General Considerations

Role of Hypothalamus in Control of Thyroid Function. Monte A. Greer[7] (Nat'l Inst. of Health) found that when the pituitary is not in direct contiguity with the hypothalamus (hypophysectomized animals with hypophyseal transplants) or when certain areas of the anterior hypothalamus are destroyed by electrolytic lesions, the hypophysis is not able to stimulate the growth of the thyroid cells but is able to maintain an approximately normal thyroidal iodine metabolism. This indicates that the pituitary may secrete two thyrotrophic factors, arbitrarily called the growth factor and the metabolic factor. The latter seems independent of the hypothalamus and enables the thyroid to concentrate and bind iodine. This factor is apparently regulated, at least to a certain extent, by the level of circulating thyroid hormone, since antithyroid drugs (propylthiouracil) will increase the iodide concentration in the thyroid and thyroxin will lower it. This regulation of pituitary secretion does not seem to be mediated directly through the nervous system.

The growth factor seems to regulate thyroid cell height and gross thyroid size. This principle apparently depends on the integrity of a certain area of the hypothalamus and on some manner of direct communication of this area with the anterior pituitary for maintenance. The secretion of the growth factor also appears to be governed, at least partly, by the level of circulating thyroid hormone.

Pathogenesis of Simple Goiter: Review is presented by A. W. Spence[8] (St. Bartholomew's Hosp.). It has been established that iodine deficiency gives rise to goiter. The converse, that all simple goiters are due to deficient iodine intake, is not true. As a result of iodine deficiency, the secretion of thyroid

(7) J. Clin. Endocrinol. 12:1259-1268, October, 1952.
(8) Brit. M. J. 2:529-532, Sept. 6, 1952.

hormone is reduced; this brings about increased secretion of thyrotrophin by the anterior pituitary, which causes hyperplasia and enlargement of the thyroid. Not all persons living in the same endemic area have goiters, although they all have a deficient iodine intake; probably the combination of the deficient intake and increased demands on the thyroid gland during growth, pregnancy and puberty and other possibly unknown endogenous factors give rise to goiter. If iodine deficiency is prolonged, exhaustion atrophy of the thyroid cells ultimately takes place and hypothyroidism develops. If the goitrous thyroid of the pregnant woman is unable to maintain adequate thyroid hormone level, congenital goiter will result in the fetus.

A deficient intake of iodine is obviously not the cause of sporadic goiter, which occurs in a city like London where there is no iodine deficiency. Although infection has been implicated in India, there is no evidence that it is a cause of goiter in the Western world. Apart from iodine intake, it is doubtful what part diet plays in causing goiter. A high intake of fat or of meat protein may cause thyroid hyperplasia in laboratory animals, but it is questionable whether this finding has any clinical significance. Unbalanced diets may be contributory, and excessive ingestion of foods containing goitrogenic substances may be responsible for a high incidence of goiter in certain regions. A high calcium intake enhances the goitrogenic effect of a low iodine diet. Experimental work is contradictory, but there is no clinical evidence that vitamin deficiency plays a primary role in endemic or sporadic goiter.

Cabbage goiter is caused, not by a deficient intake of iodine, but by a positive goitrogenic agent. Other vegetables of the Brassica group, to which cabbage belongs, have been found to be goitrogenic, namely, brussels sprouts, cauliflower, kohlrabi, rutabaga and turnip; the seeds of certain brassicae, notably rape, mustard and cabbage seeds, also caused goiter when fed to rats. Because these vegetables contain high amounts of organic cyanides, methyl cyanide was investigated and found to be goitrogenic under certain conditions; other compounds, such as thiocyanate, thiourea derivatives and sulfonamides have also been shown to be goitrogenic, but the first goitrogen demonstrated in vegetables was 1-5-vinyl-2-thio-oxazolidone isolated from rutabaga and from brassica

seeds. As in goiter caused by iodine deficiency, the anterior pituitary thyrotrophic hormone is directly responsible for the thyroid changes, for thyroid enlargement cannot be produced by brassica seeds or antithyroid compounds in hypophysectomized animals. It is doubtful what bearing, if any, these goitrogenic compounds have on the spontaneous development of goiter in man, although they may account for the increased incidence in the Lowlands during the war, when large amounts of these vegetables were consumed, and they may occasionally be responsible for a sporadic goiter.

Possibly deficiency of antigoitrogenic substances other than iodine may play a part in the genesis of simple goiter. Cabbage goiter can be prevented by feeding certain fresh plants, and the antigoitrogenic action of these plants is not likely to be due to iodine. Variations in the goitrogenic potency of cabbage and similar vegetables may be due to variations in the content of the goitrogenic factor and also of an antigoitrogenic substance.

Survey of Thyroid Glands Obtained at Autopsy in So-called Goiter Area. John B. Hazard and Nathan Kaufman[9] (Western Reserve Univ.) studied 408 glands removed from adults at consecutive autopsies. All but 11 of the patients had lived in the Cleveland area for five years or longer and several had spent their entire lives there. Average weight of non-nodular glands, grossly free from other disease such as scarring or tumor, was 26.0 Gm. in 154 men and 25.6 Gm. in 59 women. The limit of nongoitrous gland was set at 35 Gm.; according to this standard, 8.2% of men and 7.8% of women (8.1% of all glands studied) showed diffuse enlargement. Maximal weights of non-nodular glands were 65 Gm. for women and 100 Gm. for men.

Some nodules were circumscribed and had the well-formed capsule of true adenoma, whereas others were partially encapsulated, with the rest of the boundary formed by interlobular fibrous stroma. Solitary nodules were found in 12.0% of all glands; two to five nodules in another 11.0% and six or more nodules (multinodular) in 19.4% Of the goitrous glands (35 Gm. or over), 8.8% were multinodular; of the nongoitrous glands, 10.6% were multinodular. The ratio of women to men was 1.4:1 for multinodular goiter.

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(9) Am. J. Clin. Path. 22:860-865, September, 1952.

Because of the importance of solitary nodules in clinical interpretation of thyroid disease, single nodules were evaluated by size. Eight of the glands (2%) had a solitary nodule of 1 cm. diameter or over; in five (1.2%) the nodule was 2 cm. or over; the largest solitary nodule was 7 cm. In most glands, the nodules were small whether or not they were solitary. In 83, the solitary nodule or the largest nodule if there were few (two to five) was measured; in 32.2% the nodules were 1 cm. or larger and in only 9.7% were they 2 cm. or more. Average size of nodules increased with the age group as determined by measuring the solitary or the largest nodule if there were two or more.

There are several interesting features to compare in the group of nodular glands. Jaffe reported that two thirds of white women past 60 have thyroid glands with nodules; in this study 63% of women, predominantly white, 60 or older, had such glands. The largest nodular goiter in Jaffe's series was 400 Gm. and in this one, 200 Gm.; his youngest patient was a girl, 12; here it was a patient in the fourth decade (even after 21 children were included in the study). Rice reported that 56.9% of glands from women have nodules; here 50% had them. The authors found solitary nodules in 12.1% of all thyroids from women, or the equivalent of 24% of nodular thyroids from women, a figure comparable to Rice's 26.7%.

Additional, miscellaneous findings in the 408 glands included one papillary adenoma, two papillary carcinomas (all three in nodular thyroids), one nonencapsulated sclerosing tumor and two secondary carcinomas. There were two instances of struma lymphomatosa.

[This valuable study should terminate the arguments of those frequently quoted authorities—mostly from goitrous areas—who deny the existence of uninodular goiters.—Ed.]

Goiter Prevention in Michigan: Results of 30 Years' Voluntary Use of Iodized Salt are presented by J. K. Altland and Brock E. Brush[1] (Lansing). In 1924, a survey of 31,612 school children in four Michigan counties revealed visibly enlarged thyroids in 47.2%; a similar survey of 53,785 children in 1951 showed enlarged thyroids in only 1.4%. During this interval an educational campaign had been carried out. It was found that unless the problem is kept continually before the people there is a great tendency for the sale of iodized salt to decrease.

(1) J. Michigan M. Soc. 51:985-989, August, 1952.

The National Research Council gives the daily requirement of iodine for an adult as 0.15-0.30 mg., and iodized salt meets this requirement. No ill effects have been noted from its use. The small amount has not, according to the American Dermatological Society, caused any difficulty in persons with a tendency to acne, an objection once raised. Others have reported that since the introduction of iodized salt in Michigan, coincident with the great decrease in the number of enlarged thyroids, there has been a decrease in the number of operations for thyroid hyperplasia and adenomas in seven large Michigan hospitals.

Study of Mechanism of Inhibition of Thyroid Gland Induced by Ingestion of Thyroid Substance indicates that the primary mechanism is pituitary inhibition. Martin Perlmutter, Shirley Weisenfeld, Stanley Slater and Eleanor Z. Wallace[2] (Maimonides Hosp., Brooklyn) measured the effect of thyroid-stimulating hormone (TSH) injection on thyroid function in euthyroid persons. This was done before and after ingestion of 120 mg. desiccated thyroid for 14-30 days. Before thyroid therapy, 60 mg. TSH raised mean I^{131} uptake from 31% to 69% (+38) and protein-bound iodine (PBI) from 4.5 to 9.2 μg./100 ml. During the inhibition produced by ingestion of thyroid substance the same dose raised I^{131} uptake from 6% to 58% (+52) and PBI from 3.9 to 7.7 μg. When thyroid function was measured two weeks after injection of 60 mg. TSH, it had "rebounded" to hypothyroid levels, but a further injection of TSH at this time raised I^{131} uptake from 9% to 73% and PBI from 3.1 to 10.3 μg. One month after injection of TSH, thyroid function was normal. Although injection of 10 mg. of TSH did not produce the "rebound" phenomenon, it did stimulate the thyroid, which had been inhibited by thyroid ingestion, in a manner similar to 60 mg. of TSH. The fact that even minimal effective doses (10 mg.) of TSH could stimulate the inhibited gland supports the thesis that thyroxin inhibition is due to decreased availability of TSH.

[This study confirms and extends previous reports by Farquharson and by Greer. Clinically, it is of great importance to withdraw excessive doses of unneeded thyroid substance gradually, in order to avoid an uncomfortable and annoying period of hypothyroidism. It is not uncommon to see patients who have been given thyroid substance because of hypometabolism. When the patient does not respond to 2 or 3 gr. thyroid substance a day, the dose is increased until he is taking 8-10 gr. daily.

(2) J. Clin. Endocrinol. 12:208-227, February,, 1952.

If, at this point, the thyroid medication is suddenly withdrawn, a transient period of hypothyroidism, often of myxedema, will ensue. But, if the dose is gradually tapered off by 2 gr. every three weeks, the patient will remain in a euthyroid state while being weaned away from the unneeded medication.—Ed.]

Radioiodine Tests of Thyroid Function in Man are discussed by N. B. Myant[3] (Univ. College Hosp. Med. School). Thyroid disease can generally be diagnosed from the history and physical signs. In thyrotoxicosis, special tests are sometimes needed because symptoms are mild or because there are inconsistencies in the clinical picture. In most doubtful cases, diagnosis can be settled by a radioiodine test. Essentially, all radioiodine tests measure either the rate of removal of iodide by the thyroid from the plasma or the rate of synthesis and secretion of thyroxine.

Radioiodide uptake by the thyroid may be measured directly with a counter placed close to the neck. In thyrotoxicosis, the thyroid takes up more than 40% of a tracer dose by 48 hours, but thyrotoxicosis cannot be excluded if uptake is less than 40%, and some normals may take up over 40%. Radioiodine uptake, expressed in a parameter of the uptake curve, such as the half-period of the rise toward the maximal value, and measurement of the "accumulation gradient," have not proved sensitive indexes. Measure of uptake rate of a tracer dose in relation to plasma concentration (thyroid clearance rate) which in normals averages 20 ml./minute, is relatively accurate. It is not, however, routinely suitable because it requires frequent calibrated estimates of the radioiodine content of the thyroid. It may be simplified by using, as a measure of plasma radioactivity, the external counting rate over a mass of tissue, such as the thigh, which does not concentrate radioiodine. Such "thigh-neck" clearance values correlate satisfactorily and, because of the small dose of radioiodine required, have been useful in study of normal day-to-day variations in thyroid function. Based on increased ability of the thyroid to concentrate iodide in thyrotoxicosis, a test has been described in which an antithyroid drug is given before the test dose of radioiodine. In normals, very little radioiodine accumulates after an antithyroid compound; if the gland is hyperplastic, much of the dose is taken up and retained as iodide. The radioiodide in the thyroid is rapidly

(3) Brit. Med. Bull. 8:141-147, 1952.

discharged when potassium thiocyanate is given orally and its measure is claimed to permit a better distinction between normal and thyrotoxic patients.

Radioiodine uptake may also be estimated indirectly by measuring the proportion of the tracer dose excreted in the urine during the initial phase of distribution. The estimate depends on the assumption that the proportion excreted in the urine is inversely related to the proportion taken up by the gland. Few normals excrete less than 40% of the dose in 24 hours, but the overlap between values found in normals and in thyrotoxicosis patients differs widely. Clinical groups are better separated if the urine is collected over selected intervals after the dose. If rates of increase in the thyroid, of excretion in the urine, and of plasma concentration of radioiodide are all assumed to decrease exponentially with the same rate constant, this "disappearance rate," determined from urinary excretion curves, is a more sensitive index of the iodine-concentrating capacity of the thyroid than is the proportion excreted.

Excessive secretion of thyroxine is the essential disturbance in thyrotoxicosis. Uptake tests reflect the mean rate of thyroxine secretion only if, as is generally true, the uptake of radioiodide bears a constant relation to the output of hormone. However, if the uptake of iodide fluctuates rapidly, if iodine is released from the thyroid in a form other than thyroxine, and if normal thyroxine output is maintained by increased plasma iodide clearance rate when there is a low concentration of natural plasma iodide, diagnosis of doubtful cases may be confused. Attempts to measure the rate of secretion of thyroid hormone by measuring the output of radioiodine from the thyroid do not distinguish the different forms in which iodine leaves the gland and fail under the same conditions in which uptake tests fail. After the rapid fall in plasma radioiodine, there is a secondary rise due to incorporation of radioiodine in the thyroxine (protein-bound) fraction of plasma iodine (PBI). The secondary rise, which begins after 24 hours or more in normals, is seen earlier and reaches a higher maximal level in thyrotoxicosis. Measure of the proportion of total plasma radioiodine in the organic fraction at 24 hours usually also permits distinction of the thyrotoxic from the normal.

A single test of radioiodine uptake is often sufficient, but it is better also to measure PBI. With this combination, diagnosis is accurate over 95% of the time. If the diagnosis is still in doubt, different types of radioiodine tests may be used; it is usually enough, however, to follow the patient's progress or watch the response to treatment. Although radioiodine tests greatly help in diagnosing thyrotoxicosis, they are less useful in detecting minor hypoactivity of the thyroid. In hypothyroidism, the 24 hour urinary excretion of the dose is often within normal range; direct measure of thyroid uptake at 24 hours may give better clinical separation.

Probably no radioiodine test can be devised to give a clear diagnosis every time because the gradation between normal and abnormal thyroid function is continuous, because the "normal" level of functional activity varies individually and because radioiodine tests fail to measure the absolute rate of iodine metabolism.

Effect of 3,5,3′-l-Triiodothyronine and Certain Antithyroxin Substances on Oxygen Consumption of Mice. N. F. Maclagan, W. E. Sprott and J. H. Wilkinson[4] (Westminster Med. School) studied oxygen consumption in six groups of eight mice. Two groups were treated with subcutaneous injection of sodium l-thyroxin (1 mg./kg.) and two with an approximately equimolar dose of triiodothyronine (0.84 mg./kg.); two groups served as controls. Triiodothyronine produced a somewhat greater increase of oxygen consumption than thyroxin. The latent period was about the same as that for thyroxin, and the duration of the effect was similar.

Further experiments were performed to determine whether the antithyroxin drug, n-butyl 3,5-diiodo-4-hydroxybenzoate (B.D.H.B.) and the analogous n-butyl 3-iodo-4-hydroxybenzoate (B.I.H.B.) were capable of inhibiting the action of triiodothyronine. Contrary to expectation, in short term experiments B.D.H.B. potentiated the action of triiodothyronine. The combination increased the amount of oxygen consumed and in longer term experiments B.I.H.B., added to triiodothyronine, produced a similar increase. In the latter experiments this increase was all the more striking because of the considerable depression of metabolism produced by either substance given alone. The results with triiodothyronine contrast with

(4) Lancet 2:915-916, Nov. 8, 1952.

the profound decrease produced by B.D.H.B. in the metabolism of mice treated with thyroxin, which has previously been reported.

Since B.D.H.B. and B.I.H.B. depress the metabolism of normal animals despite their inability to antagonize triiodothyronine, the main circulating thyroid secretion seems more likely to be thyroxin than triiodothyronine. The findings are nevertheless consistent with the suggestion that thyroxin may require conversion to triiodothyronine in the tissues before becoming physiologically active. In this event these inhibitory compounds might owe their activity to interference with this preliminary deiodination, the inhibitor exercising some form of competition with thyroxin in the enzyme systems concerned. The synergistic effect of the "inhibitor" with triiodothyronine could be explained on a similar basis, if it is assumed that the normal mode of destruction of triiodothyronine involves further dehalogenation, which is again restrained by B.D.H.B.

[The evidence is steadily pointing to the conclusion that the circulating thyroid hormone is probably thyroxin bound to a protein. In what form the hormone acts within the cell is not known. Earlier experiments have shown that thyroxin alone does not act in vitro, but that it becomes activated on incubation with tissues. Whether it becomes bound to protein or changed to the more active triiodothyronine during incubation will have to be established before the action of the active principle can be studied. The mechanism of action of thyroid hormone is not yet known; but then, I do not think the mode of action of any pharmaceutical agent has been established, with the possible exception of the saline cathartics. This problem should be a fertile field for future investigation.—Ed.]

Human Thyroglobulin Labeled with Radioactive Iodine, in Normal State and in Basedow's Disease. Jean Roche, Odette Michel, Guy-H. Deltour and Raymond Michel[5] report on results obtained with I^{131} in the study of human thyroglobulin. Earlier studies have been subject to error because thyroglobulin solubility differs from species to species, and the purity of preparations was not constant. Use of thyroglobulin labeled with I^{131} eliminates these errors and allows analysis of human glandular extracts and their iodized protein constituent. Material for the study was taken from the thyroid glands of one normal person, aged 19, after accidental death and from seven patients with exophthalmic goiter after partial thyroidectomy.

Analysis of the results shows that human thyroglobulin is closely akin to that of other mammals. Its solubility is mediums of increasing ammonium sulfate concentration is some-

(5) Ann. endocrinol. 13:1-8, 1952.

what higher than that of the beef and pig proteins and its content of certain amino acids is similar. By means of several successive precipitations with 40-45% ammonium sulfate saturations at pH 6.5 and at 23 C., it can be obtained in a pure state. No difference could be found between the thyroid protein of the normal specimen and that of exophthalmic goiter. Previous studies showed that the thyroid stimulated to hyperactivity by prolonged thyrotrophin therapy secretes thyroglobulin identical with that secreted by untreated glands. The result is apparently the same whether the testing is experimental or pathologic. Thyroglobulin formation thus includes processes of protein genesis and iodization which are entirely distinct from one another; neither seems qualitatively modified in exophthalmic goiter. Like the hyperactivity induced by thyrotrophin, the pathologic hyperactivity of the thyroid in this condition results in an excess of thyroglobulin with no alteration in the process by which it is produced.

Case of Struma Cibaria is reported by G. Fisher, D. Epstein and K. E. Paschkis[6] (Jefferson Med. College).

Negress, 56, complained of swelling in the neck of five years' duration and mild somnolence and forgetfulness. She was essentially normal on physical examination except for obesity (242 lb.) and diffuse, soft enlargement of the thyroid gland (two to three times normal size) with a firm nodule near the left lower pole. Minimal substernal extension, with tracheal displacement, was demonstrated by x-ray. The 24 hour radioiodine uptake by the thyroid was 8%. Because of a limited budget and an unlimited appetite for the preceding five years, the patient had eaten rutabaga often twice daily, ordinary turnips five times weekly, cabbage three times weekly and parsnips "frequently." A tentative diagnosis of struma cibaria was made, and she was told to avoid goitrogenic vegetables. After she had conscientiously adhered to dietary instructions for one month, the goiter had regressed almost completely, except for the nodule, which had diminished in size. The 24 hour I^{131} uptake was still low, although there were no signs of severe hypothyroidism. She continued to refrain from eating goitrogenic vegetables. There has been no recurrence of goiter, the nodule has remained unchanged, and subsequent determinations of the I^{131} uptake were 19% and 16%.

[The reader will doubtless enjoy rereading, as I have, the excellent paper of E. B. Astwood, A. Bissell and A. M. Hughes, entitled "Further Studies on Chemical Nature of Compounds Which Inhibit Function of Thyroid Gland" (Endocrinology, 37:456-481, 1945), and also the delightful review by the late William T. Salter, entitled *Chemical Developments in Thyroidology* (Springfield, Ill.: Charles C Thomas, Publisher, 1950). They pointed out that cabbage, turnip, rape, rutabaga and kale contain

(6) J. Clin. Endocrinol. 12:1100-1101, August, 1952.

goitrogenic substances similar in action and potency to propylthiouracil. Some of us are pleased to have a good excuse for not eating these vegetables.—Ed.]

Observations Concerning Metabolism of Cholesterol in Hypo- and Hyperthyroid Rat. In a study of the inverse relation of plasma cholesterol concentration and level of thyroid activity, Ray H. Rosenman, Meyer Friedman and Sanford O. Byers[7] (Mount Zion Hosp., San Francisco) used rats made hypothyroid with thiouracil or hyperthyroid with thyroid substance. Plasma concentration of cholesterol was significantly increased and biliary concentration and daily output considerably reduced in hypothyroid rats, in contrast to hyperthyroid rats, in which the converse was noted. After biliary obstruction, the hyperthyroid rat accumulated cholesterol in plasma much more rapidly than the euthyroid or hypothyroid rat. Intravenously administered rat plasma cholesterol disappeared from plasma of the hyperthyroid rat faster than in the euthyroid or hypothyroid rat. It is concluded that manufacture and discharge of cholesterol by the liver is significantly increased in the hyperthyroid rat and the converse is true in the hypothyroid rat.

Changes in Excretion of Intestinal Cholesterol and Sterol Digitonides in Hyper- and Hypothyroidism. Meyer Friedman, Sanford O. Byers and Ray H. Rosenman[8] (Mount Zion Hosp., San Francisco) demonstrated that plasma cholesterol is synthesized in the liver at a rate measurable by estimating the daily biliary cholesterol and then discovered that the excretion was greatly increased in hyperthyroid and decreased in hypothyroid rats. If biliary obstruction is produced, the plasma cholesterol content rises far more rapidly in the hyperthyroid rat. Since plasma cholesterol level is normal or even low in hyperthyroid animals despite the increased rate of synthesis, there must be a matching increase in excretion or destruction. Using 29 male rats divided into hyperthyroid, hypothyroid and control groups, the authors measured the fecal output of cholesterol and noncholesterol sterols. Total sterol output in milligrams/72 hours was 44, 17 and 30 for the three groups, thereby clearly demonstrating the striking increase in sterol excretion in hyperthyroid rats and the converse in hypothyroid rats.

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(7) Circulation 5:589-593, April, 1952.
(8) Ibid., pp. 657-660, May, 1952.

[Estimations of serum cholesterol levels as a check on thyroid status are of greatest value in hypothyroidism, and particularly in frank myxedema. Apparently a high level must be associated with a reduced rate of removal of the substance, inasmuch as these studies show that the rate of synthesis is decreased. It would be interesting to know the rate of cholesterol synthesis to hypopituitarism, for occasionally one sees a hypopituitary patient who appears to have myxedema but whose cholesterol level is either normal or low, thereby excluding primary thyroidal deficiency.—Ed.]

Menstrual Pattern in Thyroid Disease. Richard E. Goldsmith, Somers H. Sturgis, Jacob Lerman and John B. Stanbury[9] studied 28 supposedly premenopausal women attending the thyroid clinic of Massachusetts General Hospital over 12 months. Pretreatment studies indicated that only 1 of 18 with thyrotoxicosis had normal menses; the others had either oligomenorrhea or amenorrhea. Two of these were found to be flowing from a proliferative endometrium. The three with amenorrhea had evidence of ovulatory failure, as indicated by endometrial biopsy and absence of pregnanediol in the urine, and hypoestrinism; one of these was subsequently found to be menopausal. The other 13 showed evidence that, despite a scanty or irregular flow, ovulation was occurring, and therefore there was no major interference with the pituitary-ovarian axis. Follow-up on 16 patients showed that all resumed a normal menstrual pattern after appropriate therapy for the thyrotoxicosis.

Eight of 10 women with primary myxedema had menstrual abnormalities; 7 showed no evidence of ovulation and 1 demonstrated inadequate corpus luteum effect. Menstrual disturbances included amenorrhea in one, clinical metropathia haemorrhagica in five and menorrhagia in two. The other two had normal ovulation and normal menses. All patients resumed a normal menstrual pattern after receiving desiccated thyroid. The abnormalities were considered the result of inadequate production of luteinizing hormone or effectiveness. Preliminary data suggest that these patients will respond to injected chorionic gonadotrophin, with formation of progesterone and a secretory endometrium. This would place the defect in the myxedematous patient in the LH-producing cells of the anterior pituitary and suggests that thyroid hormone is a necessary adjuvant in the proper functioning of these cells.

[This careful and valuable study confirms the old clinical observation that hypothyroidism is characterized by menorrhagia, whereas hyper-

(9) J. Clin. Endocrinol. 12:846-855, July, 1952.

thyroidism is characterized by amenorrhea or hypomenorrhea. Empirically, certain of the menorrhagias, particularly in young women, respond to the administration of thyroid substance, even when the most careful clinical and laboratory examinations fail to disclose any evidence of hypothyroidism. I do not know whether this is a form of hypothyroidism in which only one organ system is involved or whether some other action of thyroid substance is responsible for this effect. In any event, results of this type of therapy are highly gratifying.—Ed.]

Hypothyroidism

Hypothyroidism: Geriatric Problem. Hypothyroidism is often difficult to diagnose in the aged because the manifestations of hypothyroidism are considered a part of ordinary senescence and because laboratory data are not entirely reliable, according to Seruch T. Kimble and Edward J. Stieglitz[1] (Bethesda, Md.). Proof of diagnosis may have to rest on the relief of the patient's symptoms and disappearance of physical signs following replacement therapy. The diagnosis is so often overlooked that a BMR should be included in all health inventories in persons over 40.

In 134 of 360 consecutive, unselected patients, a BMR was determined because of a history suggestive of hypothyroidism. Rates below —15% were obtained in 110, of whom 82 were past 40. The authors report on this latter group.

The most frequent symptoms were fatigue, difficulty in "getting started" in the morning, sleepiness and indifference. Cold intolerance, weight gain with no diet increase, dry skin, muscular aches, cardiac palpitations and chronic constipation were also significant complaints. Physical examination provided no clue to the diagnosis in 31.7%. Among the others, dry, stiff hair was often noted and dry skin. The patients averaged 9 lb. overweight, but 40 were in the normal range and 5 were considerably underweight. There was no correlation between weight deviation from normal and the BMR. The authors agree with Williams that hypothyroidism does not play an important role in obesity.

Work-up included BMR, urinalysis and complete hemogram. Routine cholesterol and protein-bound iodine determinations were not done. Only 12 patients had a hemoglobin value below 75% and only 4 had an electrocardiogram suggesting the diagnosis.

Treatment was begun with 1 gr. of USP desiccated thyroid,

(1) Geriatrics 7:20-31, Jan.-Feb., 1952.

and at four to six week intervals each subject was re-examined and the BMR again determined. Dosage was altered until signs and symptoms were eliminated and the metabolic rate reached normal. This took one to six months. Treatment was never given for a low BMR alone. Physical evidence of the disease or electrocardiographic abnormalities were a prerequisite to therapy. An increase in maintenance dosage was required in 16 under prolonged treatment. This was attributed to increased fibrosis of the thyroid gland.

The authors regard atrophy of the thyroid as one aspect of general glandular deterioration with age, which in turn promotes degeneration of various target organs such as the skin, muscle and cardiovascular system and which can be arrested or reversed by adequate amounts of thyroid extract. Overmedication was avoided by starting with a small initial dosage (usually 1 gr.) and increasing in a stepwise fashion. Transient nervousness occurred in 10% of the patients treated.

[It is difficult to determine whether some of the symptoms and signs of hypothyroidism found in elderly persons are due to a physiologic slowing down or to true hypothyroidism. If the former were the case, thyroid substitution therapy would seem irrational and contraindicated; whereas, if the latter, replacement therapy would be definitely indicated. It seems to me that the deciding factor should be the reaction of the patient. If he is freed of annoying symptoms and is able to live a happier, more fruitful life when taking thyroid substance, this type of therapy is justified. Naturally, as the authors stress, the therapeutic success will depend on accurate dosage, use of a small initial dose and careful avoidance of overmedication.—Ed.]

Thyroid Function in Nephrosis. The recent demonstration that the concentration of protein-bound iodine (PBI) in the serum is reduced in nephrosis led Lillian Recant and Douglas S. Riggs[2] (Boston) to study thyroid function in this syndrome. As expected, the serum cholesterol level was high and the BMR often subnormal, even when calculated on the basis of edema-free weight. The concentration of serum PBI in 16 patients was subnormal: below 3 μg./100 cc. in 13, borderline in 2 and normal (3.5-7 μg.) in only 1 (mean 2.2 μg.). Avidity of the thyroid gland for radioactive iodine as measured by rate of uptake or fraction retained was normal or above normal. Since the capacity to accumulate iodide is dependent on a normal supply of thyrotrophic hormone, pituitary deficiency seems unlikely.

The time required for serum PBI to return to initial levels

(2) J. Clin. Invest. 31:789-797, August, 1952.

after the rise induced by intravenous d,l-thyroxin was studied in two nephrotic patients, two patients with untreated myxedema and one normal subject. There was a relatively rapid initial decrease in concentration during the first 12 hours, probably due to the distribution of thyroxin from the blood stream to the tissues. The subsequent slow decline of concentration was presumably dependent on the rate of utilization and excretion of thyroxin after distribution equilibrium had been attained. This second rate of decline was no more rapid in the nephrotic patients than in the normal subject. The time needed for PBI concentration to decrease 50% was about 4.3 days both for the normal subject and for the nephrotic patients, and 8.3 days for the patients with untreated hypothyroidism. In the two nephrotic patients and the one normal subject given thyroxin, the avidity of the thyroid gland for iodine decreased greatly after administration of thyroxin. In two other nephrotic patients, thyrotrophic hormone caused a rise in both serum and urine PBI. Finally, no thyroid enlargement was noted in any of the nephrotic patients.

These results indicate that thyroid function in nephrosis is essentially normal and that neither anterior pituitary failure nor inability of the thyroid gland to manufacture thyroid hormone in adequate amounts accounts for the low serum PBI. The PBI lost in urine usually represented but a small portion of the estimated normal daily secretion of thyroid hormone. Furthermore, although PBI in urine increased when serum PBI was raised by intravenous administration of thyroxin, urinary loss during the first two days amounted to only about 6% of the administered dose, and rate of decrease of serum PBI after thyroxin was no greater than in a normal subject. It seems improbable that urinary loss of hormone can by itself account for the subnormal concentration of PBI in the serum. The authors suggest that in nephrosis the decreased concentration of protein in the plasma accounts for the low serum PBI and permits the transport and delivery of a normal supply of thyroid hormone to the tissues with a decreased concentration of hormone in the blood stream. In certain patients with nephrosis the thyroid gland may actually become somewhat hyperactive in order to compensate for the continuous loss of hormone in the urine. The subnormal BMR cannot be ascribed to hypothyroidism but must be due to

some other factor, perhaps the pronounced protein deficiency which occurs in nephrosis.

[Clinically, patients with nephrosis appear very like those with myxedema. Not only the puffy, pasty face with swelling and dry skin but also the coarseness of hair, lethargy, bradycardia, constipation and arthralgias are similar in the two disorders. The BMR is usually low in nephrosis, often minus 35-50%, just as in myxedema. Lipemia and hypercholesteremia are likewise found in both. It is therefore not surprising that the effect of thyroid substance in nephrosis has been the subject of study for years. Previous reports have shown that some patients with nephrosis can tolerate remarkably large quantities of thyroid substance, with very little effect on their disease or on BMR. In an occasional patient, diuresis promptly follows administration of thyroid substance.

This report destroys an attractive hypothesis that the myxedema-like features of nephrosis are the result of loss of protein-bound thyroid hormone through the urine as part of the "diabetes albuminuricus."—Ed.]

Value of Measurements of Thyroid Uptake and Urinary Excretion of I^{131} in Assessing Thyroid Function of Normal and Congenitally Hypothyroid Children. William A. Reilly

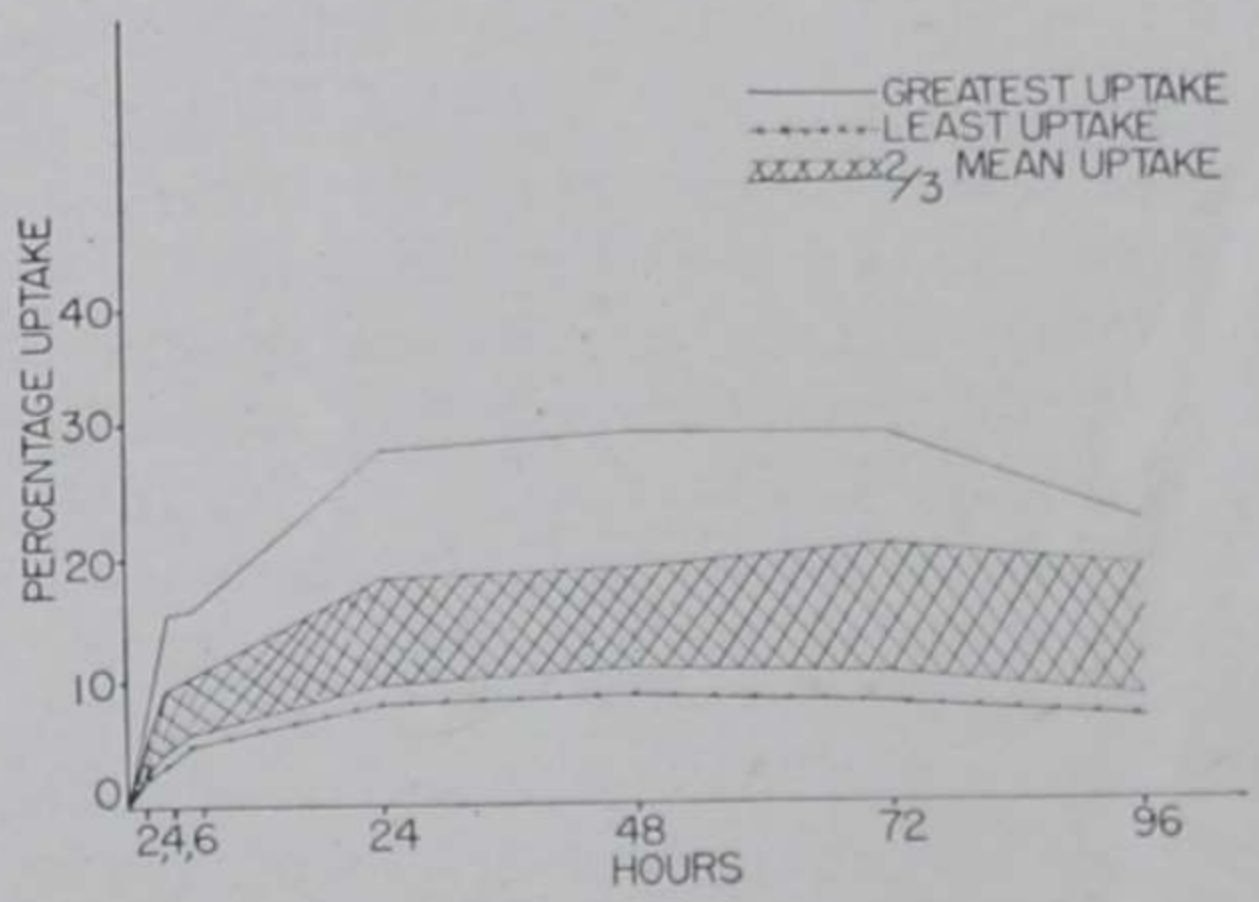

Fig. 10.—Thyroid uptake of I^{131} in 25 euthyroid children aged 9 months to 15 years. (Courtesy of Reilly, W. A., and Bayer, D. I.: J. Pediat. 40:714-721, June, 1952.)

and Dina I. Bayer[3] (Univ. of Arkansas) measured iodine uptake in the thyroid gland and its excretion in the urine in 25 normal and 5 congenitally hypothyroid children. I^{131} was given in smaller than usual amounts to avoid serious irradiation of the thyroid gland and in doses of iodine below the usual daily human requirement. Oral test doses of 5-10 μc. I^{131} were combined with 1-2 μg. inorganic carrier iodine. It may not be possible otherwise to quantitate accurately carrier-free I^{131} because it adheres to glassware, tubing, mucosae, etc.

(3) J. Pediat. 40:714-721, June, 1952.

Counting was performed with a Geiger-Müller tube, aluminum shielded to exclude all beta particles. Measurements were taken over the thyroid gland and over an equal area of the thigh and the thigh counts subtracted, as background, from the thyroid counts. The hypothyroid children were tested when

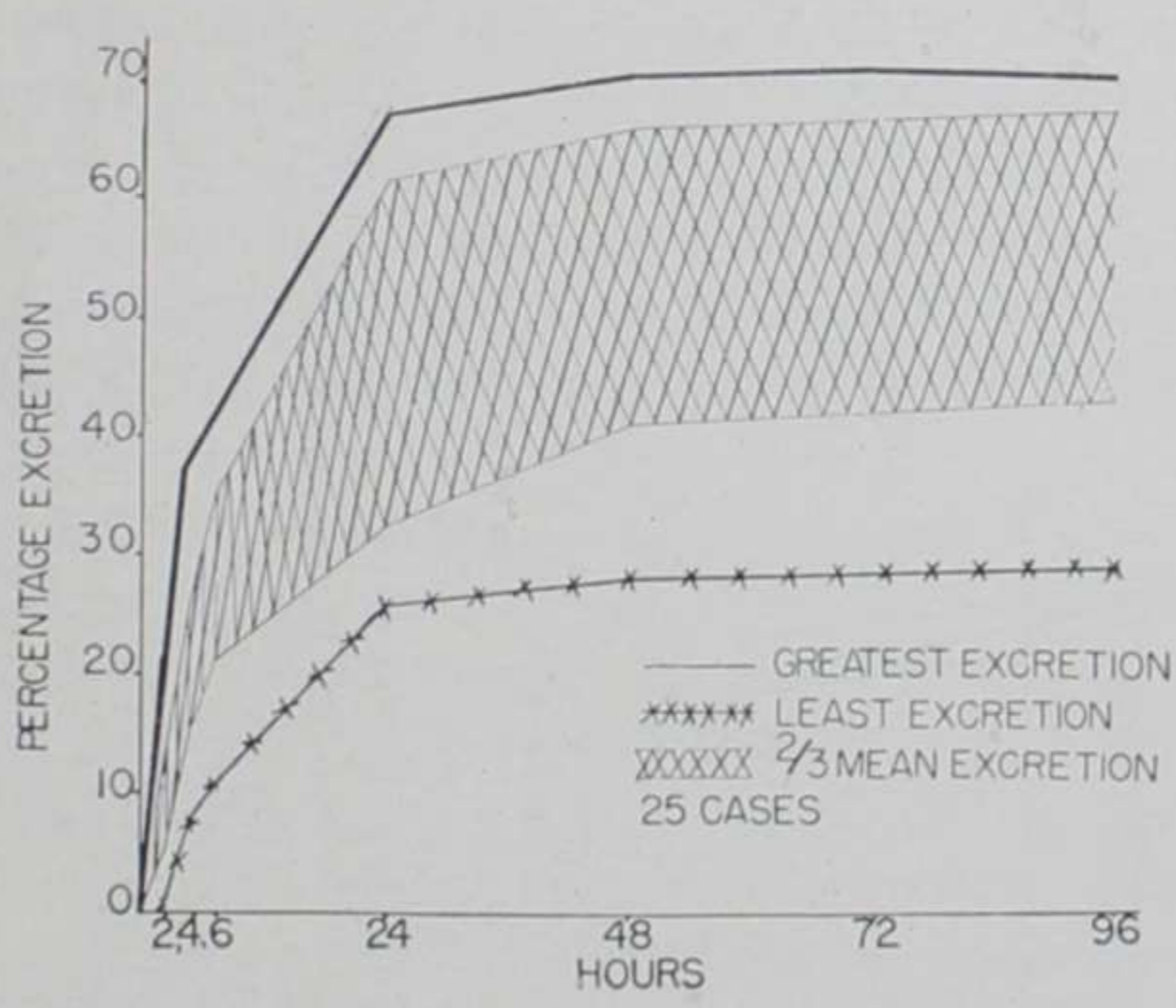

Fig. 11.—Urinary excretion of I^{131} in the 25 euthyroid children. (Courtesy of Reilly, W. A., and Bayer, D. I.: J. Pediat. 40:714-721, June, 1952.)

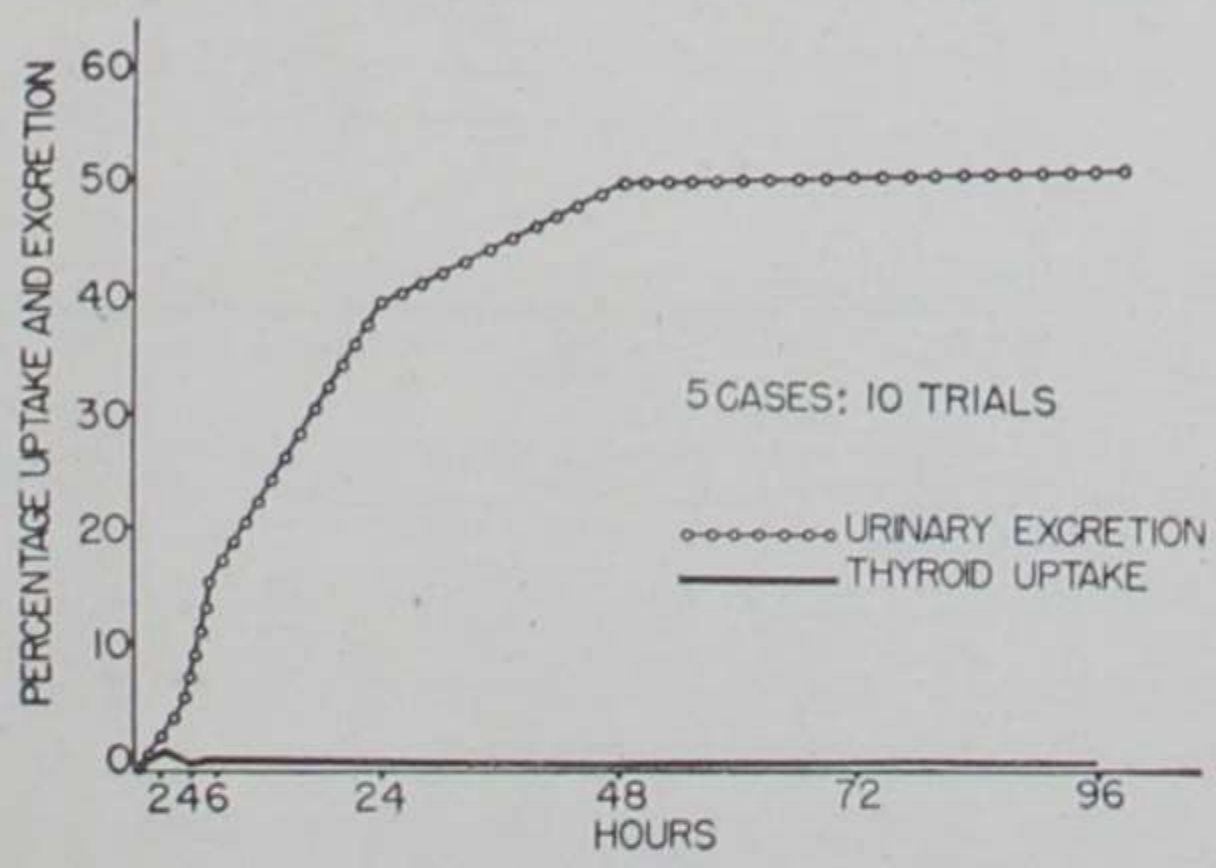

Fig. 12.—Thyroid uptake and urinary excretion of I^{131} in cretins receiving thyroid medication. (Courtesy of Reilly, W. A., and Bayer, D. I.: J. Pediat. 40:714-721, June, 1952.)

taking 65 mg. thyroid substance daily and again four to six weeks after this medication was discontinued.

Figure 10 is a composite of uptake results in the normal children. Uptake ranged from 8.7 to 29.8% and was not influenced by age, sex, color or season. Urinary excretion ranged from 29.3 to 70.6%, with an average total of 54.7%

(Fig. 11). Excretion was negligible after 48 hours. In striking contrast, the cretins showed an uptake of only 1-2% whether on or off thyroid medication (Figs. 12 and 13). Urinary excretion without thyroid medication averaged 29% in the first 6 hours, 30% more in the next 18 hours and 79.5% for the 96 hour period. While on thyroid therapy the 6 hour excretion was 18.6%, the 6-24 hour excretion was 23.7% and the total for 96 hours was 55%. The addition of 25 μg. of carrier inorganic iodine to the tracer dose just before administration did not alter the uptake or excretion figures.

The low uptake in cretins is consistent with the absence of

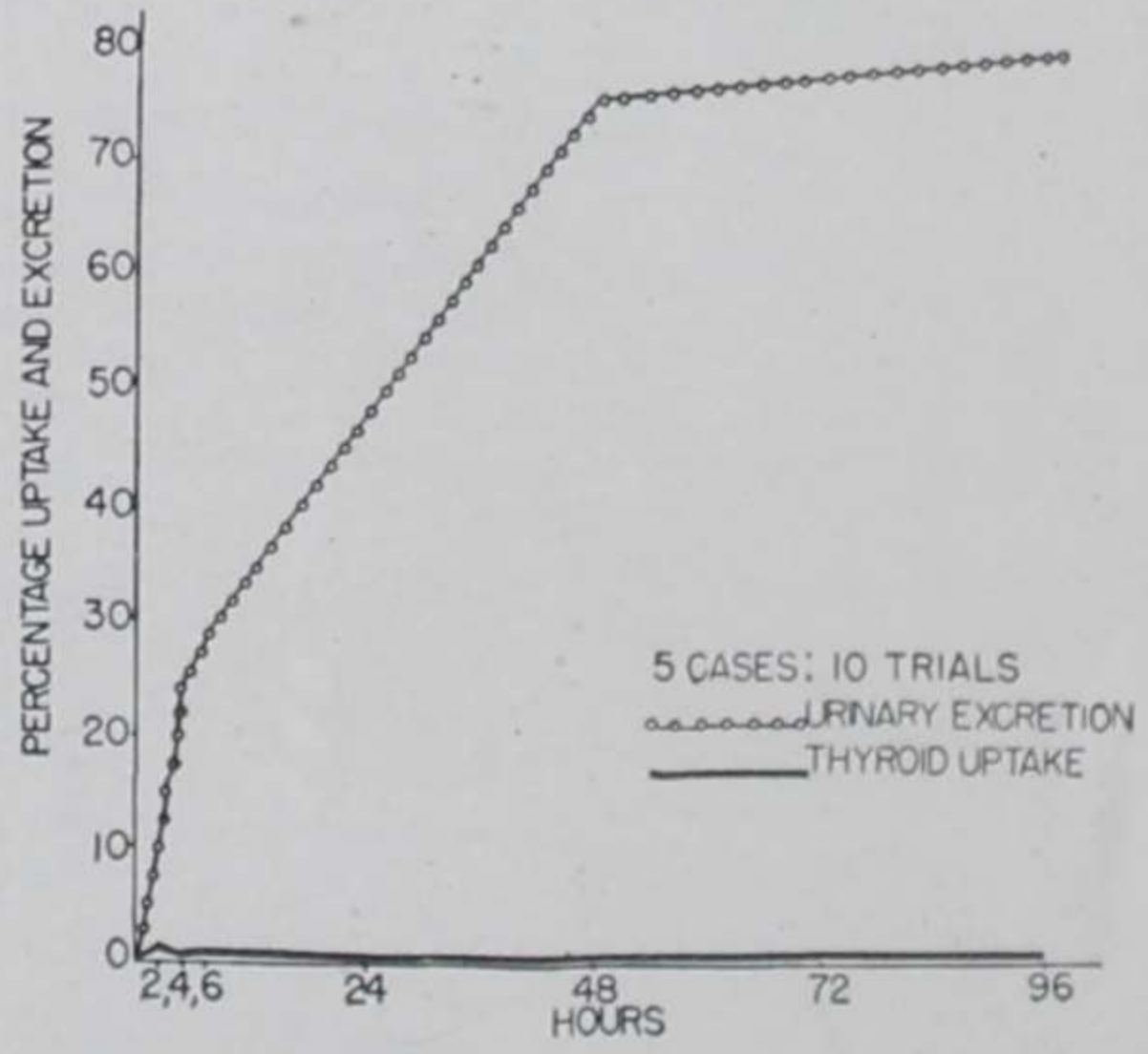

Fig. 13.—Thyroid uptake and urinary excretion of I^{131} in untreated cretins. (Courtesy of Reilly, W. A., and Bayer, D. I.: J. Pediat. 40:714-721, June, 1952.)

functioning thyroid tissue. Exploratory operation and biopsy on two patients did not reveal any thyroid gland. The lower urinary excretion during thyroid therapy may be due to an uptake of iodine by the thyroid extract proteins which may have been unsaturated with iodine, or it may represent extra-thyroidal trapping of iodine.

The uptake of I^{131} is believed to be a reliable diagnostic test of the presence of vestiges of thyroid gland.

Serial Observations of I^{131} Levels in Plasma as an Aid to Diagnosis of Hypothyroidism. Because it is difficult to separate borderline states of thyroid disease by simple I^{131} uptake and excretion studies, serial plasma levels were meas-

ured, to derive a radioactive iodine tolerance curve, by H. Rollman, D. W. Petit and Paul Starr[4] (Univ. of Southern California). Radioactive iodine, 100 μc., was given orally to 36 patients (13 hypothyroid, 11 hyperthyroid and 12 euthyroid). Radioactivity in 0.2 ml. samples of plasma was determined at frequent intervals for as long as 16 days. The curve of rising and falling radioactivity was compared with the standard 24 hour neck count and 24 and 48 hour urinary excretion. At least five factors affect plasma radioactivity: (1) absorption from the intestines, (2) urinary excretion, (3) thyroid trapping, (4) labeling of stable body iodine, and (5) release of labeled thyroid hormone into the blood stream.

The hyperthyroid patient shows a more rapid rise in the serum radioactivity, but the peak is not as high as in the euthyroid patient because more radioactivity is retained in the thyroid. In myxedema the slow absorption and excretion produces a delayed peak with a prolonged fall in plasma radioactivity. Euthyroid and hyperthyroid patients were not clearly separated by these serial plasma radioactivity measurements.

Mental Symptoms from Myxedema. Although most physicians know that dulness and poor memory may accompany myxedema, few realize the possibility of frank psychosis. Rutledge Miller[5] (Univ. of Michigan) reports on two such cases.

Case 1.—Woman, 26, entered a mental hospital with tentative diagnosis of manic-depressive psychosis. She showed no interest in surroundings, had guilt feelings about her poor housekeeping and about lack of sexual interest in her husband and had strong suspicions regarding her husband's fidelity. About five months earlier she had had radical thyroidectomy and neck dissection for thyroid carcinoma, followed by carefully managed calcium therapy but no other metabolic studies. Periodic calcium estimates had shown satisfactory levels.

Except for hypotension and pale, dry skin, results of physical examination were normal. The BMR was —39% and serum cholesterol level 395 mg./100 cc. She was started on 0.1 Gm. desiccated thyroid daily and parathyroid replacement therapy was continued. Initially she presented typical symptoms of depression. Her time was spent sitting in a chair, taking an interest in nothing and crying frequently. She refused occupational therapy and declined to help with housekeeping duties in her ward. The attitude began to change, however, after only 10 days of thyroid therapy. She became more alert and gradually began to take an interest in her surroundings

(4) J. Lab. & Clin. Med. 39:697-703, May, 1952.
(5) Ibid. 40:267-270, August, 1952.

and the proffered activities. One month later, she was mentally normal and showed an insight, not characteristic of depressed psychosis, into the past depression. Consensus was that mental disturbance was attributable solely to myxedema.

Case 2.—Man, 35, a promising business executive, in the months preceding entry into a mental hospital showed such deterioration of behavior, appearance and work efficiency that he was suspected of drinking to excess, using drugs or being mentally ill. Eventually acute depression was diagnosed and he was committed. Again myxedema was considered and confirmed by BMR of —41% and a serum cholesterol level of 405 mg./100 cc. Desiccated thyroid, 0.1 Gm. daily, was prescribed. Response was rapid, all symptoms disappearing in eight weeks. Serum cholesterol level and BMR both returned to normal after 20 weeks of therapy and he returned to his former position, doing excellent work while continuing thyroid therapy. He also had failed to show either typical myxedematous appearance or other physical signs; his general condition would have been considered normal.

[Reviews of this subject cannot appear too frequently. Myxedematous madness, as it was called by Asher (Brit. M. J. 2:555, 1949), is rarely recognized, yet it is curable in practically all cases by the administration of thyroid substance. Delay in institution of therapy may result in the development of irreversible changes in the brain, just as in prolonged hyperglycemia or hypocalcemia. The best description of this disorder that I have seen was written by a well known physician-author, A. J. Cronin, in *The Citadel*. The physician who enjoys fine writing will read this account with pleasure.—Ed].

Effect of Myxedema on Cardiovascular System was studied in five patients by Laurence B. Ellis, J. Gilmer Mebane, George Maresh, Herbert N. Hultgren and Richard A. Bloomfield[6] (Harvard Med. School), using cardiac catheterization to measure changes in circulatory physiology.

Case 1.—Woman, 21, was hospitalized with cough, dyspnea and ankle edema. She was obese, had pale, dry, coarse skin and enlarged tongue, the heart was enlarged and lungs had bilateral basal râles. Temperature was 100.8 F., blood pressure 100/70, venous pressure 140 mm. water. She had mild anemia, normal urine, nonprotein nitrogen 36 mg./100 ml., cholesterol 230 mg., BMR —30% and insulin tolerance normal. Edema, râles and fever cleared after bed rest, salt-free diet and penicillin. Circulatory studies showed that cardiac output was lower (2.5 L./minute) than that expected from decreased BMR. With exercise, cardiac output increased to 3.9 L./minute (a normal increase). Mean pulmonary artery, right auricular and peripheral venous pressures and circulatory times were normal. Two months after therapy with 0.1 Gm. thyroid substance daily, symptoms had entirely disappeared; BMR was —2 and —16% on two occasions. Heart size and circulation at rest and after exercise were normal.

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(6) Am. Heart J. 43:341-356, March. 1952.

Case 2.—Man, 63, after thyroidectomy for hyperthyroidism took thyroid for relief from cold intolerance, dry skin and mental retardation. These symptoms recurred four years later when he stopped taking thyroid because of exertional angina which in turn then disappeared. For five years before hospitalization he had increasing exertional dyspnea and angina. He had puffy face, dry skin, slightly enlarged heart with distant sounds. Blood pressure was 95/60. There were no signs of congestive failure. Laboratory tests showed slight anemia, normal urine, nonprotein nitrogen 35 mg./100 ml., fasting blood sugar 114 mg./100 ml., cholesterol 465 mg./100 ml., normal eosinopenia after ACTH and normal insulin tolerance. X-rays revealed congestive lung fields. Circulatory studies revealed prolonged circulation time (40 seconds) and cardiac output (2.7 L./minute) diminished beyond that expected from lowered BMR. Intracardiac pressures were normal. Exercise increased cardiac output but caused definitely increased mean pulmonary artery pressure and right ventricular diastolic pressure—findings similar to those seen in mild right and left heart failure. Thyroid therapy was started and gradually adjusted to avoid excessive angina. Three months after leaving the hospital he was taking 80 mg. daily, which partially relieved hypothyroid symptoms and, although angina persisted, it was much less than before treatment. Circulation time was 33 seconds, BMR —33%, and cholesterol 267 mg./100 ml.

Case 3.—Woman, 55, with known hypertension for four years, noted the onset of hoarse voice, cold intolerance, periorbital puffiness and a lump in the neck. She had dry skin, large tongue and enlarged nodular goiter. Heart was slightly enlarged. Blood pressure averaged 160/100; there was no venous distention and lungs were clear. Laboratory tests showed slight anemia and slightly elevated cholesterol level. Symptoms of hypothyroidism cleared with thyroid therapy but episodes of substernal distress appeared while she was taking 65 mg. thyroid daily.

Case 4.—Woman, 69, had gradual weight loss, abdominal distress with emesis, headaches, constipation, blood pressure 160/70, normal heart and clear lungs. Laboratory tests showed no excretion of follicle-stimulating hormone, serum cholesterol level 278 mg./100 ml. and decreased insulin tolerance. Symptoms improved with 30 mg. thyroid daily.

Case 5.—Woman, 50, with known myxedema that responded to thyroid; took medication irregularly and had taken none for a year before the study. The clinical picture was one of typical myxedema. Laboratory tests revealed slight anemia, serum cholesterol level of 199 mg./100 ml. and normal insulin tolerance.

The last three patients had the same cardiovascular dynamics: cardiac output was reduced in proportion to reduced BMR and normal intracardiac pressures. Patient 3 was studied again after taking thyroid for eight weeks. Heart size had decreased and cardiac output had increased from 3.8 to 4.4 L./minute.

One of the two uniform findings in this series was a fall in cardiac output. In the last three patients, who had no evidence of congestive failure, this paralleled lowered BMR, and circulatory efficiency remained normal. The first two patients had a severe lowering of cardiac output which could be raised with exercise. Patient 1 had symptoms of cardiac insufficiency with pulmonary congestion but normal pulmonary pressures. It is postulated that the râles and dyspnea could be due to pulmonary myxedema. In every instance but Case 3, increased peripheral resistance was found without accompanying hypertension. This finding in the face of decreased cardiac output can be explained only by reduced cross-section area of the vascular bed (which was reversible by therapy in patient 1). If this mechanism operated in excess to produce hypertension, it could explain the occasional hypertension in myxedema that is relieved by thyroid.

[It has been generally thought that myxedema predisposes to coronary atherosclerosis. Kecent studies by Blumgart and his collaborators (Tr. A. Am. Physicians 65:114-120, 1952) cast doubt on this relationship. Interestingly, Blumgart's conclusion is identical with that reached by the Clinical Society of London in a similar study made 65 years ago.—Ed.]

Secondary Eruptive Xanthomatosis Due to Myxedema: Genetic and Metabolic Study. The common association of hypercholesteremia with hypothyroidism and particularly myxedema would suggest that a secondary eruptive form of xanthomatosis should sometimes occur in either of these conditions. Actually, only three such reports have been published. Arthur C. Curtis and Hoyt C. Blaylock[7] (Univ. of Michigan) present another.

Man, 38, had for two months had asymptomatic eruption on the arms, legs and trunk; there were many grouped yellow-orange papules, 1-3 mm. in diameter, firm, nonpainful and not fixed to underlying tissue. He had noted fatigability, weight gain, increased sensitivity to cold, loss of hair and libido and dry skin for a year. He showed apathy, hoarseness, dry skin and puffy eyelids. Results of routine studies were not remarkable except for BMR of —32%. Total blood cholesterol value was 568 mg./100 cc.; free cholesterol, 177 mg.; total fatty acids, 732.7 mg. (normal 190-450 mg.); lipid phosphorus, 13.8 mg. (normal, 6-10 mg.) and lecithin 345 mg./100 cc. (normal, 150-230 mg.). Biopsy specimen of a lesion showed slightly atrophied epidermis with hyperkeratosis and severely edematous corium with histiocyte and foam cell infiltration and a few lymphocytes. The family pedigree for three generations proved there was no primary essential familial hypercholesteremia.

(7) A.M.A. Arch. Dermat. & Syph. 66:460-465, October, 1952.

He was given 2 gr. desiccated thyroid daily, which reduced the xanthomatous lesions in size and improved his general health; BMR rose after four months to —18%. Total blood cholesterol content decreased in the same period to 320 mg./100 cc. and free cholesterol to 103 mg./100 cc. After two years, the xanthomatous lesions, except for three or four yellowish papules over each elbow, had disappeared. Serum lipid values were still slightly above normal. Total serum cholesterol content was 393 mg./100 cc., free serum cholesterol 309 mg. and serum lecithin 32.4 mg. Clinical findings still revealed mild hypothyroidism and BMR —15%.

The hypothesis that myxedema with concurrent xanthomatosis is in reality xanthomatosis due to idiopathic hyperlipemia aggravated by myxedema could not be ruled out, but the authors do not believe that is the cause. Further studies pertaining to myxedema and associated xanthoma with particular reference to the neutral fats, phospholipid-cholesterol ratio and response to a low fat diet without thyroid medication would more definitely establish the classification of "myxedema and associated xanthoma" as a secondary eruptive xanthoma.

[The best proof that the xanthomas are caused by myxedema is the response to thyroid substitution therapy. In a patient reported by Craig *et al.* (J. Clin. Endocrinol. 4:12-16, January, 1944), photographs demonstrated clearly that the xanthomatous nodules disappeared after treatment. This was apparently the best result thus far reported, since the patient of Sweitzer and Winer (Arch Dermat. & Syph. 42:419, 1940) did not lose the cutaneous lesions, at least not at the time of the report. The patient of Christie *et al.* (Brit. J. Dermat. 42:429, 1930) was reported only as much improved after six months of treatment.—Ed.]

Pregnancy in Myxedema. Robert E. Hodges, Henry E. Hamilton and William C. Keettel[8] (State Univ. of Iowa) report on an unequivocally myxedematous woman whose symptoms were established and had persisted for 15 years, during which time she bore six children without ever having taken thyroid substance.

Pregnant woman, 25, born and raised in Michigan goiter belt, developed normally until 10, when she began to feel drowsiness and constant fatigue. Scholastic performance declined and she was forced to leave school. At about 16, a nontender goiter, which grew smaller after "a year or two," appeared and her voice had become deep and husky, skin dry and hair coarse; she did not tolerate cold weather. Menstruation began at 16, was scanty and recurred at fairly regular intervals of three months. This pattern of oligomenorrhea persisted until her last pregnancy. Since her marriage at 17, she had had great difficulty in performing routine household tasks and her memory was retarded.

(8) A.M.A. Arch. Int. Med. 90:863-868, November, 1952.

The thyroid gland was not enlarged, BMR was —12%, protein-bound iodine 2.8 μg./100 cc. and cholesterol content 500 mg./100 cc. She was given 60 mg. desiccated thyroid daily; 31 days later she delivered an apparently normal boy. By this time she had improved objectively and subjectively and started taking 180 mg. desiccated thyroid daily. On the sixth day post partum, studies in mother and infant showed respectively: plasma cholesterol, 320 and less than 50 mg./100 cc.; protein-bound iodine, 5.4 and 7.4 μg./100 cc. and I^{131} uptake after 24 hours, 1 and 15%. The boy weighed 2,830 Gm. at birth and seven weeks later he appeared normal except for small size and poor nutrition.

First pregnancy, seven years earlier, had resulted in delivery of a fetus of 1,020 Gm. which died on the first day; the second baby died of pneumonia at 7 months. Three other children were living: a boy, 5, was mentally dull; another boy, 3, was normal except for double canine tooth and undescended left testis and a girl, 16 months, was a mongolian idiot.

There was no evidence that the myxedema had any significant effect on the postnatal thyroid function of the children. Four living children were euthyroid, judging from clinical observation and laboratory studies, and none had goiters. Several congenital defects in three of the four living children suggest that myxedema provided inadequate environment for normal fetal growth and development. Malnutrition, retarded bone age, dental caries and microcephaly may, in part, be attributed to faulty nutrition, poor home environment and recurrent infections. There was no historic or clinical evidence that the thyroid tissue of the growing fetus supplied thyroid hormone in quantities sufficient to increase the metabolism of this myxedematous mother.

Oral Sodium L-Thyroxine in Treatment of Myxedema and Cretinism. The erratic effects of DL-thyroxine when administered orally, probably because of poor absorption, make it ineffective. Therefore William T. Salter and Ira Rosenblum[9] (Yale Univ.) studied the effects of sodium L-thyroxine both in children with spontaneous cretinism and in adults with complete athyreosis by following growth rate in children and concentration of serum "hormonal" iodine (SHI) in all patients; SHI was estimated after three to five weeks of therapy. Before each meal L-thyroxine tablets were given with a glass of water to adults and crushed in a teaspoonful of water to children; doses averaged 0.1 mg. for adults and 0.025 mg. for smaller children. Before each serum study, all medication was

(9) Am. J. M. Sc. 224:628-631, December, 1952.

interrupted for three days. Normal limits of SHI were arbitrarily set at 4-8 μg./100 cc. Progressive rise in SHI levels was noted on successive levels of dosage. In a woman, 51, whose thyroid was removed and metastases of thyroid carcinoma controlled with I^{131}, signs and symptoms of hypothyroidism subsided after 48 hours on 0.1 mg. sodium L-thyroxine daily; on 0.3 mg. a day SHI value was high normal and she felt well; after five days on 0.4 mg., she had paroxysmal tachycardia which subsided within a day after medication was interrupted.

Response of SHI to oral therapy was uniform. Comparing results with those for DL-thyroxine intravenously, about 67% of sodium L-thyroxine orally seems to be assimilated; this reflects not only absorption from the bowel but also fixation and excretion by the liver; recirculation similar to that of bile salts may take place. The enterohepatic circulation of hormone requires nearly three days after the last medication to insure elimination of recently absorbed iodine before SHI assay.

The synthetic preparation produces no effect not afforded by thyroid substance USP. Its advantage is its uniformity. Two preparations furnished by different pharmaceutical laboratories did not differ and each 0.1 mg. tablet appeared equivalent to nearly 1½ gr. thyroid substance USP.

[Although administration of the soluble sodium salt of thyroxin has no clinical advantage over use of the cheaper whole thyroid substance, this study has served to demonstrate the reasons for the poor results previously obtained with DL-thyroxin. The senior author, the late William T. Salter, was long a faithful and witty contributor to this field. A tribute to this physician, investigator and teacher, charmingly written by his associate, J. H. Means, appeared in the *Journal of Clinical Endocrinology* (12:1506-1508, November, 1952).—Ed.]

Hyperthyroidism

Graves' Disease: Hyperthyroidism or Hyperpituitarism? If hyperthyroidism is not mediated by the pituitary, certain consequences might be postulated to follow exogenous hormone therapy. Complete suppression of the release of endogenous thyrotrophin should result from an excess of endogenous thyroid hormone in the blood; since there is no circulating thyrotrophin, exogenous thyrotrophin should now evoke a thyroid response, whereas exogenous thyroid hormone should have little effect on an already inactive pituitary.

When euthyroidism has been produced by I^{131} therapy, these responses should be altered. Exogenous thyroid should be effective in suppressing the pituitary, which is again releasing thyrotrophin; response may, however, be somewhat less than in healthy subjects, since hyperfunction of the residual thyroid tissue probably persists. Similarly, the response to exogenous thyrotrophin by the hyperactive thyroid remnant should be less because of the reappearance of endogenous thyrotrophin with euthyroidism. The consequences postulated here are in sharp contrast to those that would occur if a hyperactive pituitary were responsible for hyperthyroidism, and thus there would be excess thyrotrophin in the hyperthyroid state.

To test these theories, Sidney C. Werner, Howard Hamilton and Martha Nemeth[1] (Columbia Univ.) gave thyrotrophin and thyroid substance to patients with active, otherwise untreated Graves' disease, and to others recently brought into a state of remission with I^{131}. In untreated patients, thyrotrophin increased the release of hormone from the thyroid as judged by an increase in serum precipitable iodine (SPI) level, whereas large doses of thyroid substance did not significantly depress the hyperthyroid gland as judged by the 24 hour uptake of radioiodine. In patients treated with I^{131}, thyrotrophin slightly increased SPI level and thyroid by mouth decreased the 24 hour uptake of I^{131}.

These data tend to indicate that hyperthyroidism arises from mechanisms not mediated through the anterior pituitary.

[I am not sure that the reported observations finally exclude the anterior lobe of the pituitary as the cause of Graves' disease. These studies were carried out in patients with hyperthyroidism, and if the homeostatic mechanism had been operating in these patients, the excess of thyroid hormone would have turned off the pituitary, thereby automatically curing the disease. Since this did not occur, I think it may be assumed that the homeostatic mechanism by which thyroid substance inhibits the production of thyrotrophin from the pituitary is lacking in patients with Graves' disease. It is true that if Graves' disease were due to an excess of thyrotrophin, the doses of thyrotrophin that were administered would probably not be expected to produce the increase of radioiodine uptake that they did. Such reasoning is, of course, based on the assumption that the Weber-Fechner law applies to thyrotrophin. I am not sure that this assumption has been tested.—Ed.]

Laboratory Diagnosis of Extrathyroidal Hypermetabolism. Charles V. Meckstroth, Richard L. Rapport, George M. Curtis and Sarah Jane Simcox[2] (Ohio State Univ.) report re-

(1) J. Clin. Endocrinol. 12:1561-1571, December, 1952.
(2) Ibid., pp. 1373-1379, October, 1952.

sults of laboratory studies on 49 patients referred to the clinic with an elevated BMR and in many instances an initial diagnosis of hyperthyroidism. Many of the patients had symptoms suggestive of toxicity, such as nervousness, weight loss, increased sweating, palpitation and easy fatigability. Some had diffuse enlargements of the thyroid and some nodular growths, whereas others showed no thyroid enlargement. All had hypermetabolism, as reflected by the elevated BMR, but this was shown to be due to extrathyroid disease rather than hyperthyroidism. Serum protein-bound iodine (PBI) levels were effective as aid in diagnosing euthyroidism in 95% of patients, radioactive iodine (RAI) uptake in 89%, serum cholesterol levels in 72% and somnolent metabolic rate (SMR) in 53%. Eleven patients had psychoneurosis, six leukemia, three diabetes and five cardiovascular disease.

Thyroid physiology is so intricate that no one test has yet been devised which will exactly evaluate the functional state of the gland. The various tests cannot be compared, since each measures a different aspect of thyroid metabolism. The RAI uptake, determined by a single 24 hour count, tells only how much I^{131} is in the gland at that time. It indicates neither the rate of uptake nor the rate of release. Serial counts are required for this additional information. The RAI is not elevated by the common functional thyroid disorders nor by organic nonthyroid diseases. Exogenous iodination obscures the results of tracer studies, and the source of iodination is often difficult to discover.

Most of the serum PBI is generally accepted to be calorigenic substance. This determination, therefore, theoretically gives the most direct measure of thyroxin formation. Although serum PBI is not affected by most diseases producing extrathyroid hypermetabolism, it is, like RAI uptake, notably affected by exogenous iodination.

The BMR measures total body metabolism, and no matter how basal the test may be, it cannot differentiate between possible etiologic factors in the hypermetabolism. Furthermore, serial BMR's must often be determined before a patient is sufficiently acclimated to assure a reliable tracing. The SMR is determined under an ideal basal state and is especially valuable in functional disorders. Moreover, in many patients with hyperthyroidism the disease is often complicated by varying

amounts of underlying nervousness, which adds to an already elevated BMR. The seemingly low value of 53% compatibility with the diagnosis in the case of the SMR is misleading as the confusing cases of extrathyroid hypermetabolism are not usually those of leukemia or diabetes but rather of psychoneuroses. The normal SMA has not been established, but the authors considered —7% the upper limit of normal. In the 11 psychoneurotic patients, the value was —6% or above on only three occasions (making a compatibility of 72%). The highest SMR was —1%. Moreover, the SMR will give a truer, more reproducible value than a BMR, which often fluctuates from day to day. Administration of iodine, thiouracil derivatives or therapeutic doses of I^{131} does not interfere with this test, which the author found to be the best single one for following all kinds of therapy for hyperthyroidism.

Analysis of Symptoms of Hyperthyroidism in Women Over 50. Classic signs and symptoms of hyperthyroidism are less pronounced in women over 50 than they are in younger patients. Certain atypical disturbances, however, are much more evident, according to a study of 35 patients over 50: 22 with toxic adenoma (Plummer type), 12 exophthalmic goiter and 1 hyperthyroidism without goiter. According to E. Trucco, M. Gambin, J. D. Cirio and E. B. del Castillo[3] (Buenos Aires), the entire group showed the three cardinal elements of hyperthyroidism: weight loss, increased BMR and cardiovascular disturbances. The weight loss and increased BMR were always moderate, whereas cardiovascular disturbances were constant and sometimes profound.

Auricular fibrillation and cardiac decompensation, whether caused by hyperthyroidism or by previous heart disease, and arterial hypertension, with or without arteriosclerosis, are especially important. They explain both the relative predominance of cardiovascular symptoms and why these patients are so often classed as heart patients only, while hyperthyroidism passes unnoticed. All complained of palpitation or dyspnea on exertion and nearly all had tachycardia, only three having pulse rates under 80. None had malignant exophthalmos and ocular symptoms were generally slight. Apart from the moderate character of the changes in weight and BMR in older patients, the most significant difference was that all had

(3) Medicina, Buenos Aires 5:271-283, 1952.

neuromuscular symptoms, consisting of asthenia and muscular atrophy with loss of muscular strength. Such symptoms are often attributed solely to age, and this is perhaps an important source of diagnostic error. Of the 35 patients studied, only 9 had correct diagnosis before hospitalization. The reason for the different reactions to hyperthyroidism in advancing age is not known.

[In a similar study, Bortin *et al.* (1951 YEAR BOOK p. 79) pointed out that elevated protein-bound iodine levels and estimation of radioiodine uptake aided them in the recognition of hyperthyroidism in patients who had been considered to have primary cardiac disease. If every patient with unexplained auricular fibrillation were considered a possible victim of hyperthyroidism and carefully examined for clinical and laboratory evidence of this disease, many elderly cardiac patients would be salvaged.—Ed.]

Apathetic Goiter. Mariano Augusto de Andrade, M. Barretto Netto and Leorys Maia Dallalana[4] (Rio de Janeiro) report apathetic hyperthyroidism in three patients. Despite severity of symptoms and debilitated condition of patients, all of whom were emaciated and dyspneic, subtotal thyroidectomy resulted in cure. Beginning insidiously, often with general symptoms dominating the clinical picture, apathetic hyperthyroidism is a severe form of atypical thyrotoxicosis often ending in death unless recognized and treated in time. It is characterized by pronounced emaciation, mental apathy and dyspnea. Heart rate may be rapid, but bradycardia is not uncommon (one patient's pulse rate was 56). There is no exophthalmos. The most common ocular sign is that of Jellinek. The liver is affected and there may be jaundice.

Basal metabolic rate is usually within normal limits or slightly elevated, only rarely rising to +30%. The goiter is usually small, hard and nodular, differing thereby from typical exophthalmic goiter, and rather suggests a gland in involution with little or no toxicity. Macroscopic study generally reveals many nodules—some compact, others vesicular—limited by fibrous tissue. Histologic examination in two cases revealed pronounced connective tissue proliferation and great structural diversity in the various nodules. Hyperplasia and adenomatous changes in addition to indications of glandular exhaustion were found in some.

The principal diagnostic difficulty is encountered in attempts to differentiate it from the attenuated forms of hyper-

(4) Arq. brasil. med. 42:235-250, July-Aug., 1952.

thyroidism: in both, laboratory tests suggest a discrete thyrotoxicosis and indicate the danger of surgical treatment. Abortive forms must also be distinguished. The apparently nonhyperplastic appearance of the goiter and the emaciation may confuse it with cachexia-producing diseases, as in one patient in whom malignant genital neoplasm was suspected; simple laparotomy would certainly have caused death, because of the gravity of the thyroid lesion, which had been overlooked. Therapeutic tests with iodine and goitrogenic drugs have only moderate value, because patients respond poorly and slowly to such measures. Crotti's "placid hyperthyroidism" in many ways resembles apathetic goiter but seems to belong among forms showing glandular exhaustion. In Jackson's iodine-resistant thyrotoxicosis, there is no weight loss nor tremor of extremities; the gland has large nodules, indicative of spontaneous involution, and iodine therapy is unsuccessful.

[The diagnosis of apathetic goiter is usually a very difficult one. In the few cases I have seen, the diagnosis was considered because of tachycardia. Laboratory tests and the response to appropriate therapy confirmed the diagnosis. I have not seen the type reported here, in which bradycardia was noted. In such a patient, the diagnosis would be well-nigh impossible.—Ed.]

Auricular Fibrillation in Thyrotoxicosis, with Special Regard to Indication for Quinidine Therapy. Of 279 patients, Anton Jervell[5] (Tönsberg, Norway) reports on 53 (19%) who also had auricular fibrillation with the thyrotoxicosis. In 12, fibrillation was transitory and attacks subsided when thyroid activity was medically or surgically controlled. In three patients fibrillation was associated with operation, even though the thyrotoxicosis had been well controlled; preoperative digitalization is therefore suggested. Among 41 patients, constant fibrillation was converted to normal sinus rhythm in 8 when the thyroid disease was controlled. Of the others with persistent arrhythmia, 14 were treated with quinidine; in 11 the result was successful and 2 others had a temporary conversion to normal sinus rhythm. The other patient died suddenly without demonstrable cause after the first dose of quinidine.

The author concludes that fibrillation which persists after thyrotoxicosis is controlled should be treated in patients under 60, who show no signs of myocardial damage. Such treatment

(5) Acta med. scandinav. (supp. 266) 142:585-593, 1952.

is contraindicated in patients over 70 and in younger patients who have considerable cardiac hypertrophy.

Hyperthyroidism and Pregnancy. Although hyperthyroidism is commoner in women than in men, it seldom is coupled with pregnancy. When, however, a hyperthyroid person becomes pregnant, complications often appear and the ensuing disorders may be serious for both mother and child, according to Guillermo Soberón A. and Rafael Rodríguez R.[6] (Mexico City). If, on the other hand, thyrotoxicosis is not well managed, hypothyroidism may result, again with possible complications for both. Toxemias of pregnancy have been seen in as many as 76.9% of patients with hyperthyroidism; intractable vomiting and nervous symptoms may also appear, and abortions, premature births and fetal anomalies often endanger the fetus. Complications resulting from badly managed hypothyroidism are especially common during the first months of gestation. Hypothyroidism gives rise to placental changes leading to toxemia. These changes can, however, be prevented by thyroid therapy. Studies on abortion have shown that low gonadotrophin levels accompany hypothyroidism.

Standards of treatment have changed. Therapeutic abortion, once favored, often precipitated hyperthyroid crises. Later, iodine therapy was recommended and operation was advised during the first half of pregnancy. Antithyroid drugs have marked a forward step, not only in preoperative medications but also in basic treatments. Cautious use will avoid hypothyroidism; with excessive dosage, the thioureas can pass through the placenta and also affect the fetus adversely. Thiouracil also passes the placental barrier and appears in high concentration in the maternal milk; therefore infants whose mothers have been treated with thiouracil and its derivatives have sometimes shown thyroid hyperplasia. Exophthalmos and growth retardation have also been noted.

Generally accepted treatment now includes: (1) high calorie diet, with a good supply of calcium; (2) estrogens and progesterone, as needed, chiefly for patients with previous abortions; (3) antithyroid drugs (BMR should not fall below +10%); (4) iodine, which drastically reduces congenital goiter and thyroid disturbances in the fetus; (5) subtotal thyroidectomy, permissible in the first two trimesters but not

(6) Rev. invest. clin. 4:19-29, January, 1952.

advisable thereafter; (6) anesthesia to prevent excitation during labor (oxygen should be given in the second stage), and (7) avoidance of lactation, because thiouracil and its derivatives are secreted in the milk.

[Opinion appears to differ somewhat as to the safety with which antithyroid drugs may be given during pregnancy. The authors' conclusion coincides with that of E. B. Astwood (J. Clin. Endocrinol. 11:1045-1056, October, 1951). The authors of this report advise against attempting to reduce the BMR too drastically. It should, of course, be borne in mind that the BMR is elevated in normal pregnancy, and most authorities believe that plus 20% is the lower limit to which it may be reduced safely.—Ed.]

Periodic Paralysis Associated with Exophthalmic Goiter. Howard D. Cogswell and Lindsay E. Beaton[7] (Tucson, Ariz.) report a case of periodic paralysis associated with thyrotoxicosis, which may be distinguished from the familial form of periodic paralysis since it can be cured by treating the thyrotoxicosis. Both forms are characterized by attacks of flaccid paralysis of the somatic musculature below the neck, with loss of deep tendon reflexes and absence of sensory or psychic disturbances. In the intervals between attacks the patient may experience weakness or stiffness in the muscles but otherwise apparently is in normal health. Muscles innervated by the cranial nerves are seldom affected, and sphincter control is preserved. Paralysis is prone to occur after prolonged rest, a high carbohydrate meal, exposure to cold or emotional upset.

Man, 36, in 1941 began to have attacks of paralysis of the legs lasting several hours. They became more severe in 1947 and were associated with weight loss, sweating, nervousness, itching, tremor and exophthalmos. The BMR was +94%. A thyroidectomy was performed after propylthiouracil treatment. With elimination of thyrotoxicosis the attacks of paralysis disappeared.

[Muscular atrophy may be very severe in hyperthyroidism, and muscular atony may be severe. Ordinarily, however, it is not periodic, as described in this interesting case.—Ed.]

Measurement of Iodide-Concentrating Power as Test of Thyroid Function. G. A. Newsholme[8] (United Birmingham Hosp.) gave 32 subjects (12 normal, 7 with definite and 13 with questionable thyrotoxicosis) 400 mg. methylthiouracil by mouth four hours or more after their last preceding meal and, an hour later, 35 μc. carrier-free radioiodine by mouth; 54 others (10 normal, 12 with definite and 32 with questionable thyrotoxicosis) were given 35 μc. radioiodine intraven-

(7) Arizona Med. 9:26-28, July, 1952.
(8) Lancet 2:805-808, Oct. 25, 1952.

ously with 10 mg. sodium iodide. After the tracer dose, counting rates over neck and thigh were followed until the highest count was reached and usually for longer.

In people given an oral dose of tracer the neck-thigh count ratio was measured after the highest thigh count had been reached since the thigh counts then reflected more faithfully the radioactivity of the plasma. In those given iodine intravenously the neck-thigh ratio was always measured after 30 minutes. The 12 normal people in the first group had a neck-thigh ratio of 0.78-1.88 (mean 1.13) and the 10 normals in the second group had ratios of 0.9-1.8; results from the two tests did not, therefore, significantly differ. In 19 clinically thyrotoxic patients the ratios were between 2.7 and 26.0, and in the other 45, with indefinite diagnosis, between 0.8 and 4.4. With one exception, all patients with neck-thigh ratios below 1.9 were classified euthyroid on other grounds; all those with ratios above 2.2 were similarly considered thyrotoxic. In eight persons, the ratios lay between 1.9 and 2.2; three of them were clinically considered euthyroid and five mildly thyrotoxic.

By either method the radioiodine was accumulated mainly as iodide and was not fixed by the gland. These two methods appear to give equivalent results, but the second is faster, with radioiodine concentration by the thyroid reaching its maximum within 20 minutes. The chief advantage of the tests is that results remain relatively unaffected by large increases in iodine intake. Moreover, most of the radioiodine taken up by the thyroid gland leaves it within 24 hours and thereby subjects it to less radiation than if protein-binding were allowed to take place.

Blood Levels after Tracer Doses of Radioactive Iodine in Diagnosis of Thyroid Disorders. Conversion of inorganic iodide into protein-bound iodine (PBI) is a good index of thyroid function but work has hitherto been handicapped by the low sensitivity of counting chambers. Solomon Silver, Mack H. Fieber and Stephen B. Yohalem[9] (Mount Sinai Hosp., New York City) therefore used the more sensitive Q-gas counter and measured the radioactivity of plasma and washed plasma protein after administration of I^{131}. In euthyroid patients radioactivity fell steadily because the I^{131} was being removed from the circulation by the thyroid gland and excreted by the

(9) Am. J. Med. 13:725-729, December, 1952.

kidneys. In hyperthyroid patients blood levels attained within the first eight hours were somewhat lower than in controls, probably because the hyperfunctioning thyroid gland extracts more I^{131} from the circulation. At about the eighth hour, the curve of radioactivity was reversed and began to ascend, reaching a plateau between the 48th and 96th hours. The curves separated so much that there was no overlap, and the lowest values for the hyperthyroids exceeded highest values for controls from the 48th to the 96th hour in 54 cases.

Single radioactivity counts were therefore made on the washed proteins derived from 1 ml. plasma drawn 72 hours after ingestion of 100 μc. carrier-free I^{131}. Of 187 euthyroid patients, all had a plasma protein radioactivity of 4 counts/second or less; of 123 hyperthyroid patients, all but 3 showed activity of 5 counts/second or more (4 counts/second corresponded to 0.0003 μc. I^{131}). Obviously if the plasma has less than 4 counts/second activity, the plasma proteins need not be checked.

The value of this and all other tests of thyroid function using I^{131} is destroyed if iodine-containing compounds or such antithyroid drugs as thiouracil have been administered. This method requires the use of a windowless counter or one of similar sensitivity but, if this is available, the technic is simple and specific. The results were better than with any other test for hyperthyroidism.

Present Status of Treatment of Toxic Goiter is reviewed by W. O. Thompson[1] (Univ. of Illinois). There are five available methods of treatment.

1. Subtotal thyroidectomy after adequate preoperative preparation is considered the best method in most centers. With propylthiouracil or other antithyroid drugs, the BMR can be lowered to normal range, making the operative risk no greater than with nontoxic goiter. The frequency of drug reactions has caused some to advocate the use of thiourea drugs only in severe thyrotoxicosis. Usually, propylthiouracil is given at home until BMR is normal. Frequent checks for drug reactions are made. Propylthiouracil is withdrawn about a week before surgery or may be continued until operation; in either case, iodine is started about one week before operation to reduce vascularity of the gland and is continued for at least

(1) J. Clin. Endocrinol. 12:130-134, January, 1952.

one week after operation to control any possible residual thyrotoxicosis. The operation is not performed unless the patient is in good health.

2. Medical management with antithyroid drugs has been disappointing because of the high incidence of relapses and drug reactions. Apparently, the usefulness of the method is limited to patients who are poor operative risks if radioactive iodine is not available.

3. Treatment with radioactive iodine is clinically as effective as surgery but as long term study, particularly as to possible cancer production, is lacking, the method has not been generally accepted as preferred. It is the choice, however, in any patient who is a great operative risk. Radioiodine is not advocated for nodular goiter with hyperthyroidism because the larger doses required increase the possibility of cancer production.

4. X-ray treatment of the thyroid is of historical interest and no longer justified.

5. X-ray treatment of the pituitary is effective only one third of the time; that it will produce remission is of interest only to those studying mechanisms of genesis of hyperthyroidism.

Sixteen Deaths in 826 Thyroid Operations are analyzed by Januario Estrada, Pedro T. Nery and Arturo K. Dimayuga[2] (Philippine Gen'l Hosp.) so as to uncover causes of death and thereby further reduce operative mortality. Of the dead, 14 had toxic goiter and were treated with Lugol's solution and/or propylthiouracil preoperatively.

Case 1.—Woman, 27, with diffuse toxic goiter had bilateral subtotal thyroidectomy after BMR had been reduced from 52 to 5%. Eight hours of postoperative bleeding necessitated reopening of the wound for ligation. Fever and pulse went up and she died three days postoperatively. Autopsy showed fatty degeneration of the liver, parenchymatous degeneration of the viscera and anemia. Death was ascribed to crisis precipitated by the ligation.

Case 2.—Woman with diffuse toxic goiter for six years had bilateral subtotal thyroidectomy. Many dental caries were found preoperatively. She died 12 hours postoperatively with hoarseness, stertorous breathing, pulse 130 and temperature 104 F. Death was ascribed to crisis precipitated by focal infection, too much surgery and faulty technic.

Case 3.—Patient, 25, with toxic goiter, scattered pulmonary râles and palpable spleen, after being afebrile for seven days, had bi-

(2) Philippine J. Surg. 6:218-220, Sept.-Oct., 1951.

lateral subtotal thyroidectomy. Hoarseness and tetany developed and death occurred 10 days postoperatively. Death was ascribed to pneumonia that had been overlooked.

Case 4.—Woman had had toxic goiter for five months and periodic fever. Bilateral ligation of the superior thyroid vessels was done only because of severe toxicity. She died shortly after operation in crisis, probably precipitated by infection.

Case 5.—Woman, 40, had had toxic adenoma for 11 years. She had enlarged heart, auricular fibrillation and recurrent edema of the extremities and BMR was reduced from 45 to 26%. After bilateral subtotal thyroidectomy, she had rapid pulse and fever and died. Autopsy revealed dilated left ventricle, bilateral basal atelectasis, pulmonary edema and congested liver with early cirrhosis.

Case 6.—Woman, 30, had diffuse toxic goiter; BMR after preparation was —22% and pulse was irregular, ranging from 80 to 120. She died the day after bilateral subtotal thyroidectomy with hyperpyrexia and rapid pulse.

Case 7.—Woman, 40, after diffuse goiter for one year, had a BMR of 48% and pulse between 60 and 80. She died after bilateral subtotal thyroidectomy followed by restlessness, dyspnea and oozing from the wound. Autopsy revealed hemorrhage in the superior anterior mediastinum with pressure on the trachea.

Case 8.—Patient, 37, with diffuse toxic goiter and rapid pulse (95-115) died two days after subtotal bilateral thyroidectomy in thyroid storm.

Case 9.—Girl, 20, with diffuse nontoxic goiter, had bilateral subtotal thyroidectomy and, the same day, gradually went into shock and died. Autopsy revealed enlarged thymus and hypertrophied lymph follicles. Death was due to status thymicolymphaticus.

Case 10.—Patient, 16, with nontoxic goiter, had bilateral subtotal thyroidectomy and died shortly thereafter. Autopsy revealed extensive hemorrhage into the anterior mediastinum.

It is concluded that each goiter patient must be considered individually and that sound surgical technic is prerequisite to successful outcome.

[The authors deserve congratulation for this frank presentation. In these days of potent antithyroid medication before operation, excellent surgical technic and skilfully administered anesthesia, a survey of the causes of death and the incidence of other postoperative complications of surgical treatment of hyperthyroidism is extremely valuable. Thyroid crisis, common a generation ago, is no longer seen; at least I have never seen it, though I have been called many times to examine patients who had fever and tachycardia following thyroidectomy. Invariably, the symptoms have turned out to be associated with atelectasis, pneumonia or, in one case, an acute episode of hemolytic anemia.—Ed.]

Post-Thyroidectomy Psychoses. David Dean Brockman and Roy M. Whitman[3] (Duke Hosp.) report five cases, with emphasis on the three possible mechanisms of genesis: (1) postoperative myxedema with complicating psychosis; (2)

(3) J. Nerv. & Ment. Dis. 116:340-345, October, 1952.

pre-existing psychosis, unrecognized until operations bring it out in unmistakable form, and (3) psychosis precipitated by operation in an already tottering personality.

Case 1.—Woman, 30, had a premorbid personality structure which included meticulous compulsiveness and overzealousness. She had had occasional anxiety attacks. Hyperthyroidism developed gradually, unassociated with psychic shock. An acute psychotic episode developed two months after thyroidectomy. Serum cholesterol level was 290 m.g/100 cc. and BMR values ranged from —11% to —14%. Sedative tubs, modified insulin and thyroid extract (60 mg./day gradually increased to 120 mg.) effected a lifting of the mood and then a diminution of the malignant content.

Case 2.—Woman, 28, had a cyclothymic premorbid personality. Evidence of an unresolved personality trait was present. Five weeks after thyroidectomy, depression, hallucinations and delusions supervened characteristic of schizophrenia. Electric shock produced only temporary improvement. Desiccated thyroid, 60 mg. three times daily, was less effective. Great improvement followed prefrontal leukotomy, although malignant content remained.

Case 3.—Woman, 33, had a notably cyclothymic premorbid personality. Because of thyrotoxicosis with exophthalmos, subtotal thyroidectomy was performed; 10 days later she became agitated, restless and irritable, with loose paranoid delusions and auditory hallucinations. The BMR was +7 and +27% on two occasions. A serum cholesterol level of 295 mg./100 cc., with questionably coarse hair and dry skin, was only dubiously suggestive of hypothyroidism. Electric shock resulted in only moderate improvement. Thyroid extract was not given.

Case 4.—Woman, 45, had had three thyroidectomies. Her premorbid personality was cyclothymic. Mental status examinations showed a mood-driven content disorder, characterized by auditory hallucinations, paranoid trends, blocking, psychomotor retardation, impulsiveness, negativism and depression. Electric shock produced great improvement. Thyroid medication given after discharge maintained adequate psychic adjustment.

Case 5.—Woman, 30, had a thyroidectomy for symptoms suggestive of a tension state. Four years after operation symptoms diagnosed as myxedema and psychosis developed. Two BMR's were —27 and —28%, and the serum cholesterol level was 420 mg./100 cc. After three months of thyroid extract, the BMR was —5%. A good adjustment was maintained on 2 gr. thyroid daily.

Careful psychiatric evaluation seems virtually mandatory before thyroidectomy, and post-thyroidectomy follow-up for long periods seems also essential.

Antithyroid Drugs

Use of Antithyroid Drugs in Hyperthyroidism is discussed by Thomas Hodge McGavack[4] (New York Med. College), who

(4) M. Clin. North America 36:603-621, May, 1952.

restricts the term antithyroid compound to describe the thiouracils and imidazoles which suppress thyroid function by depressing the oxidative enzyme systems through which inorganic iodide is bound to protein to form thyroid hormone. They do not, however, simultaneously suppress thyrotrophin function. Therefore, hypertrophy, hyperplasia and vascularity of the thyroid gland are increased and the storage of colloid is diminished. Unlike the antithyroid compounds, the effect of iodine differs considerably from subject to subject and in the same subject from time to time and its action is difficult to maintain. Therefore, judicious use is envisaged of first one

ANTITHYROID DRUGS IN HYPERTHYROIDISM

COMPOUND	RECOM. DAILY DOSE, MG.			TOXIC REACTION, %	UNIT DOSE, MG.
	0 to 7 Days	7 Days to Control	Maint.		
1-Methyl-2-mercaptoimidazole (tapazole)	20-30	15-20	2-15	1.0	5
2-Mercaptoimidazole	80	80	20-40	?*	5
6-Methyl-2-thiouracil	500	400	25-200	8.0	25
6-N-Propyl-2-thiouracil	500	400	25-150	4.5	25
5-Iodo-2-thiouracil (itrumil®)	500	400	50-200	5.2	25
2-Thiouracil	600	400	50-200	12.0	50

*2-Mercaptoimidazole has been used in so few patients that satisfactory evaluation of its toxicity is precluded.

and then the other of these classes of compounds, or their proper combination, so that assured effects of the antithyroid compound may be combined with the thyroid-normalizing action of iodine.

The author emphasizes that the application of antithyroid compounds should be individualized, but that patients can now be grouped by (1) conditions under which antithyroid compounds are definitely indicated, (2) those in which they may be used electively or (3) those in which preoperative use only is advised. Their use is indicated for all hyperthyroid patients preoperatively, for children and adolescents with a first attack of Graves' disease, for aged patients, for patients with thyrotoxicosis and cardiac failure, for postoperative recurrent hyperthyroidism and as a therapeutic test when diagnosis is doubtful. Elective antithyroid therapy is indicated in Graves' disease for all patients except the immature and for patients with small toxic multinodular goiters. Preoperative use only is indicated for thyrotoxicosis with chronic thyroiditis, sub-

sternal or intrathoracic goiter, uninodular goiter and large multinodular goiter.

The regimen for prolonged therapy with the various imidazoles is outlined in the table; properly carried out, it requires 6-18 months. The initial daily dose of the selected compound should be continued until toxicity is controlled and then be reduced by one "unit" each month unless toxicity recurs, in which event the last effective dose should be resumed. Lugol's solution, 1 minim daily, should be added when the BMR has reached + 20% or less and continued for not less than three months after withdrawal of the antithyroid compound.

In preparation for operation, the same procedure is followed until the BMR is + 20% or less, when the dose of antithyroid compound is reduced by one-third to one-half and Lugol's solution, 5-15 minims three times daily, is instituted. Both are continued until the day of operation; surgery is performed as soon as the patient is euthyroid and the gland is firm to palpation.

Tapazole is probably the most useful of the antithyroid compounds so far used to control thyrotoxicosis in man.

Hyperthyroidism—Evaluation of Treatment with Antithyroid Drugs Followed by Subtotal Thyroidectomy. On the basis of results in 2,400 patients, Elmer C. Bartels[5] (Lahey Clinic) states that antithyroid drugs aid greatly in the preoperative treatment of hyperthyroidism. They must be administered under careful observation, because serious blood changes, particularly agranulocytosis, are a real danger. Patients must be treated individually, and no patient should undergo thyroidectomy until a euthyroid state is reached and all evidence of hyperthyroidism and resulting physical depletion are overcome. If this is accomplished, a low operative mortality is possible—0.2% in this series.

Antithyroid drugs can safely be given to pregnant patients with hyperthyroidism if myxedema is avoided pre- and postoperatively until the time of delivery. Normal delivery at term occurred in 21 of the 27 pregnant patients. In six, the outcome was variable and appeared completely unrelated to antithyroid treatment or thyroidectomy.

Postoperative tetany occurred in 3% of patients and was

(5) Ann. Int. Med. 37:1123-1134, December, 1952.

permanent in 1.8%. It began on the first to sixth day. Transient tetany lasted from five days to four years (average, three months). The incidence of tetany was greater in patients who had previously undergone surgery on the thyroid gland. In all patients, tetany was controlled with powdered calcium lactate alone or in combination with vitamin D.

Hyperthyroidism recurred in 33 of 1,670 patients (1.9%) followed by periodic metabolic studies for three to eight years. These patients were treated selectively; in most of them the disease was controlled either by daily administration of iodine or by a second operation, with removal of the recurrent thyroid remnants.

Postoperative myxedema occurred in 7.3% of the first 942 patients; in 5.2% it was permanent. It developed any time up to the fifth postoperative year, but usually in the first year, and became permanent if thyroid was required after the first year. Desiccated thyroid controlled all cases, the usual dose being 1½ gr. or less.

Observations on Use of Propylthiouracil in Hyperthyroidism with Especial Reference to Long Term Treatment. Elihu S. Wing, Jr., and Samuel P. Asper, Jr.,[6] report on 203 low income patients treated with propylthiouracil. Women predominated 3.3:1, except in the group over 50. Diffuse goiter was found in 77.8%. Average BMR was + 53%. Coexistent hyperthyroidism and thyroid cancer, which is rare, was found in two patients. Minimal initial dosage was 300 mg. daily, divided into three doses. Of the 203 patients, 21.7% were prepared for subtotal thyroidectomy; 16.8% failed to return after a few visits; 5.4% were transferred to personal physicians, and 56.1% have had prolonged therapy.

On the average, the BMR was within normal range within 100 days. In patients with severe weight loss before treatment, gain was rapid during treatment. Serum cholesterol concentration rose abruptly during the first two months of therapy. The goiter increased in size in only four instances. The gland became impalpable in one third of the patients with diffuse goiter. A significant increase of exophthalmos was noted in 5 of 52 patients with diffuse goiter. Malignant exophthalmos was not observed, suggesting that propylthiouracil may be the most prudent treatment in exophthalmic Graves'

(6) Bull. Johns Hopkins Hosp. 90:201-227, March, 1952.

disease. A long remission was obtained in 24 of 48 patients after withdrawal of the drug. Relapse usually appeared within six months. Toxic reactions to propylthiouracil were leukopenia with granulopenia (in 12), agranulocytosis (in 1), urticaria (in 2) and a collagen vascular disease-like state (in 1). Major surgery was successful and serious illnesses satisfactorily treated in patients receiving propylthiouracil.

Propylthiouracil and Methimazole Therapy: Comparative Experiences. Glenn W. Irwin, Helen D. Van Vactor and Max S. Norris[7] (Indianapolis) report results in 45 patients with hyperthyroidism treated with methimazole and 54 treated with propylthiouracil. Methimazole was given in equally divided doses every eight hours, 15 mg. daily for small goiters, 30-45 mg. for moderate and 60 mg. for large. Propylthiouracil was given in three equally divided doses during the day, 300 mg. for small goiters, 400-500 mg. for moderate and 600-800 mg. for large. Average daily dose of methimazole, 38.8 mg., was about one-tenth that of propylthiouracil, 355.4 mg.

Average time required for patients to reach a euthyroid state was 85.6 days for the methimazole group as compared with 148.6 days for the propylthiouracil-treated patients. The rate of fall of the BMR was about twice as rapid with methimazole as with propylthiouracil therapy. Generally, the subjective improvement in the patient was prompt with methimazole, a delay being seen in those with large nodular goiters and severe toxicity. In the group receiving propylthiouracil there was a significant incidence of unsatisfactory response, 9 of 54 (16.6%). In four, the time of treatment ranged from 212 to 405 days before hyperthyroidism was controlled. In five, treatment with propylthiouracil was discontinued because of this slow response. The incidence of toxic reactions was about the same in both groups. Previous iodine therapy did not influence the effect of the antithyroid drug so much as did the size of the goiter and degree of toxicity. A longer time was required to control severe hyperthyroidism in patients with large goiters despite large doses of antithyroid compounds.

Further Observations on Methylthiouracil Treatment of Thyrotoxicosis are reported by Erik D. Bartels and Ferd. Wulff[8] (Copenhagen) after more than four years of its use.

(7) J.A.M.A. 149:1637-1640, Aug. 30, 1952.
(8) Acta med. scandinav. (supp. 266) 142:203-208, 1952.

They stress careful selection of patients and immediately eliminate from consideration those who do not wish prolonged management, those who have heart disease, those who have large goiters and those who are pregnant.

Of 98 patients with thyrotoxicosis, treatment was restricted to 65 because of contraindications; 4 others had to be eliminated because of drug fever. Agranulocytosis appeared in two.

Of the 61 patients treated, 49 (79%) were cured (well for three to five years) without other treatment, but only 36 of the 49 were cured in one course.

Complications such as drug fever were handled by stopping treatment for a few days and then gradually beginning again. The authors believe that thyroidectomy is the treatment of choice for all patients who have had agranulocytosis. Since almost all serious complications appear in the first three weeks of therapy, they prefer starting treatment in the hospital.

Regulation of dosage is the aim of control, so after a suitable fall in the BMR and a weight gain, the initial dose of 200 mg. three times a day is cut gradually to 50 mg. a day.

The authors prefer surgery if the treatment runs over 18 months and advise keeping patients under observation at monthly intervals for a year after treatment because of the danger of relapse. They feel justified in using this treatment in all cases except those specifically eliminated by the criteria listed.

Measurements of Thyroid Epithelium in Glands Prepared for Surgery with Iodothiouracil and with Other Antithyroid Drugs. Boris Catz and Paul Starr[9] (Univ. of Southern California) used the measure of mean acinar cell height (MACH) by calibrated ocular micrometer to interpret structure of the thyroid gland in normal subjects and treated and untreated subjects with hyperthyroidism. The MACH and standard deviation for each group (number of cases in parentheses) were: normal 6.1 ± 1.0 (16); untreated hyperthyroidism 18.7 ± 3.5 (3); itrumil® 8.6 ± 2.0 (12); Lugol's solution 10.7 ± 2.5 (24); propylthiouracil followed by Lugol's solution 12.3 ± 3.0 (11); thiouracil followed by Lugol's solution 13.4 ± 3.0 (7); methylthiouracil followed by Lugol's solution 13.3 ± 1.6 (5), and thiouracil and potassium iodide pro-

(9) J. Clin. Endocrinol. 12:228-234, February, 1952.

portionately equivalent to itrumil® 10.0 ± 4.6 (2). Itrumil®-treated glands had the lowest MACH and only 2 of the 12 in this group showed abnormal cell heights. The authors feel that itrumil® may act differently from the other antithyroid drugs.

[Antithyroid drugs can be divided into two groups: the goitrogens, which include propylthiouracil, methylthiouracil and methimazole, and the antigoitrogens, which include iodine, radioiodine and iodothiouracil. In certain specific cases, goitrogenic activity is distinctly undesirable, e.g., in substernal goiter or when the gland encircles the trachea so that enlargement of an already hyperplastic gland may result in severe respiratory embarrassment. In such instances, antigoitrogenic antithyroid drugs are preferred. Final evaluation of iodothiouracil is not yet possible. It would be extremely worth while to know whether its use will prevent progressive exophthalmos.—Ed.]

Resistance of Normal Human Thyroids to Propylthiouracil. Clarence G. Sutherland, Willis E. Brown and Edwin C. Jungck[1] (Univ. of Arkansas) administered propylthiouracil in large doses to eight euthyroid women (of whom five were schizophrenic) in an attempt to induce hypothyroidism and the menstrual abnormalities associated with the hypothyroid state. Although the therapy was continued for 7½ months and the dosage for the last 6 weeks was 3,000 mg. daily in divided portions, no instances of hypothyroidism or myxedema occurred. Of the 96 menstrual cycles followed with endometrial biopsies, only 3 were anovulatory.

Propylthiouracil-Induced Agranulocytosis, Toxic Hepatitis and Death. Arthur R. Colwell, Jr., Don E. Sando and Samuel J. Long[2] (Evanston Hosp.) report a case.

Woman, 60, was hospitalized in August 1950 after two weeks of exertional dyspnea, chest discomfort and ankle edema. Examination showed a slight manual tremor, basal râles, edema and transitory auricular fibrillation; arteriosclerotic heart disease was diagnosed. When appropriate therapy failed to improve, hyperthyroidism was suspected although eye signs and palpable goiter were absent. She was given 300 mg./propylthiouracil and 0.3 cc. potassium iodide daily and was sent home improved after 19 days. A white blood cell count reported after her departure revealed a fall from 5,000 to 2,550 cells. One week later she had malaise, fever, chills and cough; she stopped medication and returned 13 days after discharge. Temperature was 103.2 F. and white blood cell count 250. Penicillin and supportive therapy were begun. The next day she was jaundiced, white count had risen to 2,380 with only 7% polymorphonuclear leukocytes, and she had 4+ albuminuria. She died the third day. Autopsy revealed acute ulcerative appendicitis and colitis, pneumonia, hepatitis and depressed marrow; the thyroid gland was normal.

(1) Proc. Soc. Exper. Biol. & Med. 8:466-468, November, 1952.
(2) J.A.M.A. 8:639-642, Feb. 23, 1952.

Death Due to Agranulocytosis Induced by Methimazole Therapy is reported by Norman W. Specht and Earl J. Boehme[3] (College of Med. Evangelists).

Woman, 67, with nodular goiter and thyrotoxicosis had normal hemogram on Oct. 2, 1951 (hemoglobin content, 13.7; white cell count, 7,000 with 42% neutrophils). On October 8, treatment was begun with 15 mg. phenobarbital and 10 mg. methimazole (tapazole) three times daily. She began to gain weight and felt stronger; on November 5 she reported further improvement and had gained 2½ lb. in all. The next day the first serious signs appeared, including extreme weakness, generalized aching, a liquid bowel movement and fever. After three days her family physician, because of the high fever and jaundice, gave an injection of penicillin. The next day, fever was higher and jaundice more pronounced. During the acute episode at home she continued to take methimazole three times a day.

On hospitalization, November 10, the white cell count was 1,300 with 87% lymphocytes, 13% monocytes and no neutrophils. Vigorous therapy to control the infection was promptly started; penicillin and terramycin, fluids and whole blood intravenously were given, and 10 mg. corticotrophin was added to fluids given intravenously. Oxygen was administered continuously by nasal catheter. After six hours she showed no improvement; she remained conscious and alert, but very dyspneic. Another 500 cc. blood and corticotrophin were given but after 18 hours she had a cold, sweaty skin, blood pressure was unobtainable and she died.

Autopsy revealed bilateral bronchopneumonia. The bone marrow showed a definite decrease of cellularity with a large number of megakaryocytes and a decreased number of myelocytic cells. Many of these showed degenerative changes with swelling of the cytoplasm, indistinct margins and pyknosis or irregular staining qualities of the nuclei.

Sore throat was not a symptom of agranulocytosis here or in another case reported elsewhere. In both instances, patients became severely ill within a few hours.

[Thiouracil, the first antithyroid drug to be given general use, was soon replaced by the propyl and methyl derivatives because the parent compound often produced agranulocytosis and drug fever. With the newer derivatives, these complications are rare, but their occurrence is sufficiently important to warrant keeping close watch on the patient receiving these drugs. Unfortunately, complications may appear suddenly and without warning. The patient therefore should be advised to be on the lookout for early symptoms, so that appropriate examination can be made and the drug discontinued.—Ed.]

Effect of Perchlorate on Human Thyroid Gland. John B. Stanbury and James B. Wyngaarden[4] (Massachusetts Gen'l Hosp.) report observations on 12 patients with typical Graves'

(3) J.A.M.A. 149:1010-1012, July 12, 1952.
(4) Metabolism 1:522-539, November, 1952.

disease. Three types of experiments were designed to determine whether perchlorate could displace iodide from the thyroid gland. In one, the subjects received a blocking dose of 1-methyl-2-mercaptoimidazole, then a tracer dose of I^{131}, and, when I^{131} had accumulated in the gland, $KClO_4$ orally. In the second series, $KClO_4$ was given before the tracer. In the third, the blocking drug was omitted and $KClO_4$ given before the tracer. Measurements of isotope uptake in the gland were made with a lead-shielded scintillation counter using a sodium iodide crystal.

Aqueous potassium perchlorate, when given orally in doses of 3-100 mg., resulted in a rapid release of previously accumulated iodide from the thyroid glands of the subjects treated with 1-methyl-2-mercaptoimidazole. Perchlorate also effectively inhibited the accumulation of I^{131}. This action is qualitatively similar to that of thiocyanate. Duration of inhibition of I^{131} uptake after a single dose of 100 mg. perchlorate was about six hours. No toxic effects of perchlorate were encountered in these patients, who were given as much as 600 mg. of the drug.

Perchlorate is known to cause goiter in rats. The experiments reported here suggest that perchlorate may be a suitable antithyroid agent for human therapeutics.

Pathologic Effects of I^{131} on the Normal Thyroid Gland of Man. Although radioactive iodine has demonstrated therapeutic efficacy in many patients with thyrotoxicosis, carcinoma of the thyroid, intractable angina pectoris and congestive failure, there is only fragmentary knowledge of its histologic effects on human thyroid tissue. A. Stone Freedberg, George S. Kurland and Herrman L. Blumgart[5] (Beth Israel Hosp., Boston) describe autopsy findings in 16 euthyroid patients who died from 7 to 1,069 days after oral administration of 17-157 mc. I^{131}. Therapy was administered for intractable angina pectoris or heart failure in 15 patients.

Autopsy on two patients seven days after administration of 17 and 20 mc. I^{131}, which delivered 14,500 and 31,000 rep respectively to the thyroid gland, revealed no histologic changes which could be attributed to I^{131}. Autopsies 14 and 24 days, respectively, after administration of 59 and 26 mc. I^{131} showed pronounced central destruction of the thyroid. There were

(5) J. Clin. Endocrinol. 12:1315-1348, October, 1952.

edema and degeneration of the stroma, striking acute vasculitis with thrombosis and hemorrhage, epithelial swelling and vacuolation, follicular destruction and polymorphonuclear infiltration. At the periphery of the gland radiation damage was less severe, but there were extensive disruption of follicles and colloid and round cell infiltration.

The thyroid glands of patients who survived longer showed

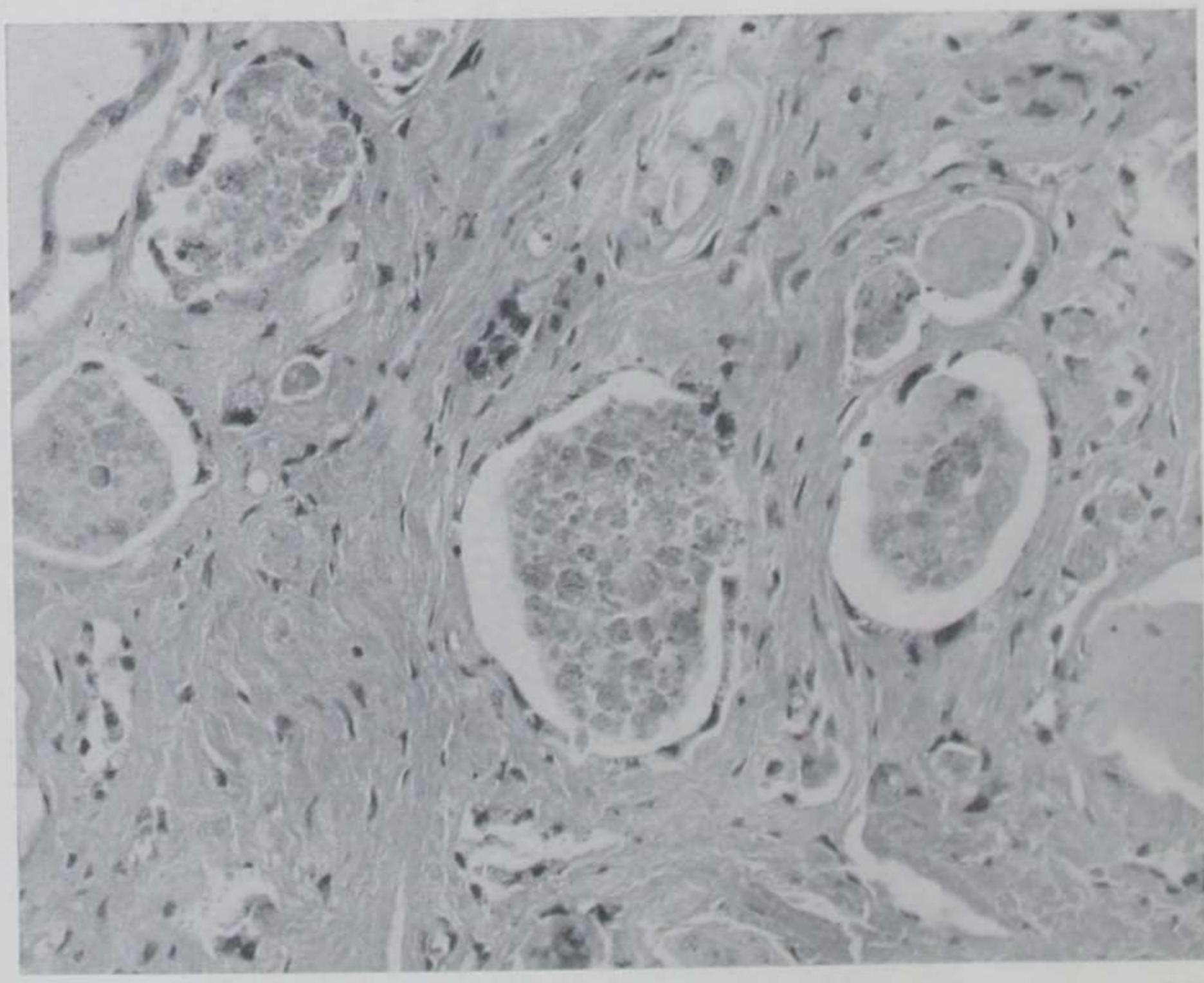


Fig. 14.—Pathologic changes in thyroid following administration of 45 mc. I^{131} from 186 to 42 days before death. There are pronounced fibrosis, fragmentation and alteration of colloid; reduced from × 400. (Courtesy of Freedberg, A. S., *et al.*: J. Clin. Endocrinol. 12:1315-1348, October, 1952.)

less acute changes. There were increased fibrous stroma, lymphocytic infiltration, arteriolar intimal thickening and hyalinization. The follicular epithelium was desquamated and admixed with a fragmented or globular colloid. Atypical cells with large hyperchromic nuclei were noted, frequently associated with masses of colloid outside follicular structures (Fig. 14).

In patients who lived 316-1,069 days after treatment with I^{131}, the thyroid gland was largely replaced by dense fibrous

tissue. Small arteries were notably thickened. The remaining follicles were decidedly disrupted, with fragmentation of colloid and destruction and desquamation of the follicular epithelium. Atypical cells with large hyperchromic nuclei were noted; mitoses were absent. Continued degeneration of thyroid follicular epithelium long after administration of I^{131} can most probably be ascribed to the constricting effect of increasing fibrosis or to progressive decrease in blood supply associated with arterial narrowing produced by subintimal and intimal thickening.

Of the parathyroid glands examined, only one was abnormal. In this instance there were swelling and vacuolation of oxyphil cells in the fragment embedded within a severely damaged thyroid gland. Clinical evidence of impaired parathyroid function has never been observed after I^{131}. No radiation injury to the trachea, larynx, adrenals, or pituitary was found, and no thyroid neoplasm was found which could be attributed to I^{131}.

Therapeutic Effects from Repeated Diagnostic Doses of I^{131} in Adult and Juvenile Hyperthyroidism. Tracer methods with small doses of I^{131} are commonly used in hyperthyroidism to follow the course of the disease under the influence of a particular therapy. It is generally assumed that these small amounts of isotope in themselves have no physiologic effect. Sidney C. Werner, Howard Hamilton and Martha R. Nemeth[6] (New York City) investigated this assumption by giving carrier-free I^{131} to 29 patients with unquestioned thyrotoxicosis according to two dosage schedules: 40 μc. weekly for five to six doses, or 100-200 μc. weekly for three doses. In many patients the initial series of doses of I^{131} was repeated after several weeks, but in a few the second series consisted of larger doses, a maximal total of 1,099 μc. being given.

There were 2 men, 21 women and 6 children (aged 7-12). Of the entire group, 8 showed complete remission of hyperthyroidism, 3 partial recovery and 18 no improvement. Of the six children, four achieved complete remission. The minimal dose of I^{131} resulting in complete remission (in four patients) was 200-240 μc. Significant changes in single laboratory values (BMR, serum precipitable-iodine or 24 hour

(6) J. Clin. Endocrinol. 12:1349-1355, October, 1952.

thyroid uptake) are noted in many of the patients failing to respond otherwise to I^{131}. None of the remissions lasted longer than three months.

Since spontaneous remissions usually occur only in 1 of 25 patients and are long lasting, it is not likely that the remissions observed can be so explained. Studies of various thyroid therapies followed with tracer uptake thus require re-evaluation. Possibly the therapeutic I^{131} dosage used in thyrotoxicosis may be reduced in some cases, although no means exist for selecting such radiosensitive thyroids. Children seem particularly sensitive to low radiation levels, and in them external irradiation might prove satisfactory for controlling thyrotoxicosis.

[The use of newer more sensitive means, especially the scintillation counter, has greatly reduced the amount of radioactive iodine used for tracer doses.—Ed.]

Treatment of Thyrotoxicosis with Radioactive Iodine is discussed by E. J. Wayne, A. G. Macgregor and G. W. Blomfield[7] (Univ. of Sheffield), who point to its safety, lack of toxic side effects and invariable effectiveness if repeated doses are possible. Although evidence apparently refutes the pos-

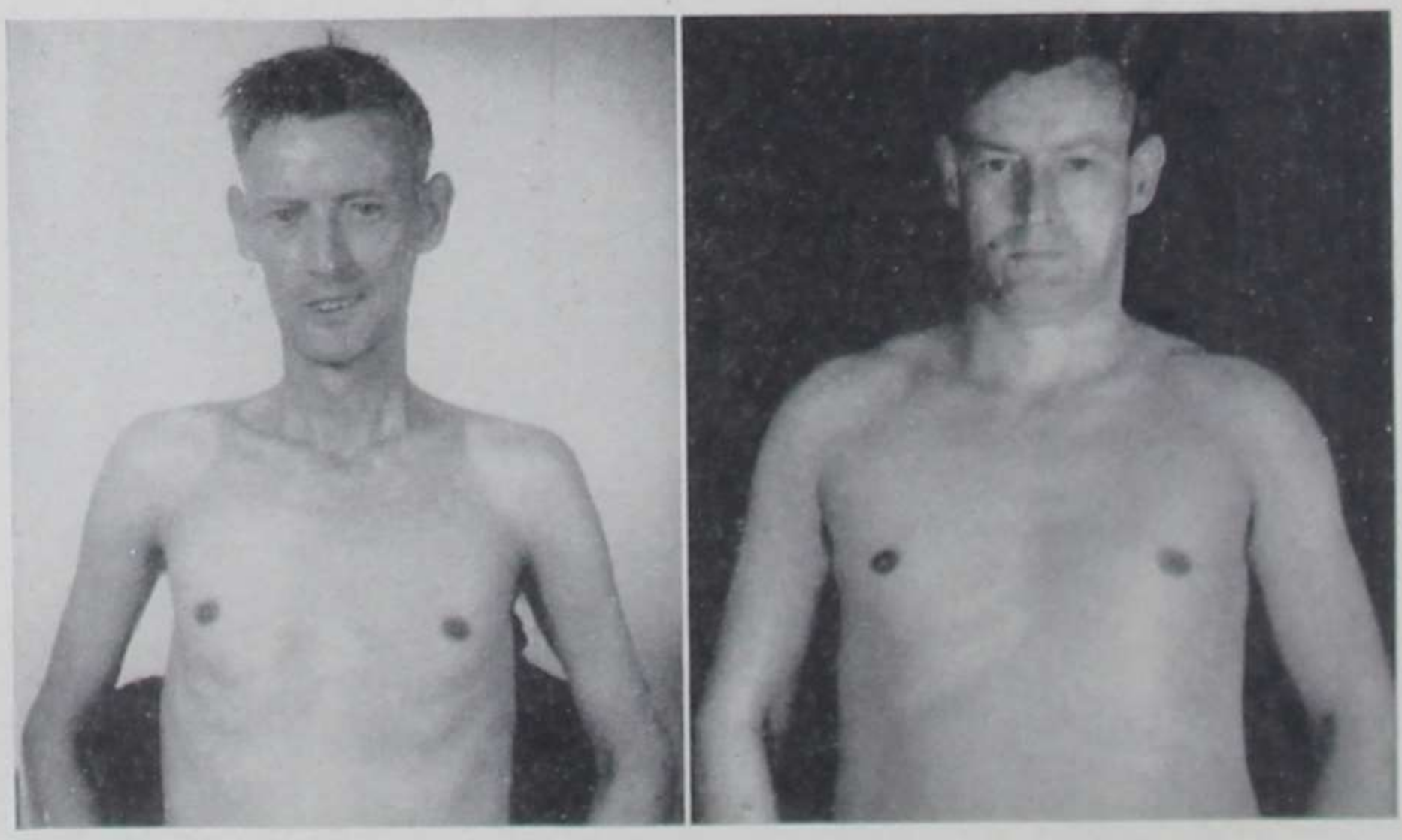


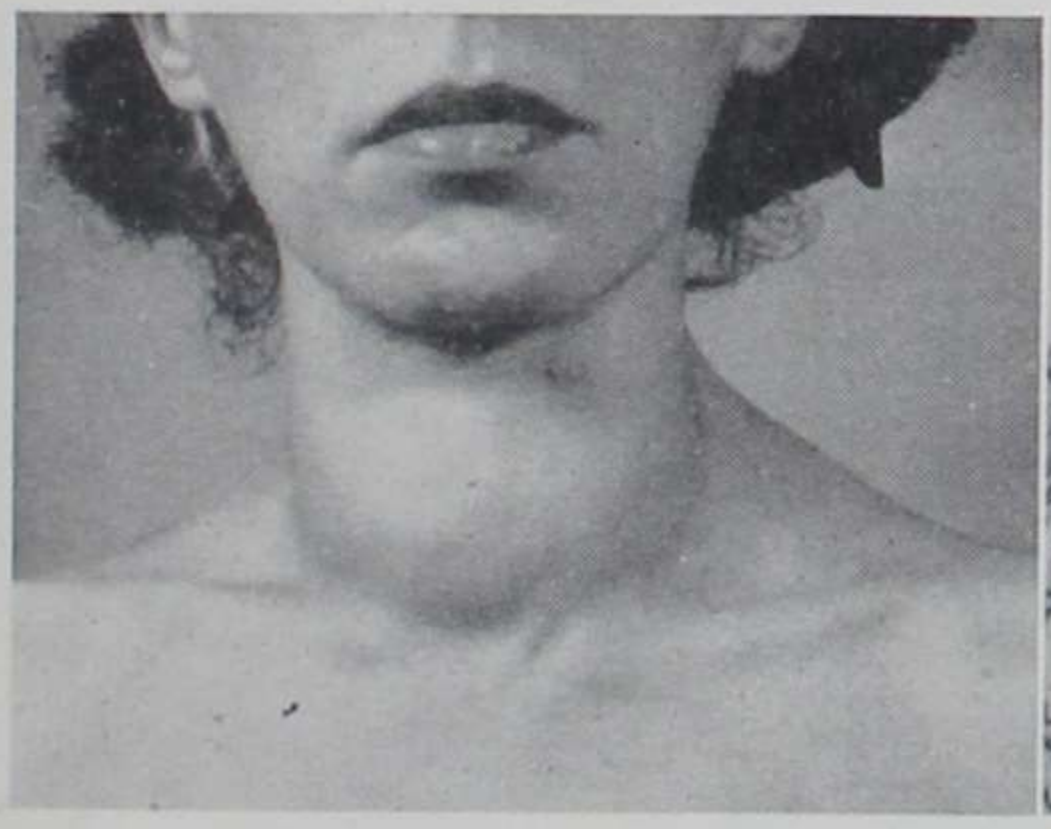
Fig. 15 (left).—Severely thyrotoxic patient with concomitant suprarenal cortical deficiency before therapy.

Fig. 16 (right).—Same patient one year after a dose of radioactive iodine calculated to deliver 9,500 roentgen equivalents to the gland. He had gained 47 lb. with residual normal thyroid function.

(Courtesy of Wayne, E. J., *et al.*: Brit. M. Bull. 8:148-154, 1952.)

(7) Brit. M. Bull. 8:148-154, 1952.

sibility that radioiodine would produce any malignant changes in man—the one important objection to isotope therapy—that possibility should be borne in mind. It is consequently recommended that isotope therapy be limited to patients with less than a 20 year life expectancy. Pregnancy is an absolute contraindication. Since toxic nodular goiter requires relatively large doses, repeated small doses are recommended. With the usual therapeutic dose, radiation effect on organs other than the thyroid are exceptional. A preparatory course of methylthiouracil is given only in more severe thyrotoxicosis. Suitable



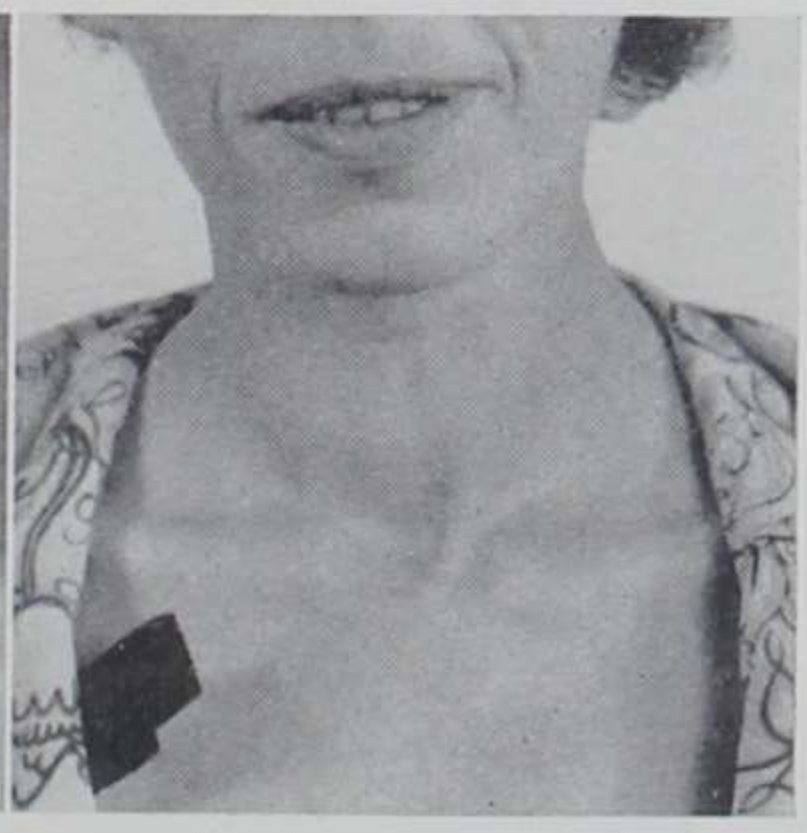


Fig. 17 (left).—Patient with severe thyrotoxicosis before treatment.
Fig. 18 (right).—Same patient 15 months after second of two doses of radioactive iodine. She was given a total of 32.5 mc. or a total dose of 22,200 roentgen equivalents.
(Courtesy of Wayne, E. J., *et al.*: Brit. M. Bull. 8:148-154, 1952.)

isotope dosage is based on radioiodine uptake, total half-life of the iodine in the gland and size of the gland.

Of 70 patients treated with an estimated 8,000-10,000 rep, 41 are euthyroid and 2 hypothyroid; there have been no relapses. The rest, followed for less than one year, will probably be cured eventually with additional radioiodine therapy. Objective improvement is apparent after about a month and euthyroidism several weeks later. Rapid loss of signs and symptoms probably presages some degree of myxedema. If after two or three months improvement is inadequate, clinical assessment and radioiodine tracer tests are repeated. If improvement is appreciable in the early months, further therapy is postponed, despite evidence of some toxicity, since remission after radioiodine may not be complete for several months; average time for establishing euthyroidism was three and

one-half months in this group. Normal thyroid function is accompanied by a striking gain in weight (Figs. 15 and 16). A large gland or pressure symptoms do not necessarily contraindicate isotope therapy, since the gland always shrinks (Figs. 17 and 18). Malignant exophthalmos accompanied by hyperthyroidism is not a contraindication to radioiodine therapy (Figs. 19 and 20). With radioiodine, exophthalmos tends

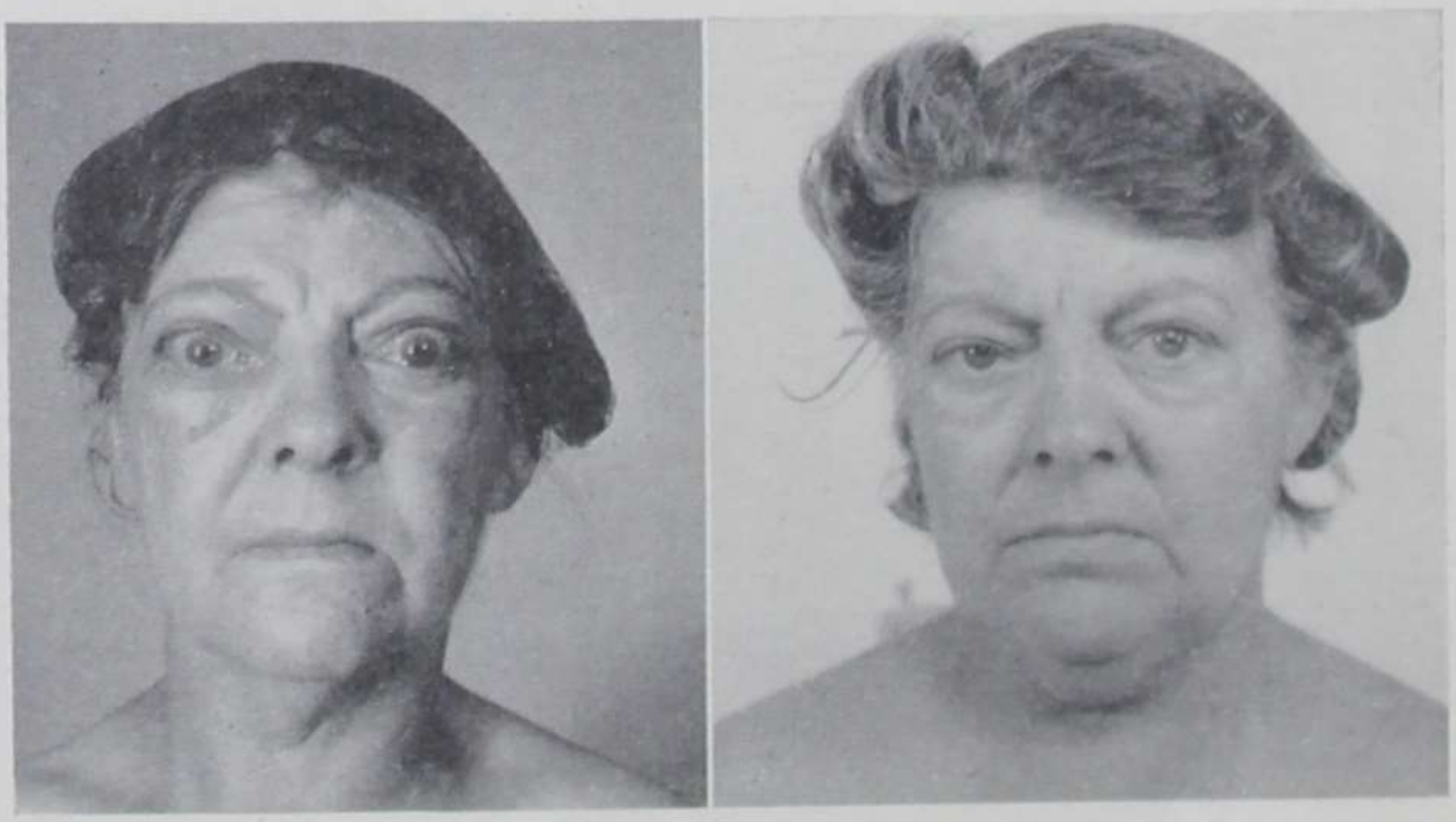


Fig. 19 (left).—Facies of patient before treatment for thyrotoxicosis.
Fig. 20 (right).—Same patient 27 months after radioactive iodine therapy. She became hypothyroid after treatment and required maintenance thyroid therapy. (Courtesy of Wayne, E. J., *et al.*: Brit. M. Bull. 8:148-154, 1952.)

to increase less after treatment than with either methylthiouracil or after partial thyroidectomy.

There were no immediate complications of treatment except in one patient who had a flare-up of thyrotoxicosis five days after radioiodine therapy; such reactions can be avoided by giving up to 25 Gm. potassium iodide for four days after treatment, starting only 24 hours after the dose of isotope.

Case of Fatal Thyroid Crisis Occurring after Radioactive Iodine Therapy. Rodney B. Nelson, John B. Cavenagh and Arthur Bernstein[8] (Cook County Hosp.) report the first such fatality.

Philippine man, 44, was hospitalized Sept. 1, 1951, after five weeks of proptosis, weight loss and ankle edema. Appetite was good. He was aware of dyspnea, hand tremor, nervousness and an irregular heart action. Pulse was 126 and irregular, blood pressure 150/70,

(8) Illinois M. J. 101:265-268, May, 1952.

temperature 98.4 F. and respiratory rate 24/minute. The eyes had a decided stare with lid lag and the thyroid was enlarged to an estimated 45 Gm. The abdomen was moderately distended and shifting dulness was demonstrated in the flanks. Pitting edema extended up to the groin. Laboratory results were essentially normal. Chest x-ray showed cardiac enlargement. He was treated with digitalis, phenobarbital and bed rest. On September 5, he was given a therapeutic dose of 5 mc. I^{131}. He insisted on going home September 7. On September 12, he reported to the clinic sweaty, tachypneic and with pitting ankle edema. Heart rate was 150 and irregular. He was given Lugol's solution, 10 drops three times a day, and 1 cc. mercuhydrin® and instructed to stay in bed until return to the clinic in one week. On September 14, he was brought to the clinic in a preterminal state. Temperature was 103; respiration 40/minute, pulse 140 and blood pressure 90/60. He was treated for shock and with penicillin and died two hours after hospitalization and nine days after receiving radioactive iodine. At autopsy the thyroid weighed 50 Gm.; high columnar cells lined the acini.

The high grade of thyrotoxicosis and thyrocardiac complications in this patient may have led to thyroid crisis under any therapy. Its occurrence precisely after radioactive iodine therapy, when an increase in thyrotoxic symptoms had been witnessed, makes the association appear significant and indicates that the therapy was a factor. For severe thyrotoxic patients to be treated with radioactive iodine, the authors use compound solution of iodine alone or with propylthiouracil to control toxic symptoms in the two weeks to four months before radiation produces remission; they advise daily observation in the first two weeks. In patients with severe toxicity and limited cardiac reserve, preliminary control with propylthiouracil is advised before starting radioactive iodine.

[This complication must be exceedingly rare. Note that no such occurrence was found in the large series which are described in the reports which precede and follow this abstract.—Ed.]

Five Year Experience with Radioactive Iodine in Treatment of Hyperthyroidism. D. E. Clark, J. H. Rule, O. H. Trippel and D. A. Cofrin[9] (Univ. of Chicago) report results in 384 patients who were followed for 6 to about 60 months and whose therapy had been completed. One or more of the following criteria were fulfilled in selection of patients: (1) uncomplicated hyperthyroidism in patients over age 40; (2) recurrent or persistent hyperthyroidism after thyroidectomy; (3) hyperthyroidism with severe cardiovascular disease or some other concurrent disease; (4) failure to respond prop-

(9) J.A.M.A. 150:1269-1272, Nov. 29, 1952.

erly to antithyroid drugs; (5) refusal of surgical or other therapy, and (6) presence of severe exophthalmos.

At present, 150 mc. (New Oak Ridge Standard) estimated gram of thyroid tissue is given as an initial dose to patients under 40 with diffusely enlarged glands and about 250 mc. to patients over 40. To patients with nodular glands, 300-350 mc./estimated gram of thyroid tissue is given initially. In previously treated patients who are mildly hyperthyroid or euthyroid, administration of I^{131} is usually deferred for four weeks after discontinuance of drug therapy. If thyrotoxicosis is moderate or severe despite previous treatment and the avidity of the gland for I^{131} is not significantly decreased, therapy is instituted after a shorter interval.

After a therapeutic dose of I^{131} is given, patients are followed at about two month intervals until a euthyroid status is achieved. If the initial dose is inadequate, additional I^{131} is given in doses commensurate with the severity of the persisting toxicosis. Clinical response to I^{131} alone seems to be slower than when iodine (I^{127}) or antithyroid drugs are given concurrently. Satisfactory remission is ascertained by clinical judgment, BMR and, in many cases, radioiodine diagnostic studies and protein-bound iodine determinations. Treatment is ambulatory, and normal activity is encouraged. None of the patients who have remained euthyroid for four months have had a recurrence to date.

Remissions were obtained in 76.1% of patients with one or two doses. All but one of the others required from three to seven doses. A satisfactory remission was obtained in 85.2% of patients, whereas in 13.8% varying degrees of hypothyroidism developed. Only 1% have permanent myxedema.

Radioactive Iodine in Treatment of Hyperthyroidism. E. Perry McCullagh[1] (Cleveland Clinic) enumerates some of the characteristics of I^{131} which make it particularly useful in therapy, especially in Graves' disease. (1) A high roentgen equivalent (rep) dosage is possible. (2) The uptake is high in hyperthyroidism and low in euthyroidism. (3) Eighty-five per cent of the radiation is beta rays, which have a very local effect. (4) Since 99% of the original strength is dissipated in 52 days, overdosage does not cause excessive damage and undertreatment can be corrected. (5) In the doses used, I^{131}

(1) Ann. Int. Med. 37:739-744, October, 1952.

does not cause urogenital or parathyroid damage. (6) It may be used until end of the third month of pregnancy. (7) It can be used for testing thyroid function, as the amounts in common use are less than 1/50,000 of the normal daily iodine requirement.

In nodular goiter, surgery is the treatment of choice, but when it is contraindicated or unacceptable, I^{131} can control the hyperthyroidism. The hyperthyroidism of nodular goiter and that of Graves' disease respond differently to I^{131}. The dose required for control is larger for nodular goiter and the rate of improvement slower. Larger doses may be given with impunity because post-treatment myxedema has not been observed. For 102 patients with nodular goiter, average dose was 34 mc., compared with 12 mc. for Graves' disease. Most cases of Graves' disease are controlled in 2-4 months, whereas nodular goiters require an average of 6½ months.

Dosage for hyperthyroidism is based on the estimated weight of the gland and the percentage uptake of I^{131}. The prescribed dose usually lies between 100 and 200 μc./Gm. thyroid. Since in Graves' disease avidity for iodine is greater when hyperthyroidism is more intense, the gland tends, within limits, to retain automatically the amount of I^{131} needed. To avoid all unnecessary hypothyroidism, two thirds of any average curative dose has been given. This has resulted in control in 75% of patients by one dose, 15% by two doses and 10% by three or more doses.

If uptake is low due to pretreatment with iodine, administration of I^{131} is postponed and propyl- or methylthiouracil or mercaptoimidazole may be given for a month to maintain control. Two or three days after withdrawal of antithyroid drug, I^{131} may be used. If there is no improvement in two months, the dose is repeated.

In the treatment of hundreds of patients with Graves' disease, the only complication other than hypothyroidism has been near-crisis after a 25 mc. dose. This may be avoided if I^{127} is given beginning two days after I^{131}. Exophthalmos behaves after I^{131} as after other forms of treatment; it may become a little worse at first, sometimes a little better. Eventually it tends to improve, but occasionally it may become extremely severe.

Among the many advantages of I^{131} treatment of Graves'

disease are: no deaths; no vocal cord paralysis; no chronic tetany; almost 100% complete control; reduction of thyroid size, usually to normal; no discomfort; no loss of time or income; no hospitalization; no greater frequency of hyperthyroidism than after surgery; fewer recurrences than with other forms of treatment; recurrences easily and successfully treated by I^{131}; cheapest form of treatment.

Temporary Hypoparathyroidism Following Radioactive Iodine Treatment for Thyrotoxicosis. William J. Tighe[2] (San Diego Gen'l Hosp.) reports a case.

Boy, 14, with thyrotoxicosis, was given 50 μc. I^{131} on May 22. Uptake over the thyroid was 80% and urinary excretion 8% after 48 hours. He then received 4 mc. I^{131} on May 25; 17% of this dose was excreted in the urine in 48 hours. By August 2, he had gained 6 lb., the enlarged thyroid had decreased in size and he felt better although thyroid uptake was still 70% after another tracer dose of 50 μc. I^{131}. On August 6 he began having muscle spasms in his arms each morning for a few minutes. On August 13 he had severe and frequent carpopedal spasm. Intravenous calcium therapy gave immediate relief. During the following six weeks, the blood calcium level was low (lowest, 6 mg./100 cc.) and the phosphorus level rose as high as 9.8 mg./100 cc., but both returned to normal at the end of that period. There were no further symptoms of tetany, but on August 28 a cuff applied for two minutes at 100 mm. pressure produced definite carpopedal spasm. This was reproduced several times during the next hour.

There have been no published reports of parathyroid injury in human beings following administration of I^{131}. Even the enormous doses used for thyroid carcinoma, which may depress bone marrow and ovarian function, have not produced hypoparathyroidism.

Transmission of Radioiodine (I^{131}) to Infants through Human Maternal Milk. Carl E. Nurnberger and Alys Lipscomb[3] report two cases.

Woman, 33, who was nursing a child, aged 4 months, was given 100 μc. carrier-free I^{131} orally after fasting. Thyroid gland uptake 24 hours later, measured in both baby and mother, was 5% and 34% of the administered dose. Aliquot specimens of milk obtained by manual expression of the mammary glands 24 hours after ingestion of I^{131} showed an average concentration of 0.002 μc. I^{131}/ml. Uptake of I^{131} by the thyroid gland was measured at 24 hour intervals for several days in mother and baby. Biologic half-life in the maternal thyroid was about nine days. Uptake in the infant's thyroid was irregular and undoubted conditioned by the ingestion of

(2) J. Clin. Endocrinol. 12:1220-1222, Mar. 3, 1952.
(3) J.A.M.A. 150:1398-1400, Dec. 6, 1952.

I^{131} in unequal amounts by feedings in the intervals between testings.

In the second case, findings were similar but maximal concentration in milk, observed when the breasts were drying out, was 0.039 μc./ml.

Radioactive iodine diagnostic tracer studies on postpartum women who breast feed their babies may be hazardous to the child. Such studies should therefore be done cautiously, if at all. In addition, the reliability of the procedure when used as a diagnostic tool in nursing mothers is open to question, because I^{131} may be diverted from the thyroid gland to the milk. Radioactive iodine therapy is contraindicated in lactating women who breast feed their babies, since the thyroid gland of the infant may take up enough I^{131} from the milk to depress seriously or ablate functional activity of the gland.

Nodular Goiter, Cancer and Thyroiditis

Hashimoto's Disease (Struma Lymphomatosa): Familial Incidence of Three Cases. According to Paul E. Craig, Joseph L. Spann and Leo Lowbeer[4] (Tulsa, Okla.), nothing conclusive is known of the cause of struma lymphomatosa, first described by Hashimoto in 1912. A total of 563 cases have been recorded since this time. The ratio of female to male patients was 28:1, and average age was 49.2 years. The existence of the disease as a separate entity is controversial.

The thyroid is diffusely enlarged, has a resilient feel and may proceed posteriorly and encircle the trachea. The gland is smooth, pink and beefy and has a pseudolobulated appearance. The cut surface is lobular with a yellowish cast. Microscopically, there is uniform degeneration of all acini, which are multishaped and shrunken. The epithelium is pale, flattened and finally degenerated with eccentrically placed nuclei. Colloid is scant to absent. Numerous lymph follicles and plasma cells are seen. Vascularity is greatly diminished, and there is a diffuse infiltration of lymphocytes throughout the gland and between the acini. Fibrosis increases as the disease progresses, assuming waving whorls about the lobules.

A presumptive diagnosis can be made if a smooth, firm goiter appears in a patient (usually a woman), reaches its maximal size in a few months, involves every part of the gland and produces moderate dyspnea but no serious pressure ef-

(4) Am. J. Surg. 84:286-292, September, 1952.

fects or thyrotoxic symptoms, pain, tenderness or other inflammatory phenomena. Absence of involvement of extrathyroid tissues and presence of some degree of hypothyroidism are substantiating features.

The authors report three cases that are of particular interest because they occurred in a nongoitrous region in full sisters at an average age of 31. Hashimoto's disease was correctly diagnosed preoperatively in two of them.

Besnier-Boeck Sarcoid of the Thyroid: Its Differentiation from Pseudotuberculous Thyroiditis. A. Rywlin[5] (Univ. of Geneva) reports a case.

Woman, 58, had paroxysmal tachycardia, hypertension for many

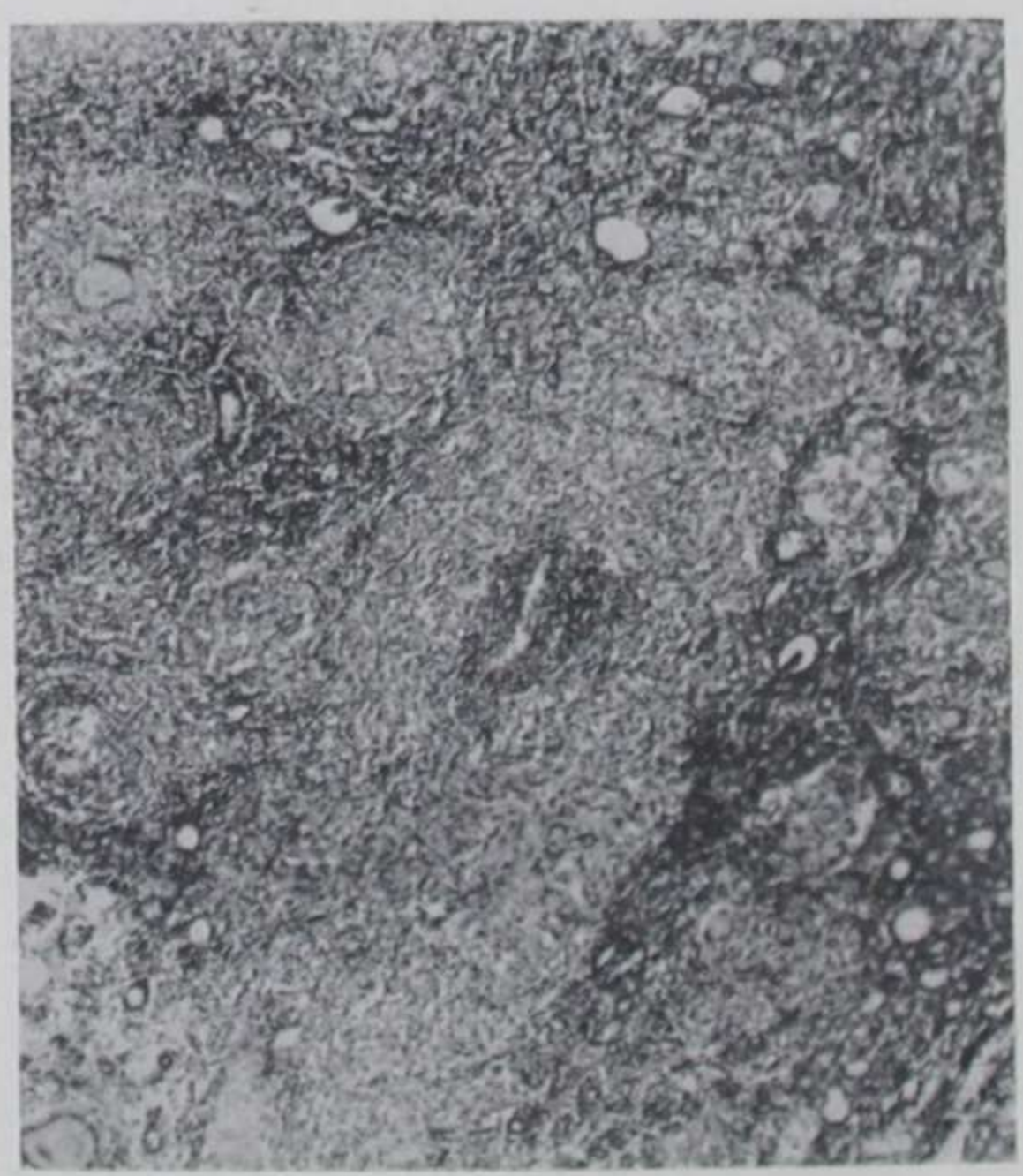


Fig. 21.—Epithelioid formation involving a vein whose wall shows lymphocytic and plasmacytic infiltration without caseation. Hematoxylin-eosin; reduced from × 50. (Courtesy of Rywlin, A.: Presse méd. 60:1278-1280, Oct. 1, 1952.)

years and progressive cardiac insufficiency. A firm thyroid tumor, the size of an orange on the left and smaller on the right side, had developed over three years. Satellite nodes were increased in size, but firm and mobile. White cell count was 4,500 with 75% neutrophils; BMR was + 59% and ECG showed auricular fibrillation. The tumor and surrounding glands were excised. She went home, much improved, with BMR of + 27 to + 59%. Eight months later, she died several days after hospitalization for cerebral hemorrhage. At that time urea level was 0.26 Gm./L., calcium 10.7 mg./

(5) Presse méd. 60:1278-1280, Oct. 1, 1952.

100 ml. and serum proteins 108.3 Gm./L. Autopsy revealed renal sarcoidosis.

The operative specimen showed microfollicular adenomas with numerous dilated veins at the center and formations of epithelioid cells at the periphery. At the center there were giant cells with eosinophilic protoplasm containing basophilic inclusions with nuclei, in varied number, either grouped at a pole or diffusely distributed through the protoplasm. These epithelioid formations, compressing the adjoining parenchyma, were sometimes surrounded by lymphocytes or argyrophilic fibers but never by a fibrous capsule. Sometimes they centered on a vein, whose wall showed lymphocytic and plasmacyte infiltration (Fig. 21). The structure of the nodes was altered by epithelioid follicles with large giant cells but without any trace of caseation at the center. No Koch's bacilli were found in sections of either nodes or thyroid.

Sarcoid of the thyroid was diagnosed in view of the epithelioid tubercles, often perivascular, rich in giant cells, without caseation or Koch's bacilli. In sarcoid, the lesions are interstitial, often perivascular, and are formed by histiocytes with a fine reticular network, whereas in pseudotuberculous thyroiditis the pleomorphic changes take place within the follicle and the cells are desquamated epithelial cells without any reticular network.

Subacute Thyroiditis. Russell Fraser and R. J. Harrison[6] (Postgraduate Med. School, London) discuss subacute thyroiditis treated successfully in three patients with methylthiouracil. Onset of thyroiditis was typical, with sore throat, malaise, pain in the thyroid radiating behind the ear, aggravated with low grade fever, elevated sedimentation rate and a diffusely enlarged, tender thyroid gland. The BMR and plasma cholesterol levels were normal. Protein-bound iodine, measured in two patients, was normal. Radioiodine uptake was not measurable but each excreted 90% of the amount administered in the urine. With 0.6 Gm. methylthiouracil daily (given for 9-44 days), improvement was evident in 2 days and remission complete in 2-4 weeks and radioiodine uptake returned to normal. The findings suggest that subacute thyroiditis is a thyroid inflammation which involves specific interference with the thyroid's capacity for hormonal synthesis but not with its release of hormone; thiouracil rapidly disperses the causal agent, which may be a virus.

[The use of antithyroid drugs in the treatment of thyroiditis, initiated, I believe, by King and Rossellini (J.A.M.A. 129:267, 1945), has become standard. They used thiouracil; subsequently propylthiouracil and methylthiouracil have proved effective but less dangerous.—Ed.]

(6) Lancet 1:382-386, Feb. 23, 1952.

Thyroiditis and Carcinoma. That chronic inflammation can create a local predisposition to tumor is generally admitted, and chronic thyroiditis which has evolved as sarcoma has been reported by various authors. A. Rywlin[7] (Geneva) reports two instances of thyroid carcinoma associated with an inflammatory condition. Such an association has apparently not previously attracted attention.

Case 1.—Man, 57, had chronic thyroiditis of the Riedel type, in which an undifferentiated carcinoma with large, highly atypical clear cells and a vascular, lymphoplasmocytic stroma developed. Its multicentric origin was shown by the intense proliferation of the follicles outside the tumor area, with solid epithelial formations, and the appearance of large carcinomatous clear cells.

Case 2.—Woman, 37, had thyroiditis of the de Quervain type. Small solid epithelial proliferations appeared in numerous areas; they were accompanied in the left lobe, which was adenomatous, by many atypical cellular and nuclear forms and by giant cells resulting from amitosis. This aspect and the lymphatic invasion of the adjacent tissues indicated a malignant adenoma of Langhans' *wuchernde Struma* type. This represented advanced de Quervain's thyroiditis in which the epithelial proliferation had created a genuine tumor accompanied by lymphatic invasion.

Clinically, thyroiditis and carcinoma may be extremely difficult to differentiate. The possible coexistence of the two conditions should put the physician on his guard and lead him to obtain a biopsy.

According to the "biphasic" theory of cancerization, "mutagenic" substances give the cells a blastomatous potentiality which manifests itself only when an "auxogenic" or growth-producing substance is also present. The commonness of epithelial proliferation in chronic thyroid inflammation, on the one hand, and the rarity of thyroiditis with associated carcinoma on the other, lead the author to consider the inflammation as an "auxogenic" factor stimulating growth, which in the presence of a "mutagenic" factor may, in such cases, determine cancer development.

[Lindsay *et al.* (J. Clin. Endocrinol. 12:1578-1600, December, 1952) have shown that the association of thyroid carcinoma with "Hashimoto" thyroiditis is remarkably high. They found 37 malignant neoplasms in 302 glands showing "Hashimoto" thyroiditis—an incidence of 12%, in contrast to an incidence of only 3% in thyroid glands free from thyroiditis. This difference is highly significant.—Ed.]

(7) Presse méd. 60:593-594, Apr. 23, 1952.

Induction of Thyroid Cancer in the Rat by Radioactive Iodine. R. C. Goldberg and I. L. Chaikoff[8] (Univ. of California) injected 400 μc. of I^{131} into each of 25 rats aged 3 months. When killed 1½-2 years later, nine had thyroid tumors. Seven were carcinomas (four types) as judged by histologic appearance and by the fact that there were metastases.

Spontaneous cancer of the thyroid is extremely rare in rats. A high level of stimulating thyrotrophic hormone due to thyroid insufficiency was not the causative agent because 125 rats given propylthiouracil for 18-32 months developed goiters as much as 50 times normal thyroid size without showing any malignant changes despite the many benign adenomas which were noted. It is a reasonable inference that the ionizing radiation of the I^{131} caused the cancers.

Treatment of Nodular Goiter. After a study of 200 patients operated on for nodular goiter, Louis Hermanson, S. L. Gargill and Mark F. Lesses[9] (Harvard Med. School) conclude that surgical exploration is necessary to establish the nature of the nodule or nodules and to remove the disease. Of 200 patients, 25 (12.5%) had histologic evidence of carcinoma but only 1 of them had clinical signs. Since 14.4% of solitary nodules and 10.4% of multinodular goiters were malignant, degree of nodularity was apparently of little importance in determining possible malignancy. Moreover, the clinical evaluation of nodularity was found to be in considerable error. Of 137 goiters believed to have a solitary nodule, 43 proved to be multinodular, whereas 18 of those with diffuse enlargement of the thyroid contained nodules.

Recurrent "Nodular Goiter" in Children. R. H. Heptinstall and Arthur Porritt[1] (St. Mary's Hosp., London) report three cases of this rarely reported goiter of childhood. In two, the goiter had been present for many years. In none was thyrotoxicosis present. None came from a goitrous district. Resection was performed three, four and five times in the three cases. Follow-up for 21 and 15 years and 15 months suggests an excellent prognosis. Careful histologic review of the tissue revealed an abnormality of the gland as a whole, with numerous seedling nodules scattered throughout interpreted as areas of hyperplasia; no colloid was present. In two cases there

(8) A.M.A. Arch. Path. 53:22-28, January, 1952.
(9) J. Clin. Endocrinol. 12:112-129, January, 1952.
(1) Brit. J. Surg. 39:433-440, March, 1952.

were solid adenomas that consisted of poorly differentiated thyroid tissue. Nuclear pleomorphism was observed, but mitoses were very scanty. The nodules were well encapsulated, with no microscopic evidence of infiltration, nor was there vascular invasion. In the third case there were papillary formations, but they were not frequent and did not resemble the cellular papillary projections found in a true carcinoma of this type. After a careful review of these cases, it is felt that there is no evidence of frank malignancy, yet the very cellular appearance of some nodules, with papillary outgrowths in others, would lead some to postulate a low grade of malignancy.

Carcinoma of Thyroid and Nontoxic Nodular Goiter. Elmo J. Cerise, Spears Randall and Alton Ochsner[2] (Tulane Univ.) compare 51 proved cases of carcinoma of the thyroid with 529 of nontoxic nodular goiter. Of carcinomas discovered at operation, 19.8% were in glands with single nodules and 12.8% in glands with multiple nodules. There were 438 women and 91 men with nontoxic nodular goiter and 38 women and 13 men with carcinoma of the thyroid, indicating that although thyroid carcinoma is more common in women, the relative incidence is greater among men. In carcinoma, average interval between discovery of the tumor and institution of definitive treatment was 5.7 years, and between discovery of the tumor and initial examination of the thyroid by a physician, 2.8 years.

Thyroid carcinoma was clinically manifested by a mass in the neck in 44, hoarseness in 7, vocal cord paralysis in 6, dyspnea in 7, pressure sensation in 6 patients. Only six noted rapid and six gradual increase in size of the mass; four had no symptoms. A histologic diagnosis of malignancy had been made in 10 patients when they were first seen by the authors. Of the other 41, 3 had suspected malignancy and 12 had malignancy definitely recognized preoperatively (a preoperative diagnostic accuracy of 36.6%). Malignancy was recognized at operation in 10 (24.4%) and in the laboratory in 16 (39%).

The authors emphasize that early carcinoma often cannot be differentiated from benign adenoma, that operation should not be delayed until positive signs of malignancy appear and that carcinoma in both single and multiple nodular

(2) Surgery 31:522-561, April, 1952.

goiters is common enough to warrant prophylactic thyroidectomy for all goiters unless there is a definite contraindication to surgery.

Only a node or nodes, found on removal to be "lateral aberrant thyroid," were palpable in the neck in 12 patients. In nine of these, exploration revealed the primary tumor in the homolateral lobe of the thyroid, indicating that "lateral aberrant thyroids" are in reality metastases in cervical lymph nodes.

[When the diagnosis of carcinoma of the thyroid is made by the pathologist and comes as a surprise to the surgeon, the patient's clinical course will probably be favorable. This course contrasts greatly with that of patients with clinically obvious carcinoma of the thyroid. I cannot be certain that the pathologist is in error, or even that the histologic criteria of carcinoma of the thyroid are adequately established. It does seem, however, that nodules should be removed before they reach the stage where they are clinically malignant. A nodule in the thyroid should have exactly the same significance as a nodule in the breast. The most skilled physician cannot be sure what he is palpating through the skin; therefore a histologic diagnosis is in order.—Ed.]

Physiologic Concepts of Thyroid Tumors as Revealed with Newer Tools of Study. Rulon W. Rawson and J. E. Rall[3] (Cornell Univ.) review recent advances in understanding the genesis of thyroid tumors. Even malignant tumors are not necessarily autonomous but may be produced by prolonged and excessive stimulation. In the single gland of a cretin, subjected to prolonged stimulation by the pituitary, trabecular, tubular, microfollicular, colloid and papillary cystadenomas have been observed. Similar tumors are seen in patients receiving thiouracil over many months. The functional capacity of benign adenomas was in doubt until the use of radioactive iodine proved that hyperfunction may occur. Although thyroid carcinomas can be produced in rats by prolonged administration of both a carcinogen (dibenzanthracene) and thiouracil, this has not been demonstrated in man.

Thyroid carcinomas usually do not function, but 46% collect enough radioiodine to produce an autoradiogram. This avidity for iodine was increased in 21 of 37 patients with metastatic cancer of the thyroid by giving a "thyroidectomizing" dose of radioiodine to eliminate the normal thyroid. The administration of thyroid-stimulating hormone caused a similar increase in iodine uptake by metastases in 6 of 16 patients. This clearly indicates that certain malignant tumors are not completely autonomous. Because thiouracil is known to aug-

(3) M. Clin. North America 36:639-662, May, 1952.

ment the effect of thyroid-stimulating hormone, this agent was given to 30 patients with metastatic cancer whose normal gland had been removed. A marked increase in iodine collec- tion in the metastases occurred in 21 cases (3 metastasizing struma, 9 follicular carcinoma, 6 papillary and follicular carcinoma, 2 papillary, 1 solid, and 1 Hürthle cell carcinoma). There were also failures in each of these categories, but some of these may have been due to an inadequate treatment period. When avidity of tumor tissue for iodine is increased, smaller doses may be given with greater effect. Before the use of thiouracil, the mean treatment dose of radioiodine was 148 mc. with 65% urinary loss; with thiouracil the mean dose is 96 mc. and only 33% is lost in the urine. Of 22 patients, 4 had significant resolution of pulmonary metastases and 6 had shrinking of palpable tumors. These principles of controlling cancer growth may lead to new discoveries of importance to cancer therapy in general.

[These valuable studies have paid off clinically, since the authors, by surgical and hormonal means, have induced neoplastic tissue to take up cancericidal doses of radiation. Of incidental interest is the fact that it took radioiodine to convince certain investigators that there is such a thing as a toxic nodule of the thyroid.—Ed.]

Indications and Contraindications for Treatment of Thyroid Cancer with Radioactive Iodine are discussed by William H. Beierwaltes[4] (Univ. of Michigan) on the basis of a study of 250 patients treated elsewhere and 24 of his own.

Total thyroidectomy with radical neck dissection remains the most effective treatment and should never be neglected for the sake of an experimental trial of radioactive iodine, I^{131}, alone. It is a prerequisite to I^{131} therapy because it prevents death from local growth and releases the pituitary from control, leading to excessive release of thyroid-stimulating hormone (TSH) which may stimulate metastases to a greater avidity for iodine. After neck dissection, x-ray therapy should be used when appropriate. Only then should I^{131} be considered.

Radioiodine may be used if the carcinoma is follicular, alveolar or papillary but not if it is undifferentiated. The value of I^{131} is related to the avidity of the cancer for iodine as shown by (1) a positive autoradiogram, (2) high uptake in the metastasis demonstrated by external counting of gamma emissions, (3) excretion of 30% of an administered dose of

(4) Ann. Int. Med. 37:23-30, July, 1952.

I^{131} in the urine in the first 48-96 hours after the dose or (4) low level of I^{131} in the circulating blood after a tracer dose. Response to radioiodine can be enhanced by increasing the TSH effect on metastases through total thyroidectomy, thiouracil administration and exogenous administration of TSH. Temporary contraindications include clinical myxedema, administration of desiccated thyroid or iodides and hypoplasia of bone marrow.

Squamous Metaplasia of Thyroid Gland. Weldon K. Bullock, George J. Hummer and James E. Kahler[5] (Los Angeles)

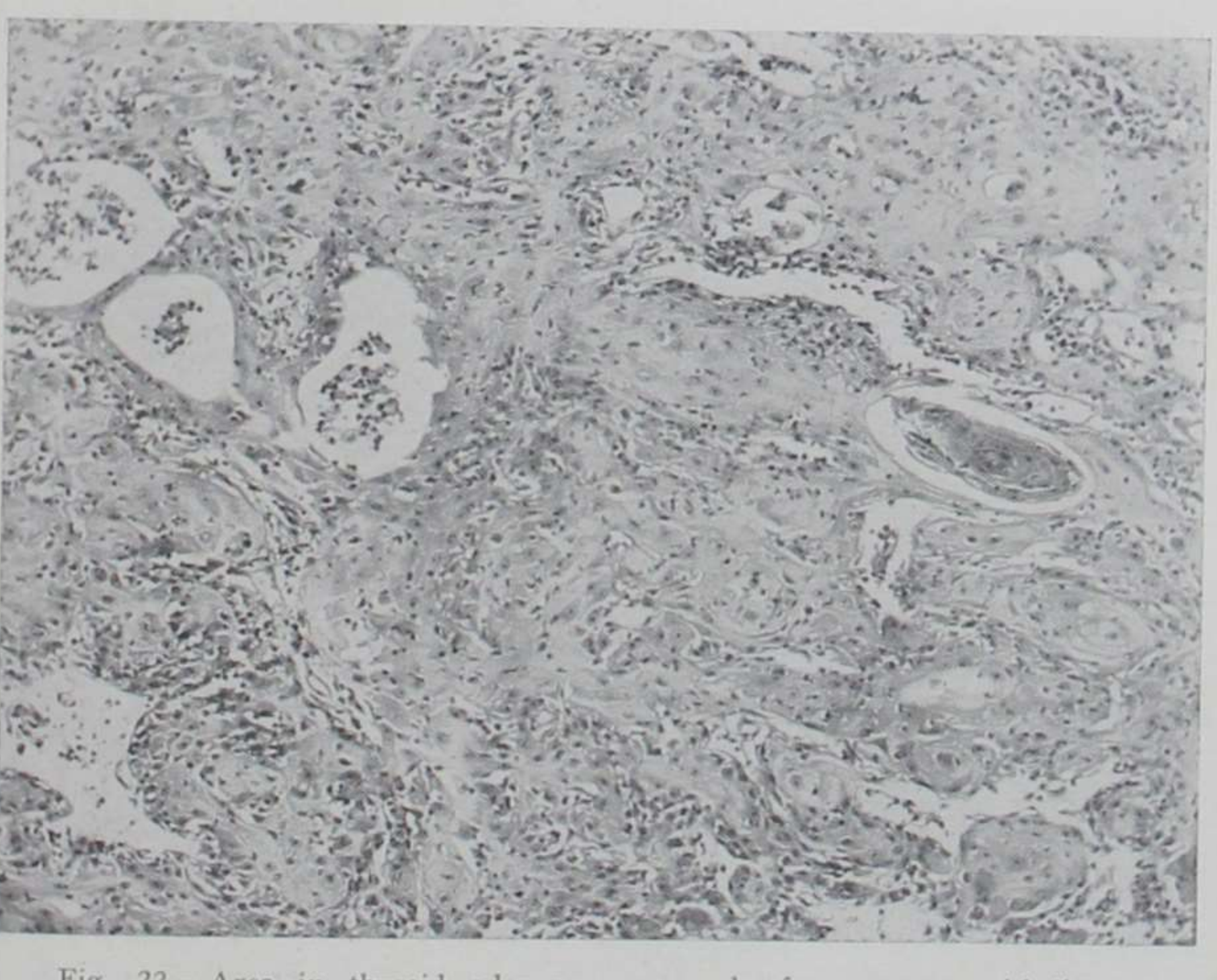


Fig. 22.—Area in thyroid adenoma composed of squamous epithelium with epithelial pearls and numerous inflammatory cells; reduced from × 100. (Courtesy of Bullock, W. K., *et al.*: Cancer 5:966-974, September, 1952.)

report 4 cases of this rare neoplasm and review 52 from the literature. In three patients, women aged 57, 18 and 71, the neoplasm was found in association with chronic thyroiditis, and in one, a woman, 53, it occurred in a thyroid adenoma. The embryonic rest theory is advocated by some authors to explain the unusual histologic picture (Fig. 22) in these cases, but Bullock *et al.* agree with Jaffé and Saxén that the

(5) Cancer 5:966-974, September, 1952.

squamous epithelium encountered in such glands is due to metaplasia resulting from attempts of the atrophic follicular epithelium to regenerate. Epidermoid metaplasia, when extensive, should be carefully distinguished from squamous cell carcinoma. In the four cases presented there is no evidence (up to three years after operation) to suggest that the squamous metaplasia is a precursor to squamous cell carcinoma of the thyroid.

Metastatic Carcinoma of Thyroid Gland as Initial Manifestation of the Disease. H. H. Searls, Orland Davies and Stuart Lindsay[6] (Univ. of California) report that of 260 patients with thyroid carcinoma treated surgically during the past 38 years, 26 had an admission complaint of a painless asymptomatic mass in or near the side of the neck. The thyroid gland was considered normal on clinical examination. When biopsy revealed thyroid tissue, re-examination of the gland occasionally revealed a suspicious area, but usually no tumor could be palpated. The age range of the 26 patients was 10-61 years; for the entire series of 260, it was 8-86 years.

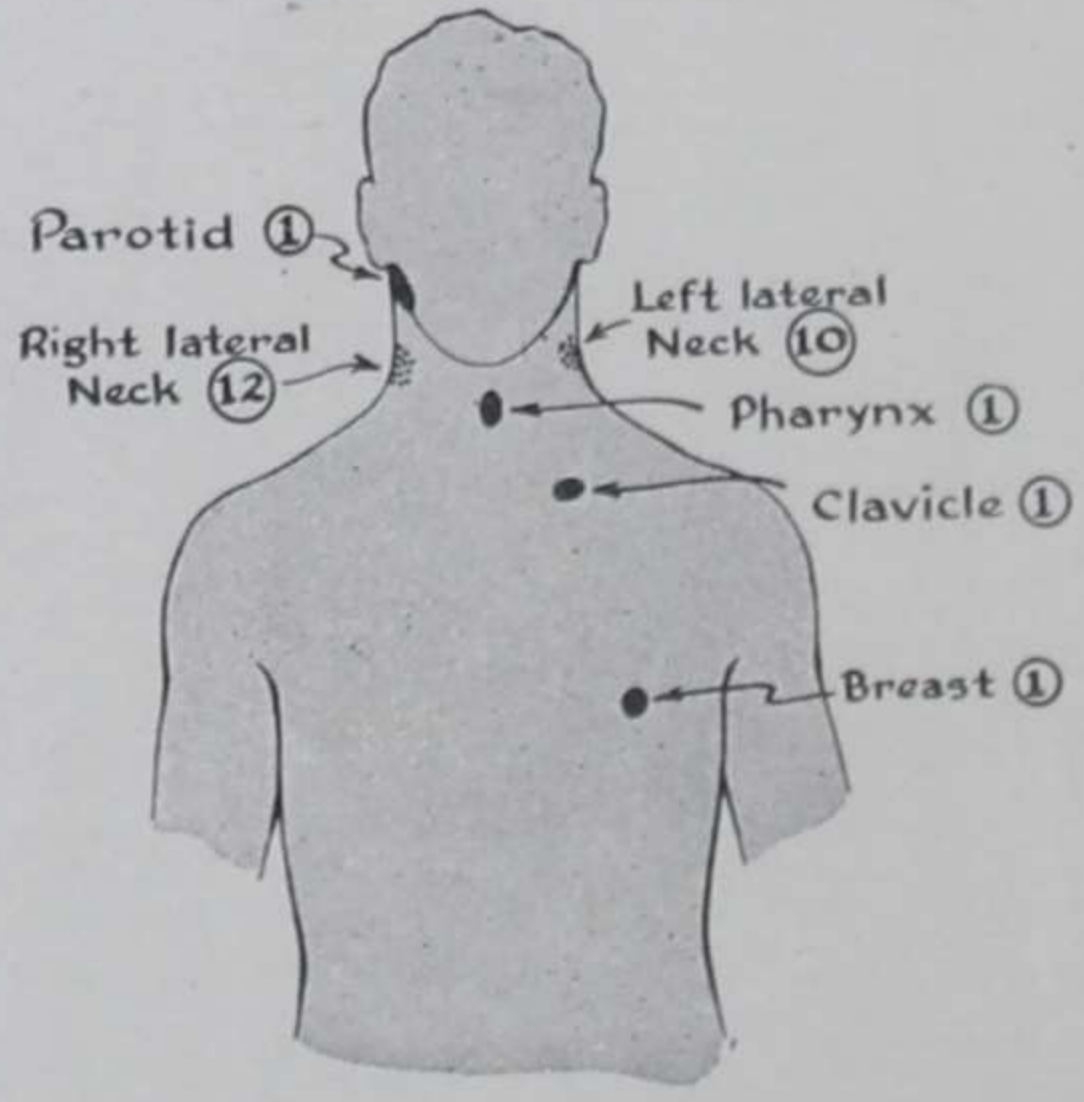


Fig. 23.—Location of metastatic tumors in 26 cases of thyroid carcinoma. (Courtesy of Searls, H. H., *et al.*: California Med. 76:62-65, February, 1952.)

The mass was usually on the side of the neck, but in four instances the sites were the clavicle, pharynx, breast and pa-

(6) California Med. 76:62-65, February, 1952.

rotid gland (Fig. 23). Most patients had been aware of the nodule for 1-4 years (range, 2 months to 18 years). Seventy-three per cent were female. The majority of patients were treated with total thyroid lobectomy on the side of the lesion, together with excision of palpable masses or radical neck dissection. Ten patients also received x-ray therapy. Histologically, the tumors in 22 of the 26 cases were papillary carcinomas. There was one embryonal cell carcinoma, and three tumors were reported to be benign, although in retrospect they are believed to be malignant. Follow-up showed 17 of the 26 patients to be alive, without evidence of recurrence, 1 month to 15 years after operation. Four were asymptomatic with known metastases 12, 10, 4 and 2 years after operation. Only four patients died as a direct result of cancer and metastases.

[Not so long ago these cases would have been called examples of "benign metastasizing adenoma." The fact that tissue taken from a metastasis in the clavicle cannot be differentiated from normal thyroid tissue makes one wonder about pathologists' criteria for the histologic diagnosis of thyroid carcinoma.—Ed.]

THE PARATHYROIDS, CALCIUM METABOLISM AND METABOLIC BONE DISEASES

I must backtrack somewhat on my statement in last year's YEAR BOOK that the action of the parathyroid hormone can be explained by the diuresis of phosphate which it produces. This statement is not entirely true, for it has been shown recently, chiefly by Dent (J. Bone & Joint Surg. 34-B:266, May, 1952) and by Fanconi and Girardet (this YEAR BOOK, p. 125) that phosphate loss causes osteomalacia, and not hyperparathyroid bone disease (Recklinghausen's disease of bone). It appears, then, that in addition to causing loss of phosphate, parathyroid hormone must also have direct effect on bone—a conclusion reached long ago by Collip and subsequently confirmed by Ingalls, Donaldson and Albright (J. Clin. Invest. 22:603-608, July, 1943). It is still necessary, of course, to invoke the phosphate-excreting power of parathyroid hormone to explain the low serum phosphate level characteristic of hyperparathyroidism.

As in other endocrine disturbances, the central nervous system in hypo- and hyperparathyroidism has come in for renewed interest. It is gratifying to note that urinary calculi are being recognized as symptoms of underlying metabolic diseases as well as the consequences of infection and stasis of the urinary tract. Fresh emphasis is being placed on the treatment of the underlying disease conditions, in addition to the emergency treatment of the patient who is passing a renal stone.

For a report of transient hypoparathyroidism following administration of radioiodine for thyrotoxicosis, see the article by Tighe (this YEAR BOOK, p. 94).—Ed.

Hypoparathyroidism

Postoperative Tetany. H. Wijnbladh[7] (Stockholm) presents data on 40 patients with tetany after operation for goiter. Ocular cataracts unpredictably occurred in five. They may develop as soon as seven months after thyroidectomy and occur in patients without evidence of tetany. Sluggishness, apathy, inaccessibility and negativism are frequent and complicate treatment because of lack of patient co-operation.

Diagnosis may be difficult. Aside from clinical tetany, subjective paresthesias are the most important symptom. Trousseau's phenomenon may be negative. Blood calcium should be

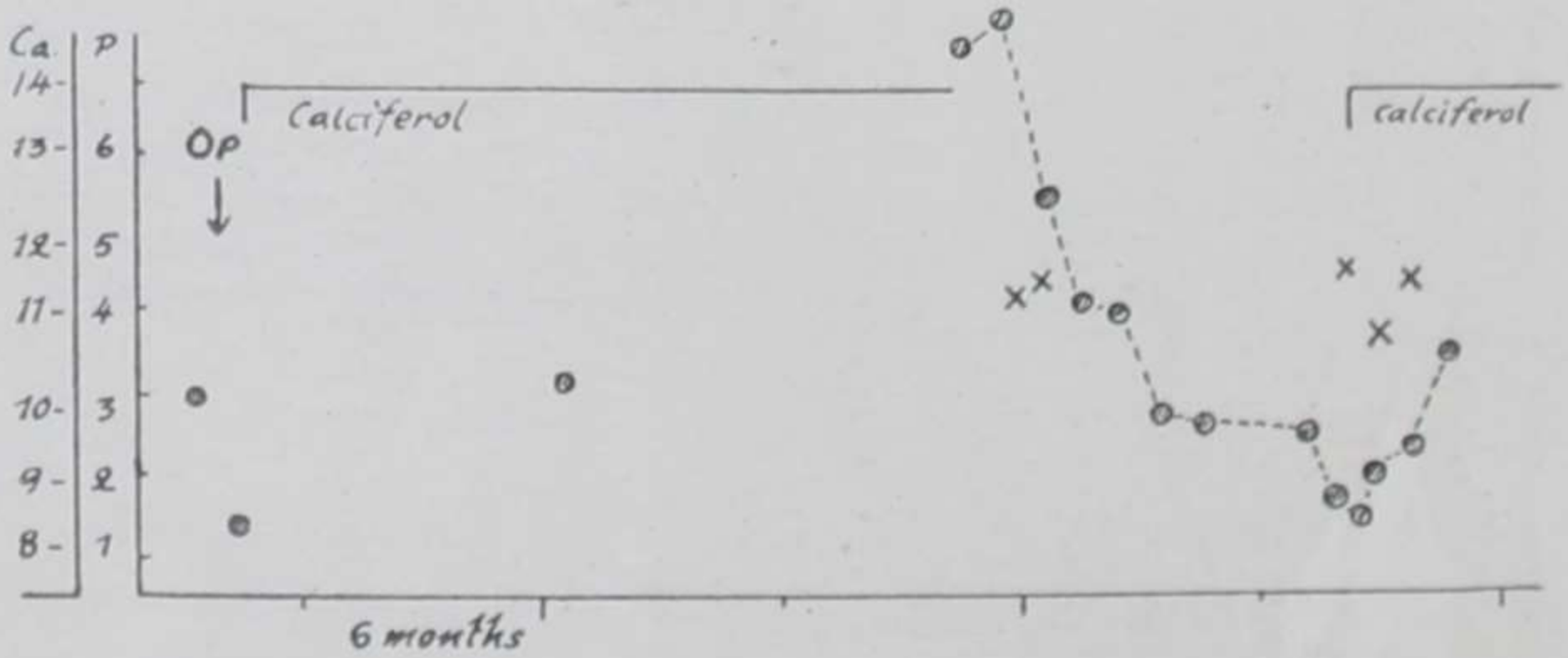


Fig. 24.—Calciferol intoxication. Administration of maintenance dose (15-10-15 drops daily) over six months caused elevation of blood calcium level and symptoms of renal failure. The latter subsided by degrees. Patient was again treated for tetany. (Courtesy of Wijnbladh, H.: Acta endocrinol. 10:1-16, 1952.)

determined before and the day after any operation on the thyroid gland. In this series, a drop of 10% or slightly less was found to indicate tetany, which will become manifest after a variable period of time. If either this test or clinical observation suggested tetany, repeated calcium estimations were made. Determinations of dializable calcium failed to yield information of practical value. Of particular importance is the fact that manifest tetany may be provoked by various "stressful" conditions such as menstruation, lactation or infections.

In the treatment of chronic tetany, calciferol, without additional calcium, produced regression of symptoms and elevation of the blood calcium to normal levels. Calciferol appears to be preferable to dihydrotachysterol (A.T. 10) because

(7) Acta endocrinol. 10:1-16, 1952.

it is less expensive and because, in many cases, dosage may be gradually reduced and therapy finally discontinued. Recovery is due to regeneration of hypertrophy of the parathyroid glands or residual parathyroid tissue. Since administration of either parathyroid hormone or A.T. 10 depresses parathyroid activity, the authors suggest that functional recovery of the parathyroids in patients treated with calciferol may indicate that calciferol is less harmful to regeneration.

In 2 of the 40 patients, calciferol produced untoward effects, in one about eight years postoperatively and after three years of continuous therapy and in the other after six months of maintenance therapy (Fig. 24). In each, renal failure developed. When calciferol therapy was discontinued, blood calcium levels decreased, symptoms of renal failure disappeared and renal function was restored to normal. Subsequently, tetany gradually reappeared and was controlled on a lower dose of calciferol.

[When one is comparing the clinical efficacy of vitamin D (calciferol) and dihydrotachysterol (A.T.10), it is useful to recall their actions on absorption of calcium from the intestine and excretion of phosphate through the kidney, as pointed out by Albright.

	Absorp. of Calcium from Intestine	Excretion of Phosphate by Kidney
Parathyroid hormone	+	+++
Dihydrotachysterol	++	++
Calciferol	+++	+

It will readily be seen that although vitamin D raises the blood calcium level, thereby bringing the patient out of tetany, it does not adequately flush out the phosphate which accumulates in the blood. As a result, the product of calcium × phosphate is elevated to the level at which metastatic calcification in soft tissue occurs. Consequently, vitamin D by itself is less effective in the management of hypoparathyroidism than dihydrotachysterol. It can, however, be used if aluminum hydroxide is given simultaneously in sufficient doses to adsorb phosphate in the intestine so that the rise in serum phosphate level is prevented. It should be emphasized that aluminum hydroxide can be expected to be effective only if the diet does not contain excessive amounts of phosphate, that is, for practical purposes, no milk or cheese. Parathyroid hormone is of no value in the prolonged treatment of hyperparathyroidism and is, indeed, contraindicated because its administration leads to the development of a refractory state.

Idiopathic hypoparathyroidism is frequently overlooked since the telltale thyroidectomy scar is not present to attract attention to the parathyroids. The symptoms may mimic the convulsive seizures of epilepsy or the stridor of asthma, or muscle spasm may cause joint stiffness similar to that found in arthritis. Chvostek and Trousseau signs will call the physician's attention to tetany, and the Sulkowitch test, by demonstrating the absence of calcium from the urine, will disclose the hypocalcemia which can be measured. To determine whether mental retardation and convulsive seizures will disappear, we have found it useful to see if the

intravenous administration of 1 Gm. calcium gluconate will restore the electroencephalogram to normal. (Schottstaedt, W., and Gordan, G. S.: California Med. 74:390-391, May, 1951.—Ed.]

Idiopathic Hypoparathyroidism: Analysis of 52 Cases, Including Report of New Case. Herman Steinberg and B. R. Waldron[8] (Jamaica, N. Y.) review the problem of the rare idiopathic variety of hypoparathyroidism, and report a new case.

Woman, 55, was hospitalized in September 1946 after suddenly awakening, screaming in the night, disoriented, incontinent and vomiting. A similar episode had occurred eight years before. A few hours after hospitalization she was alert. Examination revealed nothing; she refused lumbar puncture and left against advice. Four years later, she returned with carpopedal spasm which was relieved by calcium gluconate intravenously. She had had such attacks for 31 years, since nursing her third child; they had become a daily

TYPES OF THERAPY AND RESULTS

THERAPY	GOOD	FAIR	POOR
Conc. vit. D prep. plus Ca	8	1	5
A.T.10	13	0	0
A.T.10 plus Ca	6	0	0
Parathormone	3*	0	0
Cod liver oil plus Ca	3	0	0
Parathyroid transplants	0	0	3
Cod liver oil	0	0	2
Supp. Ca	0	1	1
Conc. vit. D prep.	0	1	1
A.T.10 plus conc. vit. D prep.	2	0	0
Calcium plus aluminum hydroxide gel	0	1	0
Parathormone plus Ca	0	0	1

*One showed resistance to the hormone after six years of therapy.

occurrence and sometimes lasted three days at a time. Attacks were often associated with nervousness, palpitations and an uncontrollable urge to such activity as rapid walking around the house or engaging passersby in rapid conversation. For four years she had had two or three epileptic seizures a year. Physicians had repeatedly attributed her attacks to "nerves" and prescribed sedatives. Family history revealed mongolism and polydactylism. Physical examination showed xanthelasma, dry puffy skin, cataracts and vitreous opacities, papilledema, edentia and normal neurologic status. Pertinent laboratory studies indicated serum calcium 7.2-7.6 mg./100 ml., phosphorus 5.3-7.4 mg.; faint or no precipitate on the Sulkowitch test and cerebrospinal fluid protein 70 mg./100 ml. Q-T interval was prolonged to 0.52 seconds. EEG was typical of grand mal. X-rays showed fine granular calcium deposits in the cerebrum and left biceps. Intravenous administration of 200 units of parathormone in the Ellsworth-Howard test produced normal phosphorus diuresis, ruling out pseudohypoparathyroidism.

(8) Medicine 31:133-154, May, 1952.

She was taught to test her Sulkowitch reaction daily and given 1 cc. of A.T. 10 daily and 1 Gm. calcium gluconate and 8 cc. gelusil® three times a day. She was advised not to drink milk because of the high phosphorus-calcium ratio. Follow-up to June 1951 revealed no complaints referable to hypocalcemia. Gradually, on the basis of the Sulkowitch test, her A.T. 10 requirements were reduced to 0.5 cc. three times a week.

Among the diagnostic criteria are: (1) low serum calcium level; (2) high serum inorganic phosphorus level; (3) no renal insufficiency, in itself a possible cause of hyperphosphatemia; (4) normal x-ray appearance of bones to exclude infantile rickets or adult osteomalacia, and (5) chronic tetany. According to 52 reported cases, the symptoms include tetany and convulsions in most, paresthesias, constipation, vomiting, psychoses and nervousness less commonly. The signs include cataracts (50%), poor dentition (36.5%), skin, nail and/or hair changes (25%), papilledema (13.5%), fungous infections (13.5%), mental retardation (7.7%), generalized physical retardation (5.8%), chronic conjunctivitis (3.8%), syndactylism (1.9%) and polydactylism (1.9%). A review of therapeutic methods is presented in the table. A.T. 10 used alone is evidently the drug of choice.

Familial Hypoparathyroidism: Report of Case. Idiopathic hypoparathyroidism is a relatively rare disease characterized by recurrent tetany, low serum calcium and high serum phosphorus levels and low urinary excretion of calcium. Other manifestations are epileptiform seizures, cataracts, dental defects, calcification of the basal ganglions or of the choroid plexus and increased bone density. R. Goldman, J. L. Reynolds, H. R. Cummings and S. H. Bassett[9] (Univ. of California at Los Angeles) report on one of three brothers, all of whom evidenced some hypoparathyroidism. The family tree (Fig. 25) also shows the incidence of diabetes. The fact that neither parent had parathyroid disease suggests that the disease may appear in juveniles because of a recessive hereditary factor.

Man, 28, first noted nocturnal leg cramps at age 10, but frank tetany did not appear until age 15, when he "froze" while trying to catch a football at team practice. The attacks were first diagnosed as epileptic seizures. He never lost his deciduous teeth which, by age 14, had gradually worn down to the gums. During adolescence, 18 permanent teeth erupted but were so imperfect that they had to be replaced with full dentures. Because of similar symptoms in two older brothers, careful studies were made that revealed low serum

(9) J.A.M.A. 150:1104-1106, Nov. 15, 1952.

calcium level. He went into the navy at 20 and was discharged after 2½ years of service following an attack of tetany.

Physical examination revealed a healthy adult. There were no cataracts. Chvostek's sign was always strong, but Trousseau's sign was never elicited. X-rays of the jaws revealed two poorly developed unerupted teeth without roots but with prominent dental membrane. Skeletal films showed increased bone density. Serum cal-

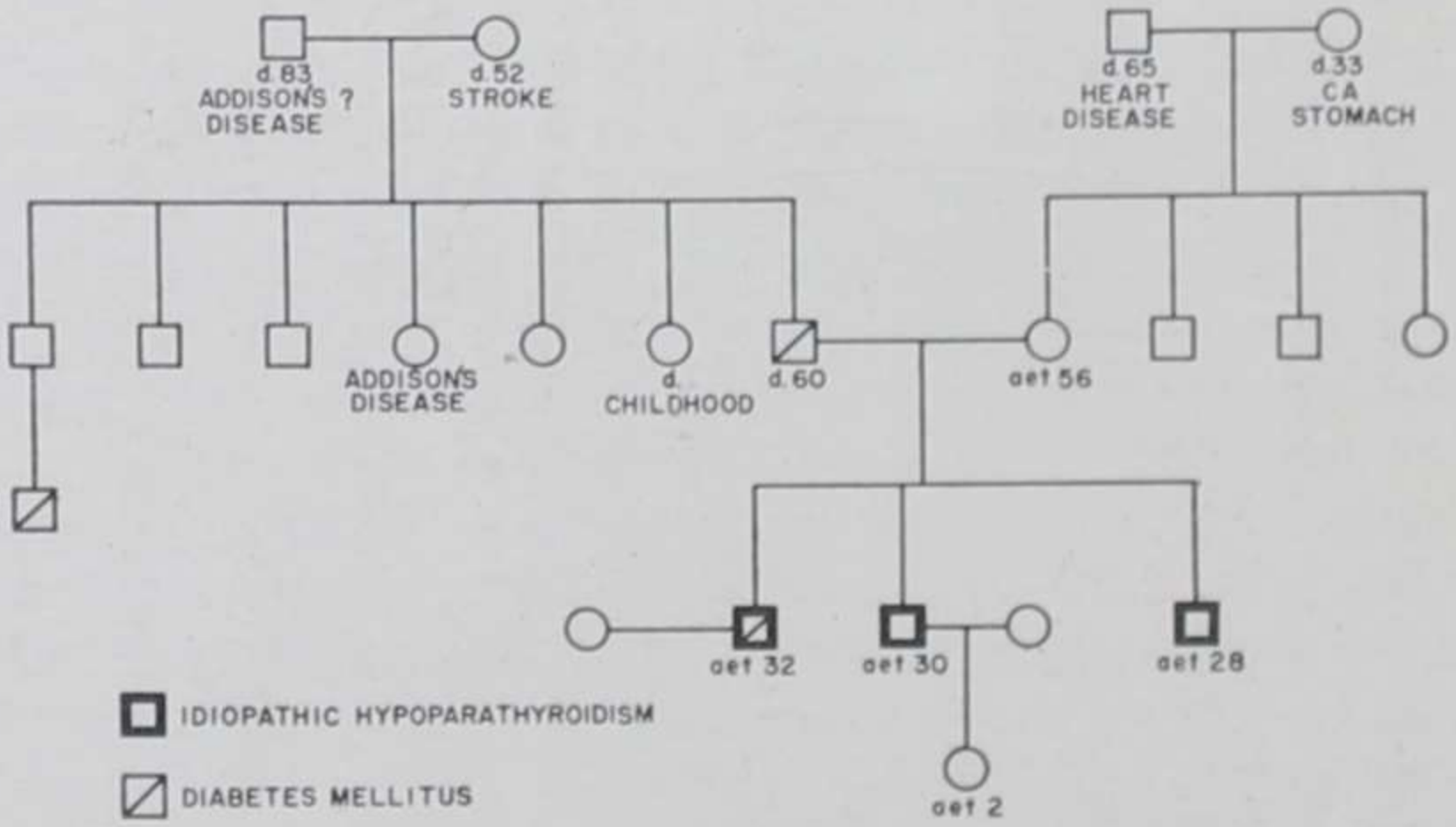


Fig. 25.—Family tree of three brothers with hypoparathyroidism. (Courtesy of Goldman, R., *et al.*: J.A.M.A. 150:1104-1106, Nov. 15, 1952.)

cium level ranged from 5 to 6.5 and phosphorus from 4.6 to 7.6 mg./100 ml. Daily urinary calcium was consistently below 20 mg. Renal function was normal. The ECG showed a prolonged Q-T interval. He was given 3.1 mg. dihydrotachysterol for two days, then 1.25 mg. daily. Chvostek's sign disappeared and serum calcium and phosphorus levels rose to normal.

Neurologic Manifestations of Idiopathic Hypoparathyroidism. John A. Simpson[1] (Univ. of Glasgow) presents two cases in detail to emphasize the occurrence of unilateral tetany, psychosis, mental deficiency, seizures, headache and weakness.

Case 1.—Boy, 9, had a solitary seizure at age 3 and was well until at age 5 fits began again, following chickenpox. They occurred in spells of several a day with long intermissions. Headache each morning led to hospitalization at age 8. It was observed that after a seizure there was a tonic spasm of the right leg with flexion and inversion of the foot. He was discharged with the diagnosis of idiopathic epilepsy and later classified as mentally defective. Severe headaches and blurred vision led to further examination the following year. Punctate opacities were seen in both lenses suggesting hypoparathyroidism. Chvostek's sign was present but Trousseau's required 30 minutes. He had typical major convulsions, carpopedal spasms, attacks of psychotic delirium and combative behavior. All

(1) Brain 75:76-90, 1952.

ceased when treatment corrected the low calcium and high phosphorus levels.

Case 2.—Woman, 46, was hospitalized because of convulsions. At age 28 she had had a "nervous breakdown" followed by 16 months of unusual fatigue, headaches and stiffness of hands in the morning. She was well for 14 years until a cataract was noted and removed. A year later, headaches and brief spells of dragging of the right foot were noted. These progressed to unilateral, then generalized, spells lasting as long as 90 minutes, during which she had no twitching and did not lose consciousness even though she was unable to speak. During tetany her scalp hair was shed, but it grew again when tetany was controlled with calciferol and calcium gluconate.

Familial Pseudohypoparathyroidism: Report of Two Cases is made by Helen Mackler, J. R. Fouts and J. W. Birsner[2] (Bakersfield, Calif.). Some characteristics of the disease were also noted in five other members of the family spanning three generations.

Pseudohypoparathyroidism is characterized by short stature, broad face, subnormal intelligence, unerupted teeth, thick skull, thick, short metacarpal and metatarsal bones, convulsive seizures, active or easily produced tetany, increased centers of ossification, electroencephalographic irregularities, calcification of the soft tissues, especially intracranial, hypocalcemia, hyperphosphoremia, hypophosphoruria, lack of response to parathormone and diminution of other glandular components.

Case 1.—Woman, 22, on hospitalization presented all the signs and symptoms characteristic of pseudohypoparathyroidism. On two previous admissions, at ages 2 and 7, she had been described as "short and squatty." She had a history of irregular attacks of convulsive seizure. At age 9 the fifth metacarpals were short, wide and curved with areas of decalcification in the central portion of the diaphyseal ends. Skull bones were greatly thickened. Serum calcium was 8.6 mg./100 cc. at one test and 7.9 mg. a few weeks later; BMR was approximately —3%.

At age 22, she was 53 in. tall and weighed 149 lb. Mental age was about 6 years. Amenorrhea had followed three menstrual periods at age 15 years. The voice was coarse and hoarse and the skin of the face florid. Trousseau's sign was readily elicited and not altered by hyperventilation. The calvarium was greatly thickened, the basal ganglions were calcified and there were only 12 erupted teeth. Metacarpals and metatarsals were characteristically shortened, with bowing of the radii. Injection of 200 units of parathyroid extract demonstrated inability to mobilize phosphorus in the urine; there was no concomitant change in the serum phosphorus.

(2) California Med. 77:332-334, November, 1952.

After six months on a high protein diet relatively low in phosphorus, with 1 Gm. calcium gluconate daily and about 150,000 units of vitamin D each week, the patient lost 30 lb. The complexion was no longer florid. She had progressed three grades in reading. Subcutaneous areas of calcification appeared and were expanding. The serum calcium level rose from 6.5 to 7.88 mg. and the phosphorus level decreased from 5.5 to 4.7 mg.

Case 2.—Brother, aged 29 months, presented more than enough characteristic signs and symptoms to indicate pseudohypoparathyroidism. Under the same regimen but with 100,000 units of vitamin D weekly, he improved.

[Albright has recently described a syndrome, "pseudopseudohypoparathyroidism," which should, at least, establish a record for the longest word in endocrinology. His patient with this syndrome has the characteristic short stature, round face, brachydactyly and ectopic ossification, but no tetany or abnormal serum calcium or phosphorus content (Tr. A. Am. Physicians 65:337-350, 1952). In this report, written in his usual, delightful fashion, Albright has described a method for eliciting a physical sign for brachydactyly: when the patient makes a fist, short metacarpals are indicated by a dimple instead of the usual knuckle.—Ed.]

Hyperparathyroidism

Mental Changes Associated with Hyperparathyroidism. Thomas E. Fitz and Bernard L. Hallman[3] (Emory Univ.) report on two hyperparathyroid patients in whom psychic manifestations were primary and delayed diagnosis for several months, almost disastrously in one.

Case 1.—Man, 55, had right lower abdominal colic with dysuria and frequency, chest pain on exertion, occipital headaches, unconscious spells and paranoid delusions and hallucinations. Serum calcium level was 14 mg./100 ml., phosphorus 2.1 mg., quantitative urinary calcium 614 mg./24 hours while on a low calcium diet. A solitary parathyroid adenoma was resected with complete return to normal.

Case 2.—Man, 52, complained of thirst, polyuria, easy fatigue, insomnia, failing memory, slow thinking, headache, low fever and leg cramps for six months. One month before hospitalization, he began to drink heavily, have rages and confusional states, became obscene and boisterous or depressed in turn. Hospitalized in an alcoholic delirium, he became drowsy and finally comatose. Serum calcium content was 19 mg. and phosphorus 2.2 mg./100 ml.; urinary excretion of calcium was 800 mg./24 hours. Exploration of the neck failed to disclose a tumor so the mediastinum was opened and a 3 cm. tumor was found near the arch of the aorta. After removal the calcemia and mental state became and remained normal.

In neither patient was the usual demineralization of bones, fractures, bone pain or renal calcinosis noted.

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(3) A.M.A. Arch. Int. Med. 89:547-551, April, 1952.

Tumors and Hyperplasia of Parathyroid Glands: Review of Pathologic Findings in 140 Cases of Primary Hyperparathyroidism is reported by Lewis B. Woolner, F. Ramond Keating, Jr., and B. Marden Black[4] (Mayo Clinic). The material consisted of 115 cases of single adenoma, 11 of multiple adenoma or adenomatosis, 12 of primary water-clear hyperplasia and 2 of carcinoma.

Histologically, adenomas may be composed of small or large chief cells, transitional water-clear cells, wasserhelle cells or oxyphils. About two-thirds could be classified according to a dominant cell type; the others showed mixtures of several or all types of cells. The chief cell adenoma was the commonest type.

The single adenomas varied in weight from approximately 25 mg. to 101 Gm. Some gross relation was evident between the size of adenoma and the degree of hyperfunction.

Five cases of multiple adenoma or adenomatosis were associated with hypoglycemia. Proved tumor of the pituitary gland or acromegaly was noted in three of these. The parathyroid changes suggested a primary nodular hyperplasia rather than formation of a true tumor (adenoma).

In the cases of primary water-clear hyperplasia, the weight of hyperplastic parathyroid tissue removed surgically varied from 760 mg. to 52.5 Gm. Two to four or more masses of parathyroid tissue may be found in the neck. Histologically, primary hyperplasia is uniform throughout, only large water-clear cells being present. In exceptional cases, an admixture of smaller clear cells or a few chief cells may be found. Histologically, hyperplasia may be separated readily from secondary hyperplasia of the parathyroids.

Hyperfunctioning, metastasizing carcinoma of the parathyroids is rare. Only six cases with metastasis to the viscera or lymph nodes have been reported. The microscopic appearance of a parathyroid tumor is not indicative of its potentialities. Metastasizing carcinoma of the parathyroids may be malignant histologically and show anaplasia and mitotic figures, but it may also appear histologically "benign" and for practical purposes, aside from invasiveness, may be indistinguishable from a chief cell adenoma with small regular nuclei.

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(4) Cancer 5:1069-1088, November, 1952.

Invasive tumors of the parathyroids that show wide infiltration of the surrounding tissues should be classified as locally invasive carcinoma regardless of the cytologic appearance. Carcinoma of the parathyroids usually is a slowly growing neoplasm. Death is generally due to the effects of hypercalcemia rather than to extensive metastatic spread of the tumor.

Primary Hyperparathyroidism. Rosemary Murphy, Lewis M. Hurxthal and George O. Bell[5] (Lahey Clinic) present an analysis of 25 cases. Diagnosis was proved by exploration in 24 and at autopsy in 1. Pathologic diagnosis was adenoma in 24 and hyperplasia in 1. Four patients required more than

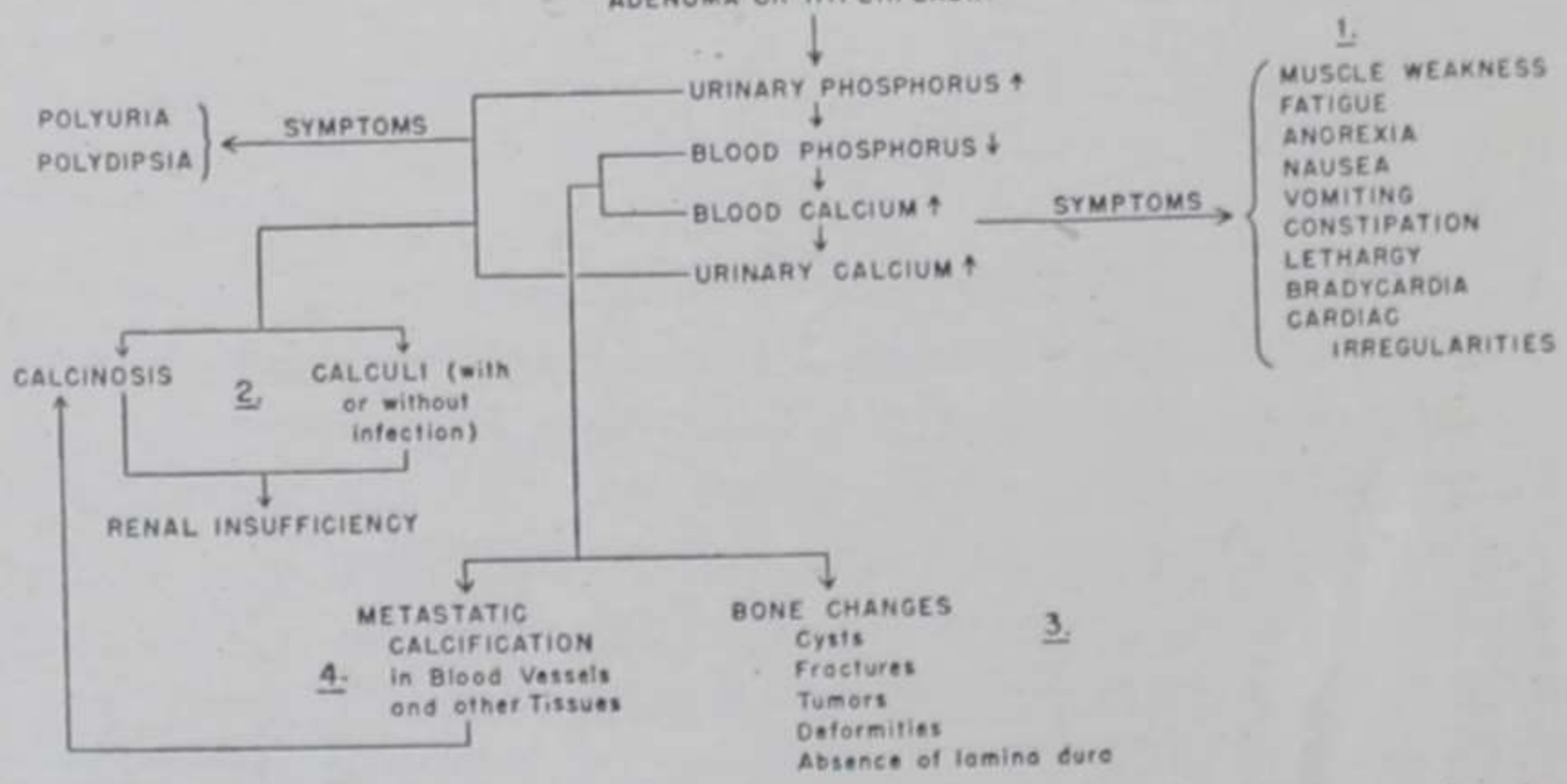

Fig. 26.—Relation of chemical findings to development of symptoms of primary hyperparathyroidism. (Courtesy of Murphy, R., *et al.*: A.M.A. Arch. Int. Med. 89:783-796, May, 1952.)

one operation before the adenoma was discovered. Ages ranged from 16 to 74, and 19 patients were females.

The estimated duration of symptoms before diagnosis varied from 1 to 23 years. The ultimate effect of an excess of parathyroid hormone is to increase the transport load of serum calcium, with production of varied systemic symptoms apparently caused by the elevated serum calcium and of secondary symptoms due to deposition of calcium in certain tissues and withdrawal of calcium from the bones (Fig. 26). Presenting symptoms were: bone pain, nine patients; renal colic, five; systemic symptoms (weakness, fatigability), three; gastrointestinal symptoms (constipation, nausea, vomiting, anorexia and cramplike abdominal pain), three, and fractures, muscle pain, cysts of jaw, urinary symptoms and skin disease, one

(5) A.M.A. Arch Int. Med. 89:783-796, May, 1952.

each. Systemic symptoms are vague; they simulate remarkably those of many functional states and are often misinterpreted for long periods. All complaints were distributed as follows: weakness and fatigability, 10 patients; gastrointestinal symptoms, 9; muscle pain, 5; weight loss, 3; renal colic, 7; frequency and nocturia, 6; polydipsia, 5; hematuria, 1; dysuria, 1; bone pain, 13; deformities, 4; loss of stature, 4; lump in the jaw, 4, and fractures, 2. Bone disease, characterized by rarefaction, with or without bone cysts, was present in 20. The lamina dura was absent in only 5 of 11 patients on whom information was available; in five of the six patients with intact lamina dura there was no evidence of bone disease and the alkaline phosphatase level was normal. The other patient had minimal bone disease, a slightly elevated alkaline phosphatase level and symptoms of only one year's duration. Paget's disease (which continued to progress after parathyroidectomy) and hyperparathyroidism coexisted in two women. Renal calculi were present in 12 patients. Blood calcium, phosphorus and alkaline phosphatase values may vary widely. A lowered serum protein level may mask an otherwise elevated serum calcium level. Renal insufficiency may cause elevation of the phosphorus value with or without an associated depression of the calcium values. The alkaline phosphatase is normal in the absence of bone disease or excessively high if Paget's disease is coexistent.

Tetany, the most frequent postoperative complication, occurred in 13 patients and may occur in any patient, although it is more frequent in those with greatly elevated preoperative calcium and/or alkaline phosphatase levels. One patient had a psychosis concomitantly with the postoperative fall in serum calcium to normal; otherwise response to treatment was excellent in every case.

Case of Palpable Parathyroid Tumor with simultaneous fractures of the necks of both femora is presented by W. D. Park and P. G. Swann.[6]

Man, 26, four months before hospitalization complained of a painful swelling of the right knee following minor trauma. The effusion gradually subsided. A month later increasing anorexia, nausea and occasional vomiting developed, accompanied by weight loss, lassitude, constipation and polyuria. Two weeks before admission severe cramplike pains developed in the muscles of the legs

(6) Brit. M. J. 2:1185-1186, Nov. 29, 1952.

and trunk but rarely affected the arms. While walking, he collapsed with severe pain in both hips and was hospitalized.

Both hips were in position of flexion. There was a well defined swelling, 2.5 cm. in diameter, in the neck to the left of the midline and below the level of the cricoid cartilage. It felt much like a thyroid adenoma. Blood pressure was 115/80.

Roentgenography showed fractures of the necks of both femora. The general trabeculation of the upper ends of the femora was obviously coarse and abnormal, and there was pronounced thinning of the cortex. Other bones, especially the humerus and small bones of the hand, showed decalcification. The characteristic cystic appearance of hyperparathyroidism was poorly shown. No renal calculi were seen.

Biochemical assay revealed: serum calcium, 18.8 mg./100 ml.; serum phosphorus, 3.4 mg.; blood urea, 74 mg.; serum alkaline phosphatase, 43.5 King-Armstrong units; serum albumin, 3.8 Gm.; serum globulin, 3.4 Gm.; hemoglobin, 74%. Urine contained a trace of albumin, but no Bence Jones proteose was detected.

The fractures were treated by extension. At surgery a pear-shaped cervical mass, $5 \times 3 \times 1.5$ cm., immediately below the left lobe of the thyroid was removed. It weighed 17.6 Gm., and its histologic appearance was that of a simple parathyroid adenoma. Postoperatively, 10 units of parathormone was given every 12 hours. Vitamin D_2 and calcium lactate, 3 Gm., were given daily. In 24 hours serum calcium fell to 13.6 mg./100 ml. and to 7.9 in the next 12 days. The patient had one episode of acute urinary suppression. Several attacks of frank tetany were controlled by calcium gluconate given intravenously. Parathormone dosage was increased to 20 units twice daily. A high carbohydrate diet with iron and vitamin C was given. Pain disappeared. Weight increased 19 kg. in three months. X-rays of bones taken 10 months later showed complete restoration of the normal pattern.

[This case provides an exception to Albright's law, which states: "Given a patient with hyperparathyroidism and a lump in the neck, the lump is not parathyroid."—Ed.]

Primary Hyperplasia of Parathyroid Glands with coincident duodenal ulcer is reported by Hollis L. Albright (Boston Univ.) and Richard C. Kerr[7] (Massachusetts Mem'l Hosp.).

Man, 48, with pain in the right flank had had renal stones for 20 years; 2 years before study two alveolar cysts of the maxilla were removed and diagnosed as benign giant cell tumor. At that time routine urinalysis gave normal results. Abdominal pain and hematemesis were caused by duodenal ulcer. Pyelograms showed bilateral renal stones. Physical examination revealed nothing remarkable other than moderate hypertension. Serum calcium content was 12.8 mg./100 ml., phosphorus 2.5 mg. and alkaline phosphatase 4 Bodansky units. He had severe anemia and urine study showed 1 + Sulkowitch, 1 + albumin and many white and red cells. X-rays of

(7) J.A.M.A. 148:1218-1221, Apr. 5, 1952.

skull, ribs and pelvis showed no bone abnormality. At operation, oblong parathyroid tumors were removed from behind each lower pole of the thyroid gland. B. Castleman diagnosed the tumors as primary hyperplasia of the parathyroids. Serum calcium and phosphorus levels gradually returned to normal. The duodenal ulcer continued to give some distress and 19 months after operation he died of a massive hematemesis.

Primary parathyroid hyperplasia is said to constitute 9% of all hyperparathyroidism and is clinically indistinguishable from that caused by adenoma. Primary hyperplasia is readily differentiated histopathologically from that secondary to renal disease. A much higher incidence (25%) of upper gastrointestinal symptoms has been found in primary hyperplasia than in adenoma. Excessive ingestion of calcium and phosphorus in milk and antacids taken for ulcer symptoms cannot, however, be shown to result in primary hyperplasia of the parathyroids. Such medication, when there is hyperparathyroidism, can cause parathyroid poisoning with nausea, emesis, lethargy and prostration. Thus intractable vomiting in ulcer patients, without x-ray evidence of gastric retention, would point to hypercalcemia.

[I am greatly surprised to read that in this case of proved primary parathyroid hyperplasia, the Sulkowitch reaction in the urine was only 1 plus. Hypercalcuria, as shown by the Sulkowitch test, is practically a *sine qua non* for the diagnosis of hyperparathyroidism. This patient appears to be exceptional. If it were not for the histologic diagnosis, I should have thought this case an example of "pseudohyperparathyroidism." See the report by McQueen (this YEAR BOOK, p. 118).—Ed.]

Primary Hyperparathyroidism (Adenoma) Simulating Sarcoidosis. H. W. Salmon and G. G. Meynell[8] report a diagnostic problem.

Woman, 33, hospitalized May 1950 with a diagnosis of rheumatism, for several years had complained of nocturnal pains in limbs and back which had become more persistent and severe. For three weeks she had noticed swelling of her ankles at night, frontal headaches, palpitations, slight constipation and loss of 7 lb. She was a pale, thin woman with congenital absence of the left wrist and hand. Red blood cell count was 3,500,000. A chest x-ray was initially interpreted as normal. A large rarefaction was seen in the proximal phalanx of the right index finger suggesting sarcoidosis. Decalcification of bones was noted on review of the chest film. Metastatic calcification of the lungs and cornea was noted. Serum calcium content was 16 mg./100 cc., phosphorus 4 mg., alkaline phosphatase 14 King-Armstrong units. Intravenous pyelograms showed bilateral nephrocalcinosis and impaired excretion of dye. A parathyroid adenoma weighing 17.5 Gm. was removed. Postoperative tetany was

(8) Brit. M. J. 2:1440-1442, Dec. 15, 1951.

treated with intramuscularly administered calcium gluconate. She was discharged symptom free despite residual renal damage.

Because sarcoidosis may cause similar bone lesions, high serum phosphatase levels, hypercalcemia, hypercalcuria and kidney stones, the mistaken diagnosis of hyperparathyroidism

CORRESPONDENCE BETWEEN HYPERPARATHYROIDISM AND SARCOIDOSIS

	Hyperparathyroidism	Sarcoidosis
Bone Changes	Generalized decalcification, cystic areas, or nil	Localized decalcification, cyst-like areas in bones, of hand, feet, and occasionally spine, or nil
Serum calcium	Generally raised	May be raised
Serum phosphorus	Low—except with retention by damaged kidneys	Usually normal; may be raised by associated renal changes
Alkaline phosphatase	Raised, with bone changes	May be raised (liver, etc.)
Serum proteins	Normal or low. A./G., normal	Raised; hyperglobulinaemia A./G., inverted in active phase
Urine	Hypercalcuria and albuminuria may occur in both disorders	
Kidneys	Metastatic calcification or stones	Sarcoid lesions or associated stones
Heart	Similar cardiographic changes are described	
Lungs	Radiographic similarity may occur	
Eyes	Metastatic calcification and band keratopathy may occur	

may be made. Conversely, whenever sarcoidosis cannot be confirmed by biopsy, the diagnosis of hyperparathyroidism should be considered. A comparison of the two diseases is given in the table.

"Milk Poisoning" and "Calcium Gout." E. G. McQueen[9] (Univ. of Queensland) reports on a patient who showed no evidence of hyperparathyroidism, pre-existing renal damage or alkalosis to explain his unusual reaction to drinking large quantities of milk which caused metastatic calcium deposition and goutlike pain and inflammation.

Man, 56, was admitted in 1950 to the psychiatric service with loss of energy, insomnia, irritability, depression, weight loss and loss of libido. These symptoms of six months' duration dated to the onset of drinking about a gallon of milk a day in addition to taking amphojel® and alkaline powders, alternately, a month at a time, for a duodenal ulcer. There were painful lumps over the left wrist and elbow and white, chalklike plaques on the sclera of each eye. X-rays revealed calcium in the iliac and radial arteries, elbow, wrist and hip and penis. Albuminuria with occasional hyaline casts was found. Urea clearance was 16% of normal. Serum calcium content was 12.5 mg./100 cc., phosphorus 3.9 mg. and alkaline phosphatase 12 King-Armstrong units. Symptoms and signs cleared rapidly with a

(9) Lancet 2:67-69, July 12, 1952.

low calcium diet. However, he was a milk addict and relapsed. On one occasion he even seized his granddaughter's baby bottle. This behavior was attributed to his search for relief from his ulcer pain.

[The syndrome of "pseudohyperparathyroidism" was first described by Burnett *et al.* (New England J. Med. 240:787, 1949). To my knowledge, excess intake of milk alone has not been held responsible for the syndrome. Simultaneous ingestion of soluble alkali is required. Consequently, the condition is almost entirely restricted to patients with refractory peptic ulcers.—Ed.]

Other Disorders of Calcium Metabolism

Differential Diagnosis and Therapy of Hypercalcuria and Nephrolithiasis is reviewed by E. Sommer.[1] Kidney stones are often the result of a specific bone, renal or endocrine disease and adequate treatment depends on recognition. Whether oxalate, phosphate or urate, stone growth depends on hypercalcuria, easily diagnosed by the Sulkowitch test.

Diseases in which hypercalcuria may also be found include (1) urinary tract infections; (2) osteoporosis, either idiopathic or secondary to immobilization, climacterium, senility, Cushing's disease or acromegaly; (3) overdosage with vitamin D or A.T. 10; (4) Boeck's disease with bone changes; (5) malignant metastasis to bone and multiple myeloma, and (6) Paget's disease. Relatively symptom-free chronic urinary infection may lead to hypercalcuria. When stones appear, urine cultures must be made and any infections treated. Immobilization osteoporosis results if the osteoblasts are deprived of the normal stimulation of mechanical stress. Calcium liberated by bone resorption cannot be utilized for bone formation and is excreted. As much as 24 Gm. calcium may be lost in five to six weeks. Hypercalcuria is only temporary, for equilibrium is finally established between calcium deposition and resorption. Therapy consists of shortening the immobilization and increasing fluid intake to prevent stone formation.

Postmenopausal and senile osteoporosis are essentially the same. The primary disease is a loss of normal estrogen or androgen stimulation of the osteoblasts. Here too, calcium excretion first increases, then returns to normal as calcium uptake and discharge are equalized. When treatment is started the uptake of calcium by the porotic bones results in decreased calcium excretion. A suggested plan is combined estrogen-androgen therapy consisting of 0.5-1.0 mg. stilbestrol and 10-

(1) Schweiz. med. Wchnschr. 82:661-666, June 21, 1952.

20 mg. methyltestosterone daily for four to six weeks with a periodic 10 day interval of rest. Osteoporosis is only one feature of Cushing's disease but the resulting pain and renal stones may be the first signs noted. Overproduction of cortisone-like hormones by the adrenal cortex causes breakdown of the matrix; this can be counteracted by testosterone which makes the bone denser and decreases hypercalcuria. The origin of osteoporosis in acromegaly is not understood; it is not as severe as in Cushing's disease and responds to estrogen therapy.

Hypercalcemia and hypercalcuria resulting from overdosage of vitamin D or A.T. 10 can be prevented with the help of daily Sulkowitch tests. For overdosage, a diet poor in calcium and phosphorus and forced fluids are prescribed. Phosphorus absorption can be decreased with aluminum hydroxide, thereby reducing the tendency to abnormal calcification. Immobilization is to be avoided. The variable hypercalcemia and hypercalcuria sometimes seen in Boeck's sarcoid is not well understood. It can be differentiated from hyperparathyroidism by the normal serum phosphorus level and bony changes restricted to hands and feet.

Metastasis to bone and multiple myeloma may lead to hypercalcuria, hypercalcemia and stone formation. Phosphatase level may be elevated but the x-ray picture usually differs from other conditions associated with calcium loss.

The cause of Paget's disease is unknown, but in the early acute stages and with immobilization severe hypercalcuria can appear. Blood calcium content can rise to critical levels and cause chemical death; calcium and phosphorus intake must therefore be low and fluid intake high.

Primary hyperparathyroidism, whatever the cause, produces hypophosphatemia, hypercalcemia, elevated serum alkaline phosphatase level, hypercalcuria and typical bone changes. With all of these signs, diagnosis is easy. However, bony changes result only from negative calcium balance and may therefore not be seen in milk drinkers and cheese-eaters. Hypercalcuria is the most consistent sign in this disease. Phosphatase level rises when there are bone changes and often there is loss of lamina dura in the teeth. When primary hyperparathyroidism is diagnosed, treatment is necessarily surgical. When bony changes are most prominent, they must be differ-

entiated from polyostotic fibrous dysplasia of Jaffe-Lichtenstein, in which the blood chemistry is not abnormal and changes are unilateral or segmental, often associated with hyperostosis of the skull. Similarly, Albright's syndrome of polyostotic fibrous dysplasia with premature puberty and cafe-au-lait spots must be considered.

In secondary hyperparathyroidism, hyperplasia results from the stimulus of low blood calcium, usually due to disturbed calcium nutrition (osteomalacia) or renal insufficiency.

SUMMARY OF DISEASES WITH DISTURBED CALCIUM METABOLISM
(d = deceased, n = normal, h = high)

DISEASE	SERUM VALUES			URINARY CALCIUM
	Ca	P	Alkaline Phosphates	
Urinary tract infection	n	n	n	n-h
Osteoporosis in:				
immobilization	n	n	n	n-h
postmenopause	n	n-h	n	n-h
senility	n	n	n	n-h
Cushing's disease	n	n	n	n-h
idiopathic form	n	n-h	n	n-h
acromegaly	n	n-h	n	n-h
Overdosage of vitamin D or A.T. 10	h	n-h	d-n	h
Boeck's disease	n-h	n	n-h	n-h
Bone metastasis, multiple myeloma	n-h	n	n-h	n-h
Paget's disease	n	n(-h)	hh	n-h
Primary hyperthyroidism	h	d	h	h-hh
Secondary hyperthyroidism	n-h	n-d	n-h	n-h
Renal rickets	d-n	h-n	n-h	h
Renal acidosis (nephrocalcinosis)	d-n	d-n	h-n	h
Fanconi's syndrome	n-d	d-n	h-n	h
Idiopathic hypercalciuria	d-n	d	h-n	h

In renal insufficiency, phosphorus retention leads to lower blood calcium level which stimulates the parathyroids. Normal calcium values may be established in blood at the expense of bone.

Nephrocalcinosis is due to a poorly understood noninflammatory disturbance of the tubules which results in inability to excrete sufficiently acid urine and leads to acidosis and hypercalcuria. There is a striking tendency to stone formation and calcification of renal parenchyma. Treatment consists of citrate-containing fluids and vitamin D to combat the osteo-

malacia. When the acidosis is reversed the hypercalcuria and tendency to calcification abate.

In Fanconi's syndrome, excretion of amino acids, lactic acid and β-oxybutyric acid is increased; there may be hypophosphatemia and albuminuria. Severe hypercalcuria can lead to stone formation and weakening of bones. The disease, apparently hereditary, is treated with base and high phosphorus diet.

In idiopathic hypercalcuria, a disease of unknown origin, blood and skeletal changes result from continued calcium loss; lowered serum calcium level may cause secondary hyperparathyroidism. Alkalis do not lower calcium excretion as in renal acidosis; osteoporosis responds well to increased calcium intake but this leads to increased stone formation. Treatment combines a calcium-poor diet, with oxalate-containing foods eliminated, and increased fluid intake.

The changes in blood calcium, phosphorus and alkaline phosphatase and urinary calcium contents in these diseases are summarized in the table.

[This valuable review leaves little room for disagreement. The author points out that Paget's disease may be associated with hypercalcuria, particularly if the patient has been immobilized. As Snapper showed some years ago, hypercalcuria is also found frequently in ambulatory patients with Paget's disease of bone. For this reason, I dislike the routine administration of vitamin D and calcium to these patients. I have seen kidney stones develop after this regimen.

It is also true that the blood calcium and phosphorus levels are usually normal in polyostotic fibrous dysplasia, but the alkaline phosphatase content may be greatly increased, and in rare instances the blood calcium level may rise, particularly with fracture and immobilization.

The recent studies of Dent, and Fanconi and Girardet, referred to in the introduction to this chapter, have shown that there are all gradations of the Fanconi syndrome. At one extreme are found patients who show nothing but a chronic urinary loss of phosphate with osteomalacia. At the other end of the scale are seen patients who have the complete defect: aminoaciduria, albuminuria, rickets, renal glycosuria, hypercalcuria, hypophosphatemia without hypercalcemia, and acidosis without azotemia. Osteomalacia, manifested radiologically by Milkman's syndrome, apparently results from the mineral loss. Since Erdheim demonstrated many years ago that secondary hyperparathyroidism may result *from* osteomalacia, it seemed possible to me that the phosphate loss might be the result of, rather than the cause of, osteomalacia. However, Professor Fanconi assures me that he has found normal parathyroid glands in patients with this syndrome, so the phosphate loss must be primary and causative.—Ed.]

Osteomalacia: Report on Two Cases with Milkman's Syndrome is presented by Harald A. Salvesen and Jens Böe[2]

(2) Acta med. scandinav. (supp. 266) 142:863-874, 1952.

(Rikshosp., Oslo). Osteomalacia is a distinct clinical entity readily differentiated from other generalized osseous diseases by serum calcium and inorganic phosphorus determinations. Patients have been divided into three types. (1) Those without compensatory overactivity of the parathyroids have low serum calcium and normal phosphorus levels; (2) those with sufficient parathyroid overactivity to maintain serum calcium at a normal level have a low serum phosphorus, and (3) those

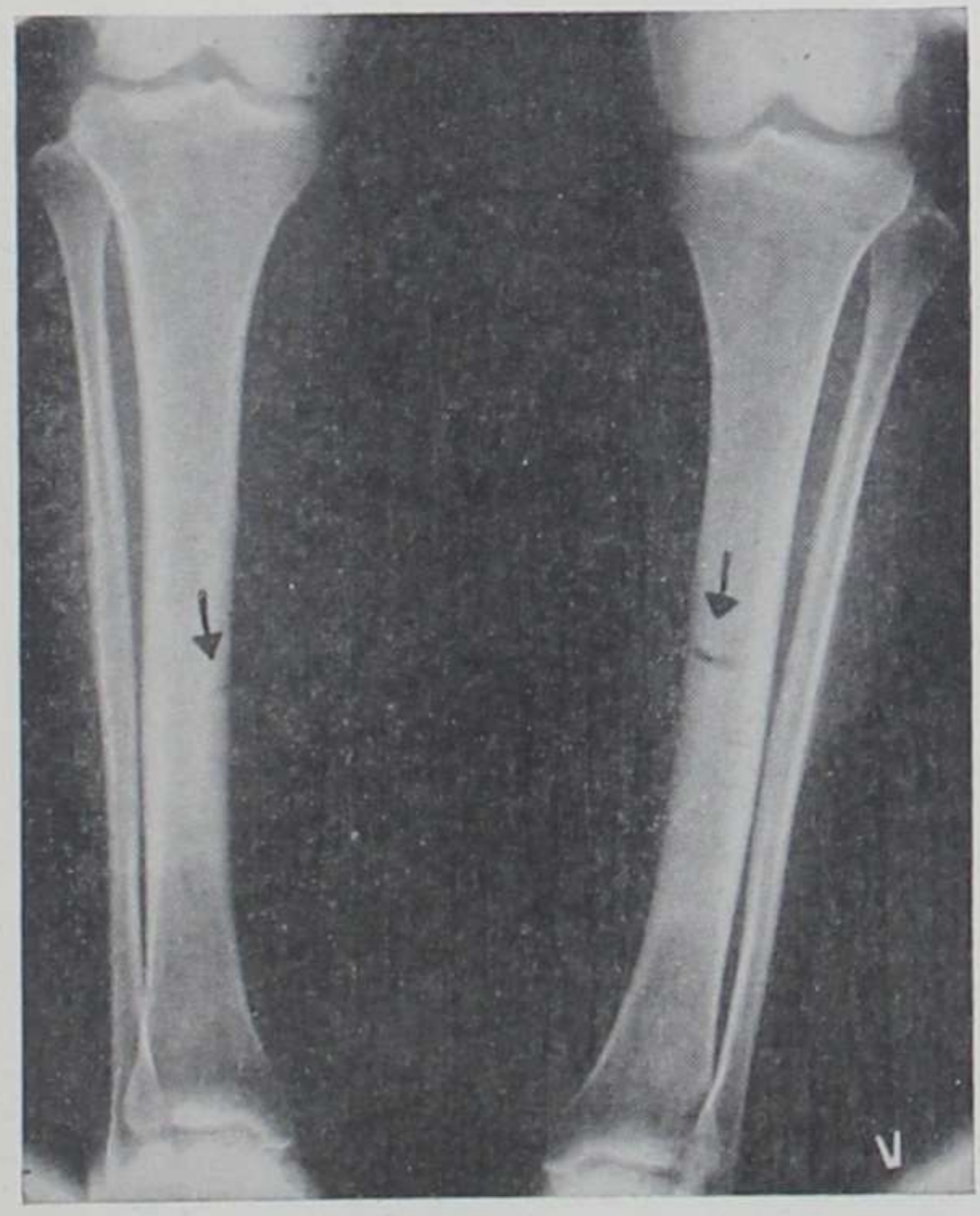

Fig. 27.—Pseudofractures (Milkman) of both tibiae. (Courtesy of Salvesen, H. A., and Böe, J.: Acta med. scandinav. (supp. 266) 142:863-874, 1952.)

with insufficient parathyroid overactivity to maintain a normal serum calcium level have low serum calcium and low phosphorus levels. All the changes of osteomalacia are secondary to lack or loss of calcium. It is determination of the cause of the calcium deficit rather than diagnosis of osteomalacia which is difficult, as illustrated here.

Case 1.—Woman, 39, complained of pains in various parts of the body, provoked by coughing and sneezing, and cramplike pain in the left arm for two years. Examination showed no abnormality except muscular weakness. The patient appeared to have lost stat-

ure. X-rays were normal. No diagnosis was established. A year later she complained of increasing muscular pain, spasms and weakness. Serum calcium level was 8.9 mg./100 cc. and inorganic phosphorus 1.6 mg. Diagnosis was osteomalacia. Multiple pseudofractures (Milkman's syndrome) of the skeleton were seen on x-ray examination (Fig. 27). Over the next 10 years studies were carried out to determine the cause of osteomalacia. With a diet containing 58 mg. calcium, 42 mg. was excreted in the urine and 214 mg. in the feces. This excluded idiopathic hypercalciuria. A normal serum acid-base equilibrium excluded "tubular insufficiency without glomerular insufficiency." Blood sugar tolerance curves, fat absorption and stool fat content were normal. Parathyroid tissue, obtained at surgi-

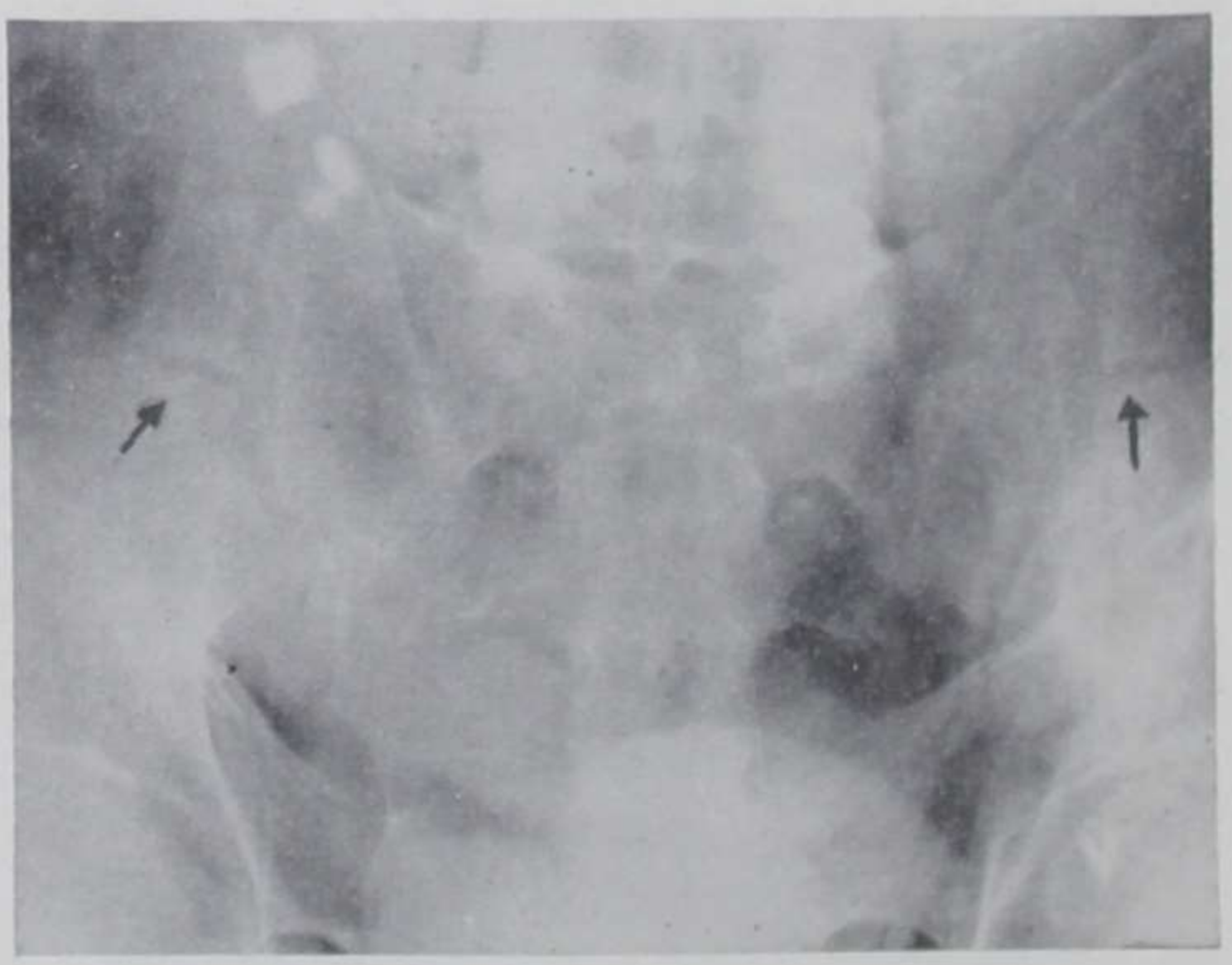

Fig. 28.—Pseudofractures of ilia. (Courtesy of Salvesen, H. A., and Bõe, J.: Acta med. scandinav. (supp. 266) 142:863-874, 1952.)

cal exploration, was normal. It was concluded that the cause of the osteomalacia was deficient absorption of dietary calcium. The failure of large doses of vitamin D to alter the serum calcium or phosphorus levels in the presence of adequate dietary calcium indicated that the basic cause was "resistance to vitamin D." The patient became steadily worse, lost height and became bedridden.

Case 2.—Man, 56, complained of pain in the back, hips and legs for two years. Results of examination were normal, except for a slow, waddling gait, limitation of forward bending, dorsal kyphosis and muscular rigidity. X-rays showed diffuse osteoporosis and symmetrical pseudofractures of both tibiae and ilia (Fig. 28), typical of the Milkman's syndrome. Serum calcium level was 919 mg./100 cc., phosphorus 1.4 mg. and phosphatase 2.2 Bodansky units. Diagnosis was osteomalacia. With a dietary intake of 108 mg. calcium, 49.9 mg. was excreted in the urine and 280 mg. in the

feces. In a single 400 Gm. stool, total fat was 5.6% of moist feces and 26.4% of dry substance, with fatty acids comprising 75% of the total fat. Blood sugar tolerance was normal. Over two months, while vitamin D_2 in doses of 210,000, 420,000 and later 140,000 units was given daily, serum calcium and phosphorus levels rose slightly, the phosphatase level rose to 8 Bodansky units, and the patient complained of increased pain, which necessitated use of a supporting corset. One year later, having used 140,000 units, and subsequently 70,000, daily, he had improved greatly with complete subsidence of all symptoms. Serum calcium level was 10.2 mg./100 cc., phosphorus 2.6 mg. and phosphatase 3.3 Bodansky units. The pseudofractures had healed. He was still in negative calcium balance on a low calcium diet plus 70,000 units of vitamin D_2 daily. On three occasions the fecal fat content was 4% (20% dry weight), 9.7% (36.5% dry weight) and 4.8% (17.3% dry weight). Prothrombin concentration was normal. The cause of osteomalacia was lack of absorption of dietary calcium, which may have been related to the rather large, though varying, content of fat in the feces. The fact that large doses of vitamin D_2 were therapeutically effective favors steatorrhea as the cause.

[Milkman's syndrome is not an occupational disease, but one named after its discoverer, Dr. L. A. Milkman of Scranton, Pa., who described the syndrome of multiple spontaneous, idiopathic, symmetrical fractures. (Am. J. Roentgenol. 24:29-37, July, 1930 and 32:622-634, November, 1934).—Ed.]

Familial Persistent Phosphatic Diabetes with Vitamin D-Resistant Rickets. G. Fanconi and P. Girardet[3] report two cases of vitamin D-resistant rickets, in mother and son, in which the main blood chemistry abnormality was chronic hypophosphatemia. Despite enormous doses of vitamin D (600,000 units twice weekly) given to the child, only moderate improvement in the rachitic bone changes resulted and hypophosphatemia remained unchanged. The serum phosphatase level was not significantly elevated and the blood calcium level was normal, the latter ruling out primary hyperparathyroidism. The urine was normal except for increased phosphate excretion, associated with minimal excretion of calcium. The authors postulated that this was a case of phosphatic diabetes, probably of renal origin.

Phosphate clearance was 2,760 cc./hour/1.73 sq. m. body surface, compared with 130 and 357 cc./hour/1.73 sq. m. body surface in control children. As was to be expected, the Ellsworth-Howard test gave an essentially negative result. Parathormone administration increased phosphate excretion only 17% and 28%, thus implying that the already minimal tubular

(3) Helvet. paediat. acta 7:14-41, 1952.

phosphate reabsorption, caused by the disease process, could not be further blocked. It is possible that the cases (about 30) of vitamin D-resistant rickets reported in the literature, especially the hereditary ones, are examples of phosphatic diabetes.

Whereas in phosphatic diabetes only reabsorption of phosphate is blocked, in cases of the Debré-de Toni-Fanconi syndrome reabsorption of glucose and amino acid is also disturbed. This explains the much more severe disease picture in the latter condition.

Dental Roentgenologic Manifestations of Systemic Disease. I. Endocrine Disturbances. Edward C. Stafne[4] (Mayo Clinic) states that the teeth themselves reflect only those changes which occurred during the period of their development. Subsequent changes in calcium metabolism cannot affect the x-ray density. Thus teeth can serve as a gauge of density or penetrometer to aid in evaluating adjacent bone densities which are subject to changes in bone metabolism. The size of teeth is not altered in endocrine disturbances. Giants do not have large teeth, or dwarfs small teeth.

Obliteration of the lamina dura is one of the evidences of demineralization usually associated with hyperparathyroidism but also is seen in Cushing's syndrome, sprue, vitamin D deficiency and Paget's disease. The chronologic development of the teeth is an index of general skeletal maturation, except for the third molars, which should be disregarded. Hypopituitarism may produce a small jaw, with normal size teeth whose growth and development sequence is retarded. In acromegaly not only is the jaw large, and the teeth widely spaced since they are of normal size, but the teeth are tilted outward because of the pressure of macroglossia—a feature not present in genetic prognathism. Only hypothyroidism which has its onset during infancy or early childhood can retard dental development. Conversely, childhood hyperthyroidism may lead to precocious development. Hypoparathyroidism may produce hypoplasia of enamel and dentin resulting in a short underdeveloped root. The jaws are invariably involved in the skeletal form of hyperparathyroidism. The trabecular pattern becomes fine and lacelike, or even cystic,

(4) Radiology 58:9-21, January, 1952.

with demineralization and absence of the lamina dura. Giant cell tumors of the jaws are common, but may occur without hyperparathyroidism. Albright's syndrome (polyostotic fibrous dysplasia) has absence of the lamina dura only in the regions of the lesions. There is no generalized osteoporosis. Development of teeth may be accelerated in adrenogenital syndrome and retarded in hypogonadism. Diabetes mellitus may be associated with periodontosis, and progeria with marked retardation.

[This article is profusely illustrated with excellent reproductions of roentgenograms demonstrating the many abnormalities touched on in the review.—Ed.]

Fragilitas Ossium Hereditaria with Blue Scleras and Its Treatment with Androgens and Estrogens. C. A. Hernberg[5] (Univ. of Helsinki) reports a family of 25 members, 11 of whom had fragilitas ossium hereditaria and blue scleras. The disease had occurred in five generations inherited as a mendelian dominant. Two members also had otosclerosis, several had poor teeth and hyperextensible joints; none had endocrine or chemical abnormalities. One of identical twin brothers, aged 18, was given intensive treatment with testosterone propionate and estradiol benzoate for 11½ months. The treated twin had sustained 47 fractures, usually 3 each year. Although x-rays failed to show any increase in bone density, no fractures occurred despite several presumably adequate injuries. The control twin had had 19 fractures and sustained another during the control period. Three others had palliation of bone pain with shorter periods of hormone therapy.

[Usually the number of fractures greatly decreases at the time of puberty, but previous attempts at treatment with "sex hormones" have not been strikingly successful. One of the practical difficulties presented by this disorder is that affected children remain short in stature because of multiple fractures of the vertebrae. Perhaps this is one condition in which early therapy with anabolic agents, such as methyltestosterone or methylandrostenediol, is justified. Estrogens are probably contraindicated in very young patients, since they retard growth and fuse epiphyses. —Ed.]

Albright's Syndrome (polyostotic fibrous dysplasia, osteitis fibrosa disseminata) is characterized by brown pigmentation of skin, cystic disease of bone and precocious puberty in females. It is important to differentiate this condition from hyperparathyroidism (osteitis fibrosa cystica) and other cystic

(5) Acta med. scandinav. 141:309-316, 1952.

diseases of bone in order to avoid unnecessary surgery. Ralph E. Hibbs and Homer P. Rush[6] (Univ. of Oregon) report a typical case.

Woman, 46, was seen because of severe intermittent left chest pain radiating into the left shoulder without relation to exertion or gastrointestinal function. She was stocky and in apparent good health. One large brown area covered the posterior aspect of the right shoulder and arm (Fig. 29). There were several other smaller café-au-lait areas with irregular, jagged borders. Cystic areas and irregular architecture with bowing of the left femur were seen on x-ray (Fig. 30). Laboratory findings were normal.

History revealed onset of normal menstruation at age 6 months

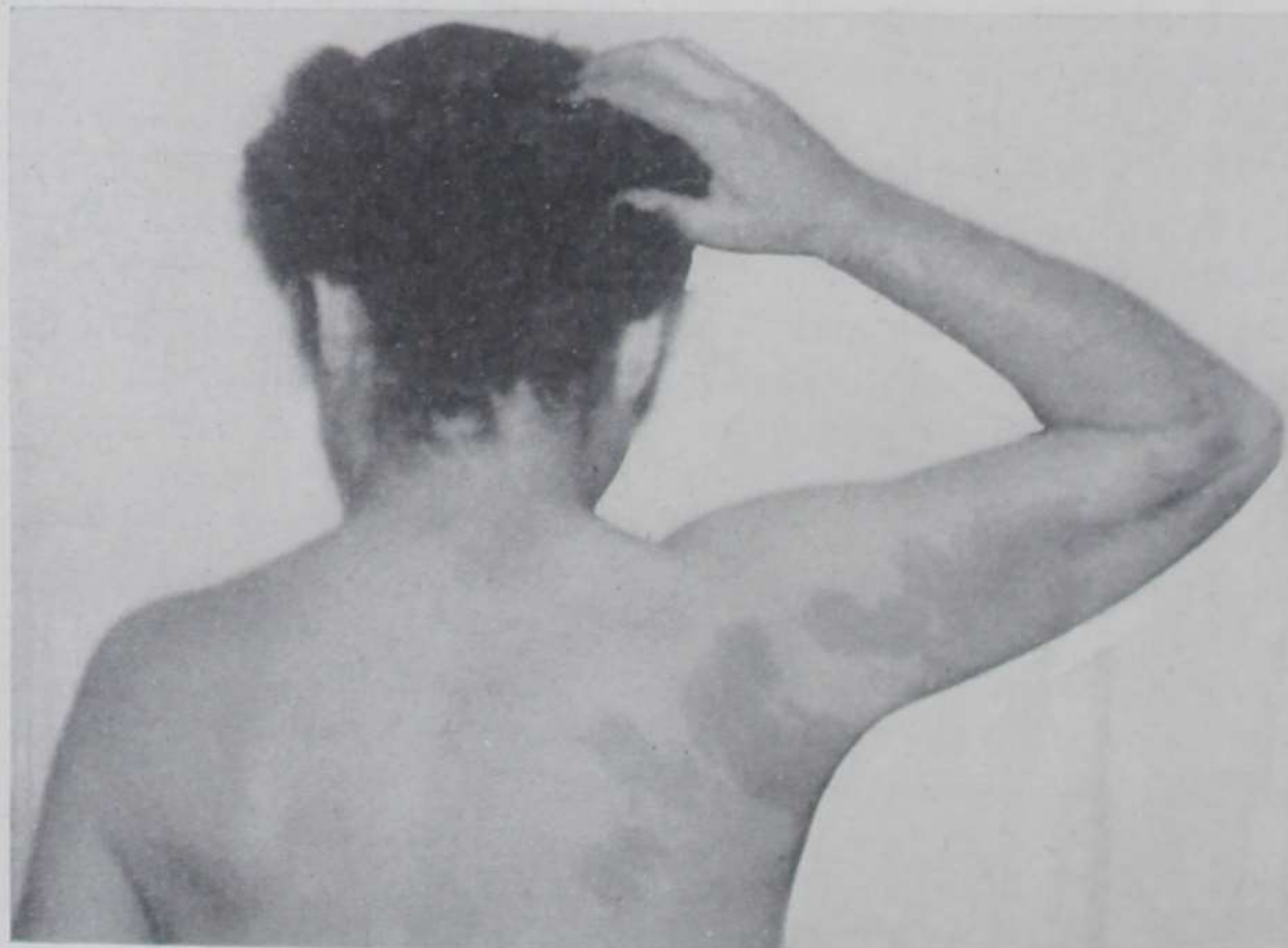

Fig. 29.—Brown pigmentation in Albright's disease. (Courtesy of Hibbs, R. E., and Rush, H. P.; Ann. Int. Med. 37:587-593, September, 1952.)

and early appearance of pubic and axillary hair. Rapid body growth during childhood stopped at age 11 when she was 5 ft. tall. At 12, the third molars erupted, and her dentist remarked, "You must be older than your stated age." Between 9 and 31 she had five fractures, which healed promptly. X-rays of the fractured neck of the left femur when she was 31 were erroneously interpreted as revealing osteitis fibrosa cystica of both ilia and femora. Although all blood values and calcium excretion were normal, the two left parathyroid glands were removed and thought to demonstrate diffuse hyperplasia. The right parathyroid glands were not seen. Her only child,

(6) Ann. Int. Med. 37:587-593, September, 1952.

a girl, 13, had been delivered by cesarean section because of pelvic deformity. The daughter had no pigmentation or precocious development, but x-rays of the left radius revealed a fusiform swelling which, on biopsy, showed polyostotic fibrous dysplasia.

History of parathyroid surgery is commonly found in patients with Albright's syndrome. The surgery in 1933 in

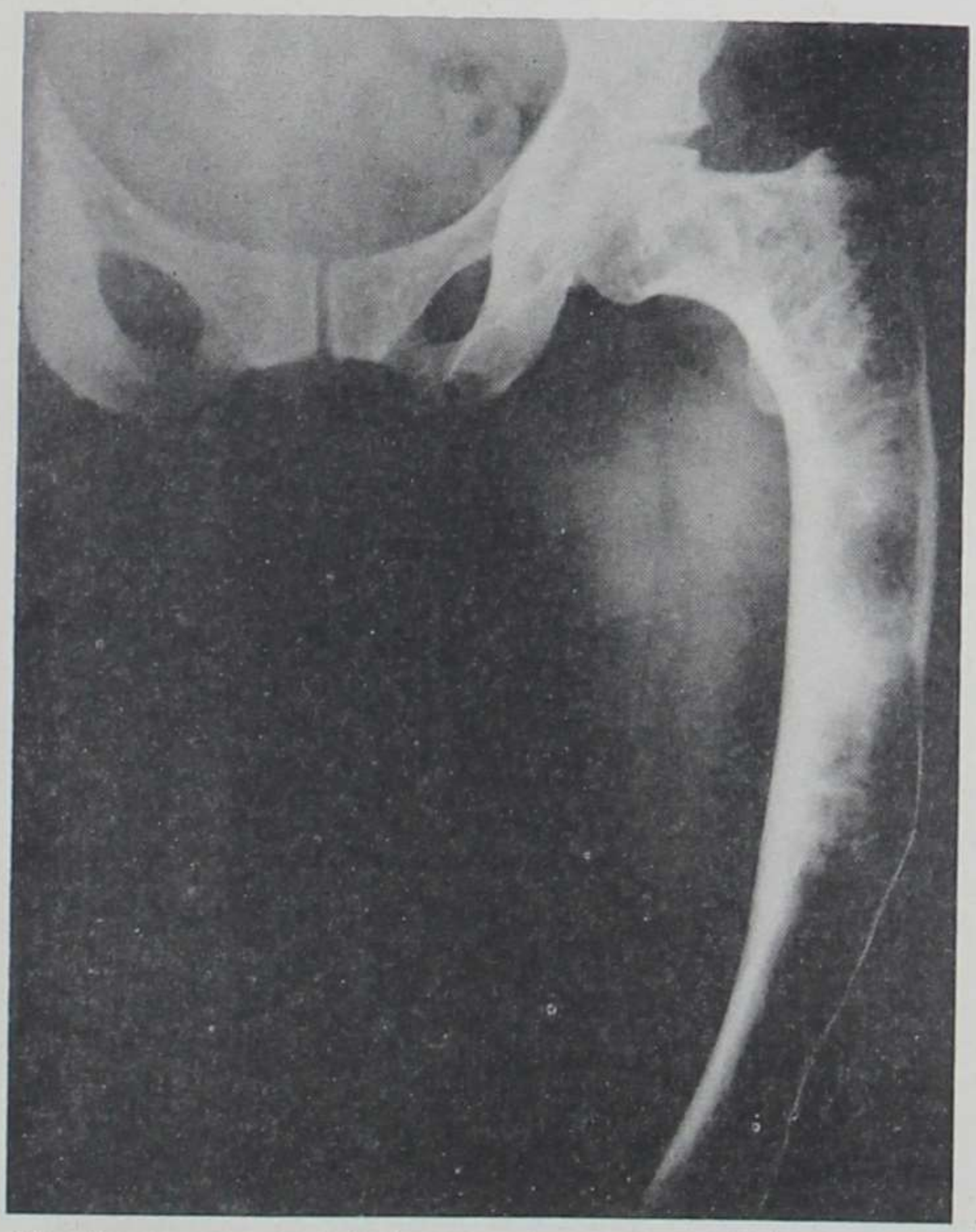

Fig. 30.—Cystic areas in left femur and around acetabulum. Outward bowing and irregular architecture of femur are result of three old fractures. (Courtesy of Hibbs, R. E., and Rush, H. P.: Ann. Int. Med. 37:587-593, September, 1952.)

this patient preceded the first description of the syndrome published in 1937. Her illness is unusual in that the skin pigmentation was confined to the right side, whereas the bone lesions were predominantly on the left. Often both lesions are on the same side. Progression of bone cysts during adulthood is also unusual. The inheritance of the incomplete syndrome by the daughter is another interesting feature.

The cause of the disease is unknown and there is no treatment other than orthopedic correction of the deformities. Albright feels that the primary disturbance is in the central nervous system, possibly in the hypothalamus, because the bone cysts have a segmental distribution corresponding to the spinal nerves. The endocrinopathy may also be the result of an interruption of the normal afferent impulses traveling to the pituitary gland.

Vitamin A Acceleration of Bone Growth Sequences in Hypophysectomized Rats. S. Burt Wolbach and Charlotte L. Maddock[7] (Children's Hosp., Boston) tried to ascertain if the anterior pituitary is an intermediator in producing skeletal response to vitamin A intoxication. Eight hypophysectomized rats were given 1,000 I.U. vitamin A/Gm. body weight. None survived beyond the fifth day; all showed exaggerated skeletal effects including fractures, accelerated epiphyseal cartilage sequences and remodeling of bone, characteristic of excessive vitamin A administration. These changes are clearly not mediated by the pituitary.

Role of Gout in Formation of Urinary Calculi. W. E. Kittredge and Ralph Downs[8] (Tulane Univ.) emphasize the correlation between gout or hyperuricemia and uric acid calculi in an analysis of 324 gouty patients seen over nine years. The old theory that uric acid is retained in the blood because of inadequate renal clearance is wrong for two reasons. (1) Renal disease may be absent in gout or may appear as an end result, never as a cause of gout. (2) The kidney damage produced by gout does not cause retention of uric acid. On the contrary, there is impairment of tubular resorption of uric acid with an excessive loss into the urine. Of course, in terminal uremia, uric acid may be retained along with all nitrogenous products.

Calculi occurred in 17% of the patients. Stones from 14 were analyzed. Only 64% were uric acid, emphasizing the fact that any patient with a metabolic disorder may have stones from unrelated causes. In the 45 patients with stones, they were multiple in 24 and bilateral in 14.

Management should include a low purine diet, although exogenous uric acid does not play an important role in uric

(7) A.M.A. Arch. Path. 53:273-278, March, 1952.
(8) J. Urol. 67:841-847, June, 1952.

acid excretion, and the urine should be kept voluminous and alkaline, with sodium bicarbonate up to 40 gr. four times a day. The use of a uricosuric such as aspirin up to 6 Gm. a day is of value. Colchicine, the drug of choice in the acute attack, does not influence uric acid excretion. Proper control of gout can prevent crystalluria and calculi formation. Only 5% of calculi require surgical removal since they are usually small, round and smooth and dissolve with proper treatment.

[Most patients with uric acid stones do not have gout, but the converse is not true, for many patients with gout have uric acid stones. This observation is of considerable practical importance, since symptoms of renal colic in a patient known to have gout should lead to the correct presumptive diagnosis and the early institution of therapy with alkali. As the authors observe, however, patients with gout are often subject to other types of stone. Thus, a snap diagnosis may be in error, and an exact diagnosis requires the procedures usually carried out in any patient suffering from stone.—Ed.]

THE ADRENAL MEDULLA

If the reported number of cases of pheochromocytoma is any indication, the diagnosis is being made much more frequently now than it was a few years ago. The difference is probably due to recognition of the fact that pheochromocytoma may be manifested by sustained hypertension alone, which mimics essential hypertension. Adequate screening tests have turned up a number of instances of pheochromocytoma in hypertensive patients. The enthusiasm with which recent graduates of medical schools search for these tumors is usually quickly damped by the discouraging infrequency of cases discovered. But, as pointed out by Cahill, a high index of suspicion must be maintained if this disorder is to be recognized. When the group at the Mayo Clinic wished to evaluate a new adrenolytic drug, regitine,® they were able to assemble seven patients with pheochromocytoma (this YEAR BOOK, p. 134).

The observation that bilateral pheochromocytomas occur suggests the possibility of some trophic influence which stimulates the growth of both adrenal medullas and, of course, one thinks of the anterior pituitary. As pointed out in the section on the pituitary gland, pituitary extracts rich in growth principle have been shown to produce bilateral adrenal hyperplasia. In addition, pheochromocytoma has been found with acromegaly (see Iversen, this YEAR BOOK, p. 18).

Not all pheochromocytomas occur within the adrenal area. They have been found along the entire length of the sympathetic chain, even in the thorax. At present pneumoretroperitoneum is becoming a popular method for demonstration of retroperitoneal masses. It is quite possible that this procedure will prove more successful in illuminating extra-adrenal pheochromocytomas than have previous measures. When properly carried out, pneumoretroperitoneum is reported to be considerably less hazardous than perirenal gas insufflation. Since the latter technic is potentially dangerous, it should not be performed unless there is strong indication of an adrenal tumor which is not demonstrable by palpation, plain film, intravenous urography, retrograde pyelography or any of the

other relatively nontoxic methods of illumination. As time goes on, I wonder if the newer pneumoretroperitoneal insufflation will be performed as frequently as it is at present. My limited experience has been that this method is less successful in defining the adrenals than perirenal gas insufflation; I fear, too, that one cannot inject gas into any of the body chambers without eventually producing embolism. Once again, a procedure is introduced which may be of great value but which stands a chance of being discredited because of premature enthusiasm and improper use. For a valuable review of this technic, see D. R. Smith *et al.*, Extraperitoneal pneumography, *Journal of Urology* 68:953-959, 1952.—Ed.

Pheochromocytoma: Diagnosis and Treatment. George F. Cahill[9] (Columbia Univ.-Presbyterian Hosp.) states that this rare tumor should be suspected in every case of hypertension with vasomotor attacks or hypermetabolism. A high index of suspicion is necessary to the diagnosis. The tumors may be silent or may produce the adrenal sympathetic syndrome, paroxysmal or persistent hypertension simulating essential hypertension. They are most common in women. They are multiple tumors in 10% and may be in the retroperitoneal ganglions or the thorax; only 9% are malignant. Typical paroxysmal hypertension, found in one-third, may, of course, occur in other conditions—eclampsia, lead poisoning, aortitis, epilepsy and head injury. Most tumor patients are emotionally stable. Attacks are usually identical in the same patient. Most patients experience pounding of the heart, coldness and blanching of the extremities, some shortness of breath, some nausea or vomiting; all sweat profusely at the end of the attack. Most tumor patients have hypermetabolism, are subject to easy and severe sweating, rapid pulse and mild fever and leukocytosis; they may have glycosuria and elevated blood sugar levels.

Provocative tests with histamine, mecholyl® or tetraethyl ammonium bromide may be of value. The histamine test is preferred, although both false positive and false negative reactions have been reported. The tests may be dangerous in older patients with vascular damage. If hypertension is sustained, a test with some antagonist like benzodioxane may be diagnostic in 90%. Pyelography revealed a tumor in 11 of 18 patients. Perirenal insufflation of air with laminagraphy is valuable in experienced hands. Surgical excision of the tumors may be aided by the use of dibenamine® or regitine.® Anoxia,

(9) J. Urol. 7:779-786, June, 1952.

since it is a potent stimulus to medullary secretion, must be avoided.

Nor-adrenaline and the Suprarenal Medulla. Evidence that nor-adrenaline is methylated in the adrenal medulla to form adrenaline led D. M. Shepherd and G. B. West[1] (Univ. of St. Andrews) to assay the relative amounts of these substances in the young of several species (man, cat, rabbit, guinea pig, dog and fowl) at various ages to clarify further the mechanism of adrenaline formation.

Gland extracts were assayed by paper chromatography, by action on blood pressure and nictitating membrane of the spinal cat and, in certain experiments, by colorimetry. Embryonic glands from mammals showed a high proportion of nor-adrenaline and only small amounts of adrenaline. This is similar to the findings in tumors of the adrenal medulla, in which the cells are relatively undifferentiated. Nor-adrenaline was the predominant hormone in glands of both young and old domestic fowl; the glands of these animals, unlike mammals, do not grow after the third month. In adult glands among various species the amount of nor-adrenaline was inversely proportional to the ratio of cortical to medullary size. This suggests that degree of methylation of nor-adrenaline is related to the adrenal cortex.

[The observation that nor-epinephrine (nor-adrenaline; arterenol) is the predominant compound present in pheochromocytomas has been repeatedly confirmed since the original report by Holton in 1949. It is currently believed that this substance is the parent compound which, when methylated, forms epinephrine. The difference between the actions of epinephrine and nor-epinephrine was discussed in the 1951 YEAR BOOK, pp. 129-130.—Ed.]

Effect of Insulin on Urinary Excretion of Adrenaline and Nor-Adrenaline: Studies in 10 Healthy Subjects and in 6 Cases of Acromegaly are reported by Ulf S. Von Euler and Rolf Luft[2] (Stockholm). All test subjects were kept fasting overnight. Bladders were emptied at 6 a.m. and control samples of urine collected between 6 a.m. and 8 a.m. At 8 a.m. insulin was injected intravenously in a dose of 0.1 I.U./kg. body weight. Capillary blood samples were taken 10, 20, 30, 45, 60, 75, 90, 120, 150 and 180 minutes after injection. Blood pressure and pulse rate were determined at 5-10 minute intervals.

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(1) Brit. J. Pharmacol. 6:665-674, December, 1951.
(2) Metabolism 1:528-532, November, 1952.

Test urines were collected between 8 and 11 in the morning.

In the healthy subjects urinary excretion of adrenaline (0.0055 ± 0.0009 μg./minute) and nor-adrenaline (0.040 ± 0.004 μg./minute) during the control period corresponded to values obtained earlier for normal subjects. Adrenaline excretion during the first three hours after administration of insulin increased to 0.055 ± 0.007 μg./minute, a significant difference. Excretion of nor-adrenaline decreased by 0.013 ± 0.004 μg./minute.

During the action of adrenaline—simultaneous with the most pronounced blood sugar decrease—there was a significant increase in pulse rate and systolic blood pressure and a fall in diastolic pressure. At the same time typical and marked hypoglycemic symptoms occurred.

During the control period the patients with acromegaly had a normal adrenaline excretion, but four had an increased nor-adrenaline excretion. After injection of insulin there was a slight but insignificant change in adrenaline excretion in five. The sixth had a more pronounced increase. Excretion of nor-adrenaline decreased greatly in three. No glycemic symptoms were noticed.

The authors' experiments showed a moderate decrease in nor-adrenaline output. It should be remembered that the human adrenal contains about three to four times as much adrenaline as nor-adrenaline, and that nor-adrenaline, normally present in the urine in quantities four to six times greater than adrenaline, is derived chiefly from the adrenergic nerves. Whether a differentiation occurs in the secretory rate of the two hormones from the adrenal medulla therefore cannot be easily assessed.

Evaluation of New Adrenolytic Drug (Regitine®) as Test for Pheochromocytoma is presented by Ray Gifford, Jr., Grace M. Roth and Walter F. Kvale[3] (Mayo Clinic and Mayo Found.). Regitine,® chemically related to priscoline,® was tested in 259 patients, all but 20 of them hypertensive; 7 had pheochromocytomas. It was given intravenously to 114 and intramuscularly to 154 patients. The reaction to 5 mg. regitine® was considered positive for pheochromocytoma when (1)

(3) J.A.M.A. 149:1628-1634, Aug. 30, 1952.

blood pressure dropped more than 35 mm. systolic and 25 mm. diastolic or to normal, and (2) depressor effect was maximal within 2 minutes of rapid intravenous injection or within 20 minutes of intramuscular injection. The test is most reliable with 5 mg. regitine® intravenously.

It had some depressor effect in 66% of patients with essential hypertension. Positive reactions were seen after intramuscular injection in 3 of 149 patients who had no pheochromocytomas and in 4 of 107 after intravenous injection; the false reactions were attributed to (1) sedation before the test (in 2 patients), (2) uremia (in 1), (3) blood pressure in low hypertensive range (in 3), and (4) unexplained depressor effect (in 1). All positive reactions should be verified with piperoxan or one of the provocative tests. There were two false negative reactions after intramuscular and none after intravenous injection. Regitine® is preferred for screening to rule out pheochromocytoma. It has almost no unpleasant side reactions and is safe for hypertensive patients because it does not raise blood pressure.

Pheochromocytoma: Case Report of Successful Thoracoabdominal Operation after Nine Negative Surgical Explorations is presented by P. Effersøe, Tyge Cl. Gertz and A. Lund[5] (Univ. of Copenhagen).

Man, 37, had severe headaches from 1935 to 1946; they were continuous, diffuse and intensified by exertion or stooping. In 1946 they became brief throbbing attacks, one hour at most, ushered in by impaired vision, cold fingers, palpitations, sweating, nausea, vomiting and sometimes micturition and defecation. During an attack the pupils became dilated and the blood pressure rose to 270/180. Histamine, 0.05 mg., or the cold pressor test provoked an attack with temporary disorientation. Although less than 0.3 mg./100 ml. nor-adrenaline was found in the serum between attacks, it rose to 2.4 mg./100 ml. during an attack. During 1950 the attacks increased to 20 a day and were accompanied by some convulsions. The only clue to localization of the tumor was his own statement, confirmed later, that pressure of a clenched fist in the epigastrium would cause an attack. Nine surgical explorations failed to find the tumor, discovered on the 10th operation under the liver behind the inferior vena cava. It weighed 21 Gm. and contained 47 mg. nor-adrenaline and 2.9 mg. adrenaline. After the operation similar attacks reappeared but, in the absence of any objective criteria, were considered functional.

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(5) Acta chir. scandinav. 103:43-51, 1952.

Pheochromocytoma from Laboratory Standpoint is discussed and a case reported by Grace M. Roth, Malcolm B. Dockerty and Nicholas C. Hightower, Jr.[4] Of chromaffin tissue tumors, 90% arise from the adrenal medulla, 60% of them on the right, 30% on the left side; 10% are either bilateral or multicentric; 80% release vasopressor substances. Only 5% are clinically palpable and only 50% are demonstrable by

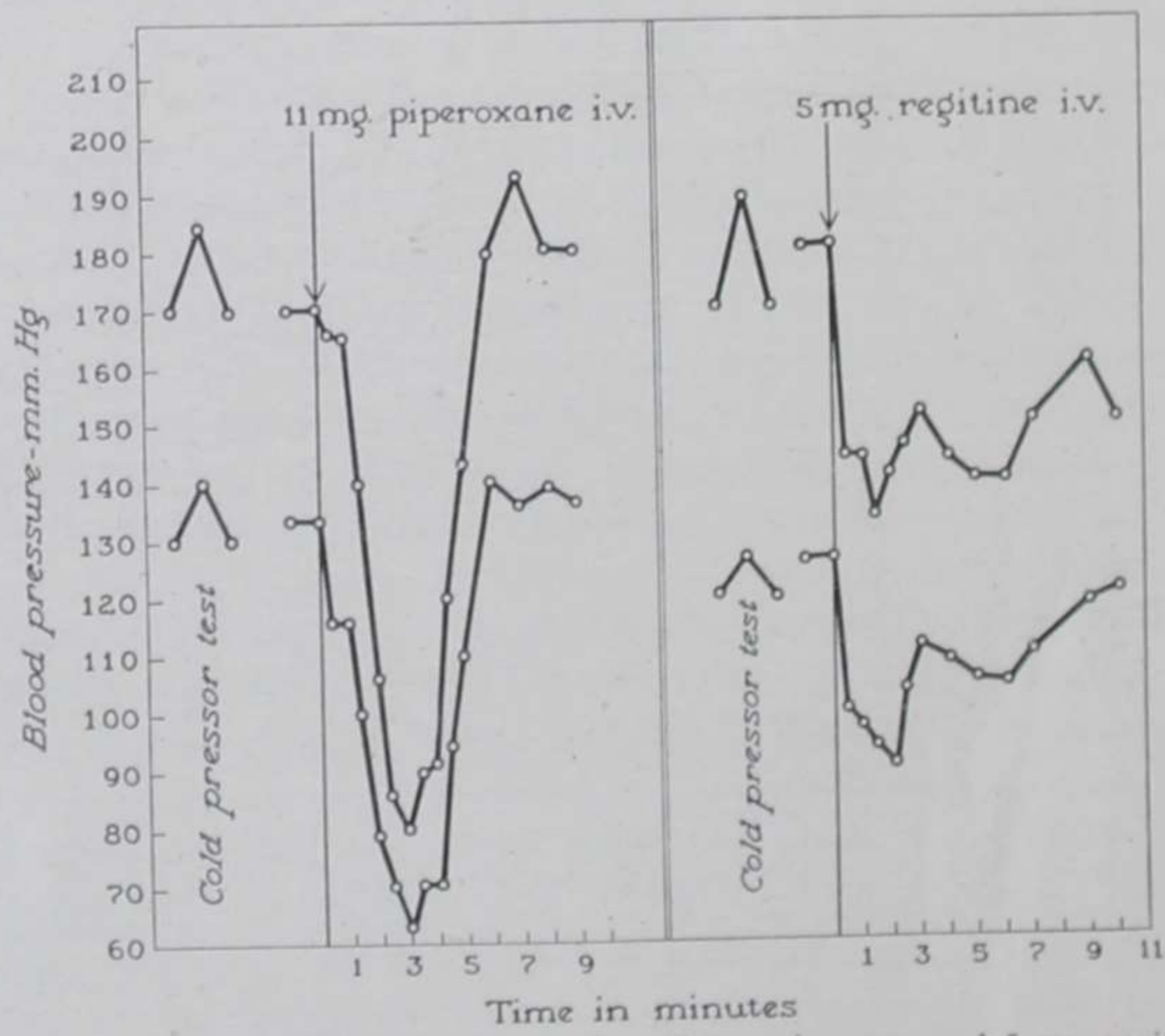

Fig. 31.—Changes in blood pressure after 11 mg. piperoxan and 5 mg. regitine® intravenously. Precipitous fall in first four minutes after injection of piperoxan is a positive result and considered indicative of pheochromocytoma, as is the fall in pressure to sub-basal, where it remained for 10 minutes after regitine® injection. (Courtesy of Roth, G. M., *et al.*: S. Clin. North America 32:1065-1077, August, 1952.)

perirenal insufflation or excretory urography. Many are lobulated; 80% are encapsulated. Only 10% metastasize clinically, although 30% of the bilateral tumors tend to spread. Subtotal removal, even of so-called benign tumors, invites local recurrence.

Physician, 38, complained of recurrent severe occipital headaches which had awakened him for two months; with them his blood pressure rose; he noted irregular tachycardia, anxiety, tremor, sweating and pallor. Between attacks, he sometimes felt weak, had rapid

(4) S. Clin. North America 32:1065-1077, August, 1952.

pulse and tremor. He had lost 10 lb. Physical and routine laboratory examinations, excretory urograms and electrocardiogram gave essentially normal results. Basal blood pressure was 112/70. Response to pharmacologic tests, performed to confirm his own clinical diagnosis of pheochromocytoma, is shown in Figures 31 and 32. Histamine, 0.05 mg., reproduced exactly the symptoms experienced with spontaneous attacks. The diagnosis appeared correct and a 10 Gm. encapsulated pheochromocytoma 2.5 cm. in diameter was removed from the right adrenal; analysis revealed 3.1 mg. of pressor sub-

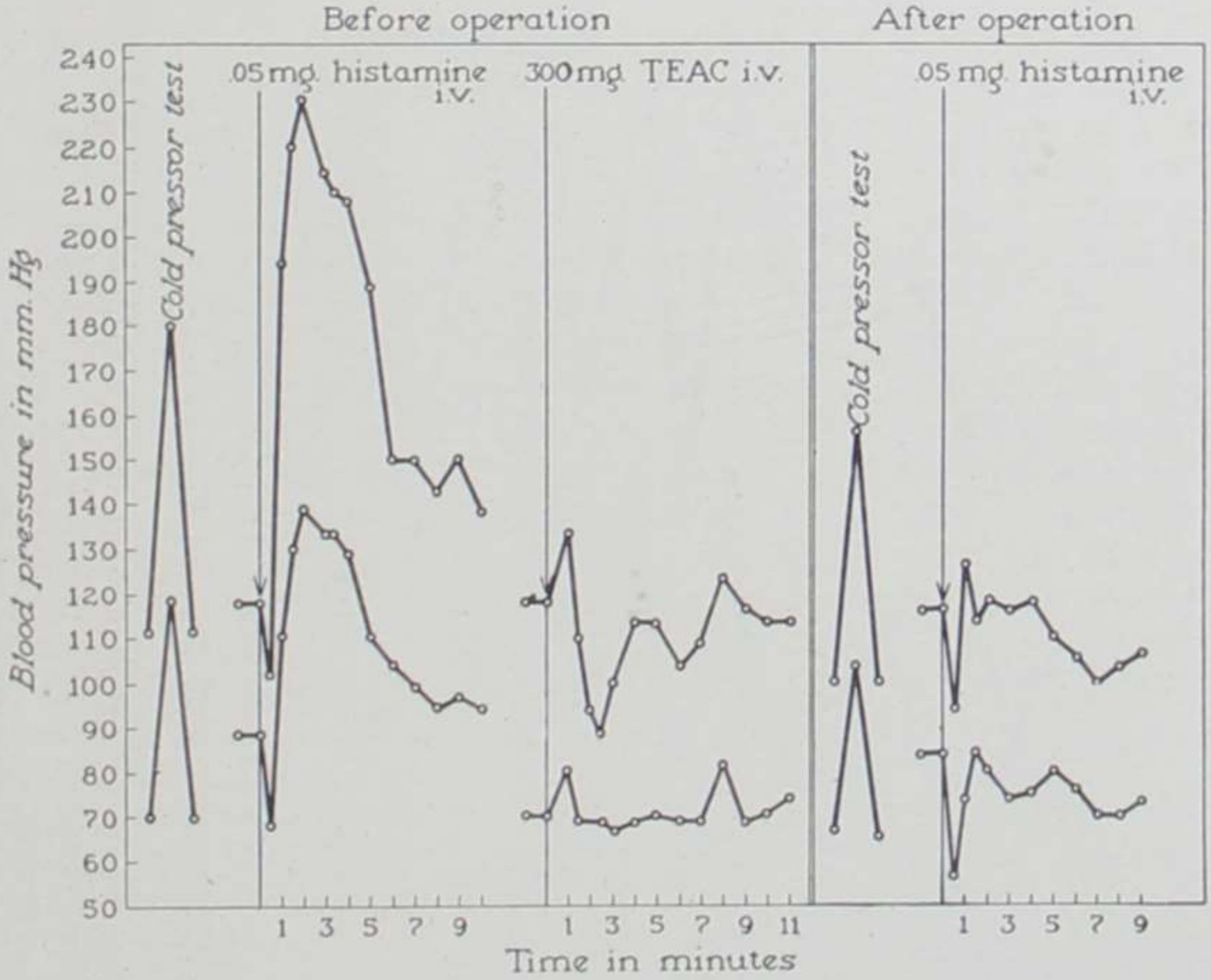

Fig. 32.—Preoperative blood pressure changes, after immersion of one hand in water at 4 C. for one minute, from 0.05 mg. histamine base in 0.5 cc. physiologic saline and 300 mg. tetraethylammonium chloride intravenously. Fall in pressure 30 seconds and rise two minutes after histamine injection is considered indicative of pheochromocytoma, whereas decrease in pressure after tetraethylammonium chloride is a negative result. Result here was false negative. (Courtesy of Roth, G. M., *et al.*: S. Clin. North America 32:1065-1077, August, 1952.)

stance/1 Gm. tissue, 77% of which was epinephrine and 23% nor-epinephrine. Figure 33 shows changes in blood pressure during operation. Manipulation of the tumor elevated the blood pressure; as soon as the tumor was isolated, there was a precipitous drop counteracted by epinephrine and nor-epinephrine intravenously. Nor-epinephrine in gradually decreasing dosage was given continuously for 27 hours postoperatively. Recovery was uneventful; the normal response to histamine 10 days after operation is recorded in Figure 32.

Since narcotics, sedatives and particularly potassium thio-

cyanate may obscure results, all medication should be withheld for 24 hours before the tests are made. If potassium thiocyanate has been given, the tests should be postponed until the drug level falls to that of laboratory normals. Pharmacologic tests should be preceded by a cold pressor test.

[As indicated here, provocative tests with histamine or similar adrenal excitants may be used to confirm the diagnosis of pheochromocytoma in

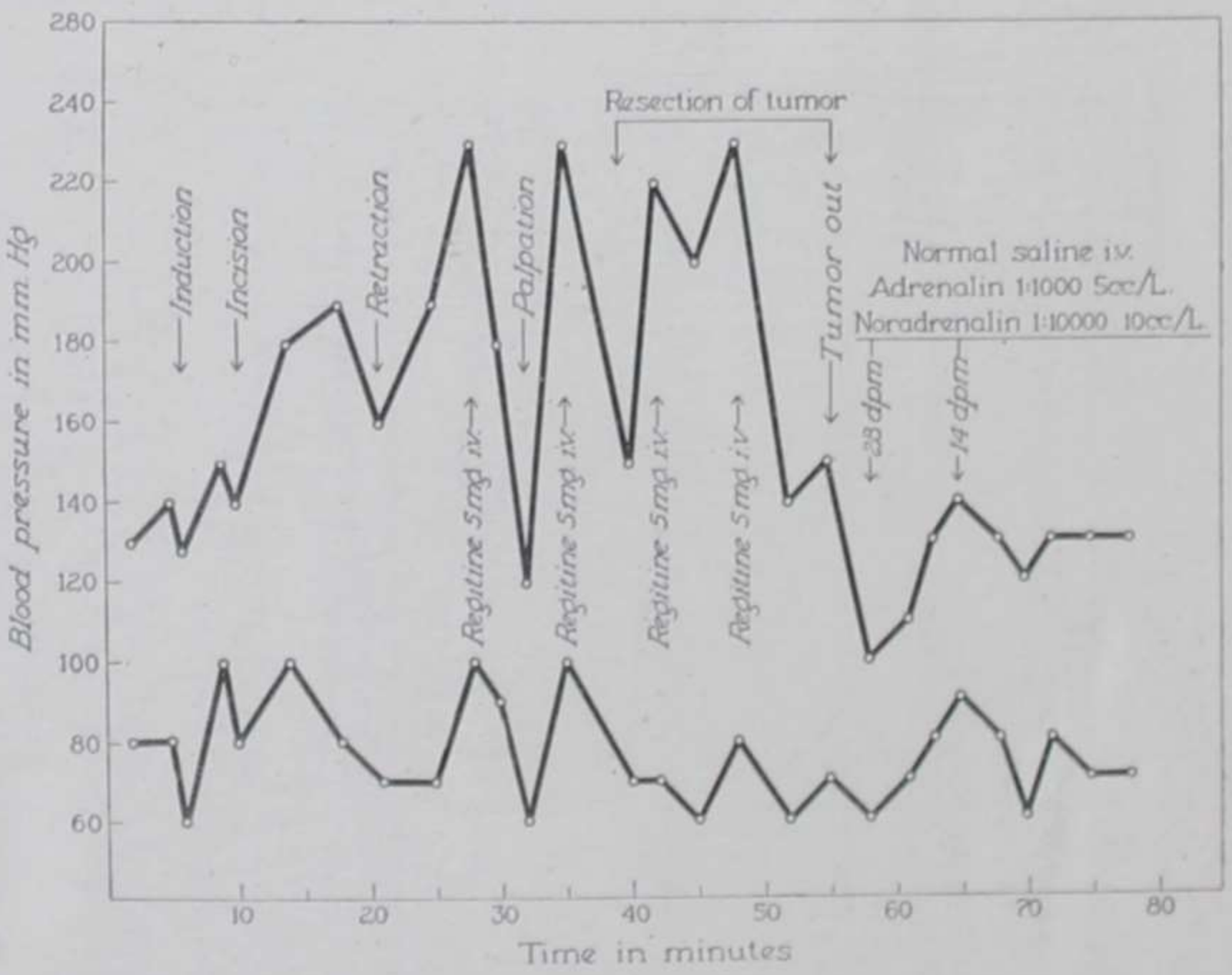

Fig. 33.—Blood pressure changes during surgical procedures. Elevations with retraction, palpation and during excision of tumor controlled by regitine® intravenously should be noted. After removal of tumor, blood pressure fell and decrease was controlled by epinephrine and nor-epinephrine intravenously. (Courtesy of Roth, G. M., *et al.*: S. Clin. North America 32:1065-1077, August, 1952.)

patients who have intermittent attacks of hypertension. Similarly, adrenal antagonists, such as benzodioxane, dibenamine® and regitine,® are useful in detecting pheochromocytomas which produce sustained hypertension. The mechanism of the action of histamine is no longer clear. It was previously thought that histamine caused a drop in blood pressure and thereby stimulated the adrenal medulla to put out epinephrine. However, Bein and Meier of Basel (Helvet. physiol. acta 10:45-47, October, 1952) showed that histamine produced a rise in blood pressure in adrenalectomized cats when epinephrine or certain other substances had been constantly infused.—Ed.]

Bilateral Pheochromocytomas were found in a case reported by E. H. Stokes[6] (Sidney).

Man, 28, had had frontal headache and fatigue for two years. He was healthy except for bilateral papilledema and blood pressure of

(6) M. J. Australia 1:144-146, Feb. 2, 1952.

250/170. He refused sympathectomy and was treated with sedatives for one year. Albuminuria, progressive retinopathy and finally heart failure appeared before he died three years after onset of symptoms. Autopsy revealed vascular malignant pheochromocytomas in both adrenal glands with several small regional metastases. In retrospect it was recalled that he had suffered one of the most characteristic features of pheochromocytoma—drenching sweats—although hypertension was never paroxysmal.

Bilateral Pheochromocytoma in 6 Year Old Boy is reported by Catherine A. Neill and Gwen Smith[7] (Queen Elizabeth Hosp. for Children, London).

Boy, 6, six weeks before hospitalization had a single attack of vomiting followed by persistent lethargy and night sweats. His health and that of the family had been good. He was thin, sallow and anxious looking, with widened palpebral fissures and slight exophthalmos. Both hands were cold, sweating and bluish pink, and a firm, nonpitting edema extended about 1½ in. above the wrists. When warm, the hands resembled those seen in acrodynia. These changes, present since infancy, had become more pronounced recently. Heart rate was 120, and all peripheral pulses were slapping in character. Blood pressure in the arms was 190/130 mm. Hg. Later a reading of 150/130 mm. was obtained in the arms, the systolic pressure in the legs being 145 mm. The heart was not clinically enlarged; no murmurs were heard. The ocular fundi showed arterial narrowing but no hemorrhages or exudates. An x-ray revealed the heart slightly enlarged to the left. There was no abnormality in the region of the pituitary fossa. An electrocardiogram showed no abnormality, and other laboratory data were not significant.

While in the hospital he had frequent attacks of profuse sweating, usually at night, associated with severe headache and occasionally nausea. During attacks the blood pressure was raised to 240/156, the pulse became thready and difficult to feel and multiple extrasystoles were present. He remained afebrile but continued to show a slight leukocytosis and a raised sedimentation rate. Pinkness of the hands increased, and a generalized sudaminal rash developed associated with marked desquamation of the hands and slight desquamation of the feet. Differential diagnosis was pink disease (juvenile acrodynia), pheochromocytoma or periarteritis nodosa. Further investigations were made to confirm or disprove the presence of a pheochromocytoma. Repeated attempts to induce hypertensive paroxysms by pressure in the renal angles failed. Sodium amytal® did not depress the blood pressure, and during the third hour a typical paroxysm developed. Results of the benzodioxane test were unsatisfactory because the patient did not co-operate. Abdominal x-rays and intravenous pyelography revealed opacities overlying both upper poles of the kidney. Perirenal insufflation on the right caused temporary respiratory arrest, and no attempt was made to insufflate the left side.

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(7) Arch. Dis. Childhood 27:286-290, June, 1952.

After four months the clinical condition was essentially unchanged. The parents would not agree to an exploratory laparotomy and removed the boy from the hospital. After three months at home he showed little change; hypertension persisted. On readmission about 10 months after onset of symptoms, he had lost 12 lb. and blood pressure was 185/120. No masses could be felt in the renal angles, although extreme constipation made abdominal palpation difficult. A minute volume test to assess renal function was planned. The patient died when urethral dilators were passed.

Autopsy revealed a well circumscribed, smooth, ovoid, yellowish brown tumor, measuring $6 \times 5 \times 4$ cm., with the remains of the left adrenal gland, primarily adrenal cortex, attached to its upper and lateral aspect. The impression was that the tumor had arisen in the medulla and broken through the cortex. The right adrenal gland showed a tumor in the medulla, measuring $3 \times 2.5 \times 1.5$ cm. The heart showed hypertrophy and moderate dilatation. Definite atheroma surrounded the orifices of the right coronary artery and all posterior intercostal arteries. The coronary arteries were normal. The liver was pale with distinct fatty change at the periphery of the lobules. Other organs were normal. The cause of death was vagal inhibition during the passage of urethral dilators. Microscopically, despite variation in the cells and occasional giant cells, the tumor was considered benign. The muscular coats of many smaller arteries in the kidney were hypertrophied, but there was no evidence of glomerular damage, malignant hypertension or scar formation. Arterial changes were even more pronounced in the spleen, where fibrinoid degeneration was prominent. The aorta showed thickening of the intima with fatty change characteristic of established atheroma.

Vascular disturbances affecting the extremities have been noted during and after attacks in adults with pheochromocytoma. The hands of these patients were apparently normal between crises. Probably, the recurrent severe anoxemia from intense arteriolar constriction caused temporary exudation of plasma, producing chronic edema in the present case. Peripheral vascular changes, sometimes comparable with those seen in acrodynia, are not uncommon in active pheochromocytoma. In distinguishing this disease from acrodynia, absence of paroxysmal hypertension does not exclude a diagnosis. In view of the diagnostic difficulties, early laparotomy in any similar case is recommended.

[It is unfortunate that Dr. Stokes's patient (preceding article) refused sympathectomy, for pheochromocytomas may be encountered during the course of this operation and cured. Neill and Smith's case emphasizes that life is brittle in the patient with a pheochromocytoma. Consequently, it is most important to take all precautions during surgical removal, particularly when it is necessary to handle the tumor. The use of such adrenolytic drugs as benzodioxane and regitine® may be expected to make this operation less hazardous.—Ed.]

Pheochromocytoma Simulating Thyrotoxicosis. J. V. S. A. Davies[8] reports a case.

Woman, 58, was referred on June 19, 1950, because of suspected thyrotoxicosis. For 12 months she had had paroxysmal vertigo associated with tinnitus and deafness on the right. More recently she had lost weight and complained of weakness and apprehension. Appetite remained excellent. There had been amenorrhea since the normal birth of her second child 28 years before. Previous health had been good, and there was no family history of goiter or deafness.

The patient was of slight build and weighed 36.3 kg. She had a strained expression and was pale but not obviously anemic. The hair was fine; the eyebrows and axillary and pubic hair were scanty. Her movements were rapid and birdlike. Other features were: a resting pulse rate of 120, blood pressure of 180/100, an apex beat in the sixth left intercostal space in the midclavicular line and a loud systolic murmur heard over all areas and maximal at the apex. There was no exophthalmos but a fine tremor of the outstretched fingers. The thyroid gland could not be felt. Abdominal examination revealed no abnormalities. The patient was mildly breathless at rest, but no abnormal signs were found in the lungs. The nervous system appeared normal apart from some nerve deafness on the right. The urine contained neither albumin nor sugar.

A threefold diagnosis of thyrotoxicosis, old rheumatic heart disease and possibly otosclerosis was made. At the suggestion of another physician an x-ray of the thoracic outlet was taken, which showed no evidence of a retrosternal goiter.

The patient was hospitalized on July 12 and five days later was given methylthiouracil, 600 mg. daily, and iodine. By July 23 she felt less agitated, but the pulse rate seldom fell below 100. Iodine was discontinued on July 27. By August 4 the condition was clearly not responding; tachycardia and tremor persisted. On August 11 the pulse rose to a sustained rate of 150 and breathlessness increased. Venous engorgement appeared in the neck. The pulse rate was 170 on August 14. The pupils were constricted, the skin was moist and the blood pressure had fallen to 116/96. Methylthiouracil was discontinued. On August 17 the patient was semiconscious; pulse rate was 120 and blood pressure 100/70. Consciousness returned for a few hours four days later; pulse rate was 110. Death occurred the following day.

At autopsy, the thyroid weighed 34 Gm. and had a smooth encapsulated surface. The cut surface showed excess colloid with no adenomas. One or two small hemorrhages were present. Grossly, the lungs showed emphysema with severe engorgement. Pericardial effusion (about 3 ml. clear yellow fluid) was present. The heart was not dilated or hypertrophied. The mitral valve was moderately distorted, with thickened chordae tendineae and clusters of small fibrinous vegetations. Other valves and the myocardium were nor-

(8) Brit. M. J. 2:77, July 12, 1952.

mal. The left coronary artery had a double orifice. The aorta showed slight sclerosis. The stomach was engorged and contained altered blood. The liver was severely engorged. The right adrenal weighed 6 Gm. and the left 20 Gm. Sections from the left adrenal show it to be composed of cords and columns of polyhedral cells with much cytoplasm and small nuclei. It was highly vascular, but there were no features to suggest malignancy. The appearance was highly reminiscent of the adrenal medulla. Unfortunately, as the tumor was unsuspected, no fixative agent containing chrome salts was available and specific staining failed.

[Since patients with pheochromocytoma often manifest exophthalmos, stare and hypermetabolism, in addition to the symptoms described here, the differential diagnosis between Graves' disease and pheochromocytoma may be extremely difficult.—Ed.]

THE ADRENAL CORTEX

Physiology and Tests of Function

Interest in the physiology and diseases of the adrenal cortex, undoubtedly stimulated by the tremendous impact of cortisone and corticotrophin, continues to account for a large proportion of publications in the field of clinical endocrinology. A surprising number of studies on the various forms of hypercorticism have been published recently; the number of reported cases of the past 5 years, in fact, exceeds by far the number reported in the preceding 20 years. It is probable that this increase does not represent an augmented incidence of the disorders, but rather indicates better recognition of these conditions and more interest in their treatment, which has been revolutionized by the advent of cortisone and corticotrophin.

Great interest has been evinced not only in the intrinsic diseases of the adrenal but in adrenal function in various other disease states. A tremendous amount of investigation has produced a vast body of precise information on adrenal physiology and also on "stress" and its effects, which some investigators have thought to be mediated by the adrenal cortex. In evaluating the recent studies one must, of course, begin with an understanding of the sensitivity and specificity of the tests used as indexes of adrenal cortical function, particularly the circulating eosinophil count and determinations of urinary 17-ketosteroid and "11-oxysteroid" excretion. All of these have been shown to lack specificity, although their usefulness in certain types of investigation, e.g., to demonstrate one of the effects of corticotrophin, cannot be doubted. In all fairness, it appears that the use of these indexes has misled some investigators into making too sweeping conclusions about the role of the adrenal in many disease states. For example, although rheumatoid arthritis is ameliorated by the administration of cortisone or corticotrophin and although some patients with rheumatoid arthritis may show subnormal excretion of 17-ketosteroids, there is still no proof that rheumatoid arthritis is caused by a deficiency of adrenal cortical function.

The potent adrenocortical preparations now available have made it possible to utilize adrenalectomy as an investigative procedure—particularly to determine whether removal of the adrenals can benefit patients with certain neoplastic diseases or patients with malignant hypertension.

Reports on the effects of this procedure on malignancies are included in the chapter on endocrine treatment of neoplastic diseases.

Advances continue to be made in the practical therapy of patients with Addison's disease. A new long-acting preparation of desoxycorticosterone reportedly has simplified treatment of patients whose condition and medication remain fairly stable. Cortisone has proved valuable in both the prevention and the management of addisonian crisis. In very small doses it has added to the well-being and productivity of a certain percentage of patients with Addison's disease, although desoxycorticosterone still must be looked upon as the primary or life-saving therapeutic agent for these patients. It is interesting that whereas most patients with Addison's disease cannot be maintained on cortisone alone, patients who have been rendered addisonian by total adrenalectomy can be maintained on this steroid without added desoxycorticosterone, although some of them seem to require an increased intake of salt.

The zealous work of Wilkins and his group, as well as the elegant studies of Jailer and of Bartter and their co-workers, has greatly clarified and extended Wilkins' original observation that cortisone may be used to suppress the elaboration of abnormal androgenic steroids in congenital androgenic adrenal cortical hyperplasia. The studies of Jailer, in particular, give a clue to the nature of the defect in steroidogenesis in this condition. It was originally pointed out by Marrian that pseudohermaphrodites excrete etiocholanolone and androsterone. Jailer's work indicates that these compounds may be excretion products of 11- or 17-hydroxyprogesterone, a weak androgen which is probably released by the adrenal in this condition. Under normal circumstances, this compound is transformed to compound F, as has been shown by the work of Hechter and Pincus. It appears, then, that the fundamental defect in congenital androgenic hyperplasia is an inability to transform the parent compound to compound F (hydrocortisone). As a result, the androgen produces virilism, whereas the lack of hydrocortisone may cause adrenal insufficiency of the salt-losing or addisonian type. This theory may also explain the occurrence of hyperplasia as a secondary phenomenon due to an excess of corticotrophin because of the lack of hydrocortisone (which normally inhibits the release of corticotrophin from the anterior pituitary).

In the practical management of patients with the congenital syndrome of androgenic adrenal hyperplasia, the adrenal must be suppressed continuously; for this reason it is better to inject cortisone intramuscularly, so that it is slowly absorbed, than to give it by mouth, in which case it must be given frequently. Intramuscularly administered cortisone has proved highly efficacious in the cases thus far reported.

The Cushing type of hypercorticism was formerly encountered very rarely. Now that the identical condition is produced frequently by the administration of cortisone or corticotrophin, most physicians have had the opportunity of seeing and becoming familiar with the syndrome. Similarly, the actions of other types of steroids are now well known (e.g., androgens, estrogens), and it is gratifying to see that the classification of hyperactive adrenal cortical tumors, originally proposed by Cahill and by Kenyon, well explains the varying clinical forms which these cytologically identical tumors may take. The April 1952 issue of *Postgraduate Medicine* was devoted to the presentation of the various clinical types. As noted in one of the contributions there, the clinical manifestations in nearly all of the reported cases of adrenal cortical tumor can be explained on the basis of well established effects of known steroids. This knowledge is not of academic interest alone; on the basis of these studies, it appears that the administration of corticotrophin to patients with the type of adrenal

cortical tumor which results in atrophy of the opposite adrenal restores the function of the atrophic adrenal and thereby permits the patient to survive surgical removal of the tumor. This prediction, suggested by Cahill as early as 1942, has been amply supported by clinical experience.

One of the most difficult of clinical problems is the differentiation of Cushing's disease arising from hyperplasia of the adrenal cortex from an identical condition caused by a tumor. Possibly better methods of identifying adrenal tumors radiologically may aid. (See introductory remarks to section on the adrenal medulla.) One criterion which may aid in distinguishing the hyperplastic from the neoplastic form of the Cushing type of hypercorticism is the response of the 17-ketosteroid excretion to the administration of cortisone. It has been suggested that administration of cortisone may produce gross reduction of the 17-ketosteroid excretion in hyperplasia, but not in adrenal tumors. It must, of course, be borne in mind that wide fluctuations of 17-ketosteroid excretion may occur spontaneously, so a careful base line must be established before the results of this maneuver can be evaluated correctly.—Ed.

Tests of Adrenal Cortical Function are discussed by William W. Engstrom[9] (Milwaukee). Although crisis in a known case of Addison's disease or chronic insufficiency when classic signs are present is not hard to diagnose, less typical cases present difficulties which can be lessened by appropriate laboratory tests. The Cutler-Power-Wilder test is designed to determine whether renal excretion of sodium chloride diminishes with rigid restriction of sodium and administration of potassium. The nonaddisonian patient will excrete less than 150 mg. chloride/100 ml. urine in the last 4 hours of the 52 hour test. Use of the test is limited because of the necessary rigid control and danger of administering potassium to patients with Addison's disease. Impaired renal sodium conservation can be more safely and as effectively demonstrated by giving the patient a low salt diet and adding known amounts of salt to it in diminishing quantities while determining the 24 hour urinary chloride excretion. Normally, chloride excretion promptly diminishes. Although faulty salt conservation is found in adrenal cortical insufficiency, it is also found in other disorders such as chronic renal disease and in some seriously ill, malnourished patients, particularly those with chronic pulmonary disease.

The Robinson-Kepler-Power water test is based on the fact that, normally, excess water is promptly excreted, whereas in adrenal cortical insufficiency excretion is delayed, there is a tendency to lose chloride and the blood urea level rises. The defect can be corrected by administration of adrenal cortical

(9) Am. Pract. 3:626-630, August, 1952.

extract or cortisone but not desoxycorticosterone. False negative responses to water tests practically never occur; false positive responses are not infrequent in patients with organic illnesses such as carcinoma, hepatic cirrhosis, sprue, rheumatoid arthritis and hyperthyroidism. The water test is of no value in states of hyperadrenalcorticism.

Usually normal persons exhibit at least a 50% fall in the number of circulating eosinophils in response to a test dose of ACTH; in primary adrenal cortical insufficiency, the adrenal cortex is unable to respond to ACTH and the total number of circulating eosinophils does not decrease. A single

DATA ON 17-KETOSTEROID EXCRETION IN ADRENAL CORTICAL DISEASE

	MG./24 HR.
Normal males	7-25 (av. 15 mg.)
Normal females	5-17 (av. 10 mg.)
Addisonian males	1-5
Addisonian females	< 2
Serious chronic illnesses	Values below normal not uncommon
Cushing's syndrome	
With adrenal neoplasm	30-1,000
Without adrenal neoplasm	8-40
Adrenogenital syndrome	
With adrenal neoplasm	30-1,000
With adrenal hyperplasia	Invariably elevated; up to 120 mg.
Postpuberal hirsute female without virilism	Majority show no evident adrenal cortical overactivity

poor eosinopenic response should be interpreted with caution. Low initial counts make interpretation almost impossible. Best and his associates reported that one sixth of the nonaddisonian subjects studied by them showed greater than a 50% fall in eosinophils on administration of placebos, whereas another one-sixth showed less than a 40% fall with ACTH. Repeated failure of ACTH to produce significant eosinopenia provides strong evidence for nonfunctioning adrenals. The ACTH test is valueless in adrenal cortical hyperfunction.

In Addison's disease, the inhibitory effect of the cortical hormone(s) on peripheral glucose utilization is diminished and gluconeogenesis is impaired. Therefore, the patient shows pronounced insulin sensitivity and, when fasted, becomes hypoglycemic. Dysfunction of carbohydrate metabolism may be demonstrated by a glucose tolerance test, insulin sensitivity

tests or fasting, all of which are dangerous and must be done in the hospital. The intravenous glucose tolerance test is preferred to the oral. Hypoglycemia may or may not develop in the patient with Addison's disease. If it does, the manifestations usually appear by the third hour and persist if untreated. A more certain, but more dangerous technic involves fasting for 24-36 hours, during which most, but not all, patients with Addison's disease will have a progressive fall in blood sugar. Insulin sensitivity tests are not recommended.

The quantitative determination of urinary 17-ketosteroid excretion can be used to evaluate adrenal cortical function (table). The finding of small amounts is supportive evidence for Addison's disease but, since many chronic illnesses may also lead to low outputs of steroid the finding does not constitute conclusive evidence. However, if the urinary excretion of 17-ketosteroids is normal, adrenal insufficiency is unlikely.

[The Cutler-Power-Wilder test was proposed at a time when the many present useful tests for the diagnosis of adrenal cortical insufficiency were not known. It is a most rigorous test of adrenal function and is potentially hazardous. Its use these days is probably rarely warranted.—Ed.]

Diagnostic Significance of 17-Ketosteroids is reviewed by Joseph W. Jailer[2] (Columbia Univ.). The measurement of the urinary steroids having a ketone group on position 17 makes use of the colorimetric Zimmerman reaction or the Pincus blue reaction. The latter is more specific because it does not react with 20-ketosteroids; however, it fails to demonstrate dehydroisoandrosterone, one of the important 17-ketosteroids excreted by patients with adrenal tumors. These colorimetric methods measure both biologically active and inert 17-ketosteroids arising from the adrenals, testes and possibly the ovaries.

The normal range is 10-20 mg./24 hours in men and 8-15 mg. in women, with lower values for children and the aged. Many factors alter these levels, including changes in renal clearance. Carinamide, for example, will block renal excretion. Since the adrenals contribute two thirds of the normal value in males, the absence of the testes may not reduce the value below normal range. For this reason male hypogonadism is not diagnosed by the 17-ketosteroid level; nor is Addison's

(2) M. Clin. North America 36:757-766, May, 1952.

disease, although the value is usually below normal. In hypopituitarism, with loss of both adrenal and gonadal function, extremely low values may be seen. However, hypothyroidism, hyperthyroidism or any chronic disease may result in very low excretion. In diagnosis of adrenal insufficiency, ACTH, 100 mg./day for two days, is administered; 17-ketosteroid excretion will show a rise of about 100% if the adrenals are normal.

Conversely, high 17-ketosteroid values are of diagnostic aid in several disorders. When precocious puberty is due to a Leydig cell tumor, values may be 100 mg./day. In adrenogenital syndrome the level may reach 200 mg./day. In the diagnosis of adrenal adenoma and especially carcinoma, the simple Allen sulfuric acid test may be used to demonstrate that as much as 50% of the 17-ketosteroid is dehydroisoandrosterone. In adrenal virilism syndromes the success of cortisone treatment may be judged by following the decline in 17-ketosteroid level. If a tumor or carcinoma is present, cortisone will be without effect since the tumor escapes from endogenous ACTH regulation. Because Cushing's disease is the result of too much cortisone, not androgen, the 17-ketosteroid level is usually normal or only slightly elevated, unless adrenal carcinoma is present to cause a great elevation. The success or failure of surgical removal can be gauged by following the subsequent urinary 17-ketosteroid values.

Simplified Water-Loading Test for Diagnosis of Addison's Disease. Louis J. Soffer and J. Lester Gabrilove[1] (Mount Sinai Hosp., New York City) present a simplified modification of the Robinson-Power-Kepler water diuresis test for the diagnosis of Addison's disease. The fasting patient voids at 8 a.m., and the urine is discarded. He then drinks 1,500 cc. tap water over 20 minutes, and the urine is collected for 5 hours.

Twelve normal subjects voided 1,200-1,900 cc. during the five hour period. In nine patients with Addison's disease treated with desoxycorticosterone and in two with untreated hypopituitarism, the greatest five hour volume was 780 cc. (Fig. 34). Cortisone, 50 mg. orally, four hours before ingestion of water, usually caused significant improvement, sometimes

(1) Metabolism 1:504-510, November, 1952.

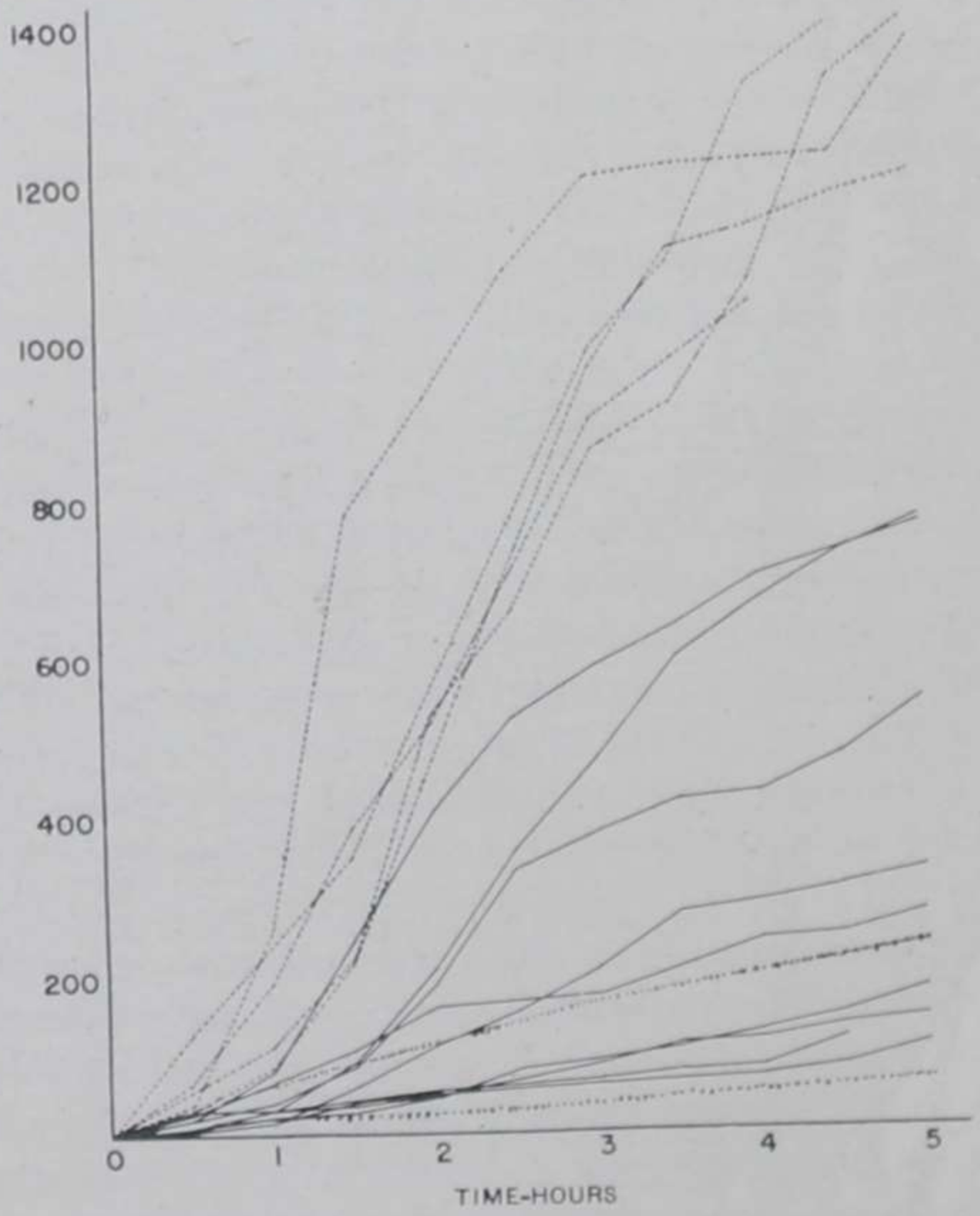

Fig. 34.—Cumulative urine volume excreted in five hours after oral ingestion of 1,500 cc. water. Dashed lines indicate normal subjects, solid lines, patients with Addison's disease and dotted lines, patients with hypopituitarism. (Courtesy of Soffer, L. J., and Gabrilove, J. L.: Metabolism 1:504-510, November, 1952.)

to normal. ACTH therapy was effective in this manner only in the patients with hypopituitarism. Failure of water diuresis may also occur in hepatic and renal disease, dehydration or edematous states.

[This test appears to be a useful simplification of the cumbersome Robinson-Power-Kepler test and should be given extensive trial.—Ed.]

Estimation of 17-Hydroxycorticoids in Urine. William J. Reddy, Dalton Jenkins and George W. Thorn[3] (Boston) describe a method for the estimation of free and conjugated adrenal cortical steroids in urine. The procedure is based on serial extractions with chloroform and butanol at pH 1.0; colorimetric measurement of 17-hydroxycorticoids is carried out with the phenylhydrazine-sulfuric acid reaction described by Porter and Silber.

(3) Metabolism 1:511-527, November, 1952.

METHOD.—Estimation of total 17-hydroxycorticoids is done on a 24 hour urine specimen collected in the cold (0-4 C.) without preservative and stored in the frozen state until extraction. Whenever possible, specimens are processed within 24 hours. An aliquot (5-20 ml., depending on the 17-hydroxycorticoid value expected) is adjusted to pH 1.0 (indicator paper) by the dropwise addition of 50% sulfuric acid. Two successive extractions are carried out with 0.5 volume n-butanol, with a minimum of three minutes each time. Emulsions are readily resolved by centrifugation. The combined extracts are washed once with 0.2 volume 0.1 N sodium hydroxide followed by 0.2 volume N sulfuric acid. Each wash is shaken one minute only. Colorimetry should be performed immediately after completion of extraction.

For estimation of free 17-hydroxycorticoid a 20 ml. aliquot of urine is extracted twice at pH 1.0 with 10 ml. chloroform. The combined $CHCl_3$ extracts are washed successively with 4 ml. each of 0.1 N sodium hydroxide, 0.01 N sulfuric acid and distilled water (until washes are neutral). The extract is dried over 2 Gm. anhydrous sodium sulfate and filtered through glass wool. The filtrate is divided into two equal volumes and evaporated to dryness at room temperature under a stream of air. Each residue is dissolved in 1 ml. butanol and the colorimetric procedure carried out. The calculation is altered only by the concentration factor achieved by evaporation.

Estimation of conjugated 17-hydroxycorticoids is determined by the procedure for total corticoids performed on a suitable aliquot of the residual urine remaining after chloroform extraction.

Butanol (Merck) has consistently proved to be free from chromogens which interfere seriously with the colorimetric procedure. The major source of potential error in the method described depends on the high reagent blanks that are intrinsic to the Porter-Silber reaction.

[The Porter-Silber color reaction is a sensitive test for corticoids. It is not, however, specific and therefore is of greatest use in the assay of extracts from which other chromogens have been removed chemically. Butanol, a highly polar solvent which extracts from urine many chromogens other than corticoids, gives a high blank reading with the Porter-Silber color reaction. Although this test is undoubtedly sufficiently sensitive for the detection of changes in corticoid excretion induced by corticotrophin, I do not believe it is adequate for the diagnosis of adrenal cortical insufficiency or mild excess.—Ed.]

Blood Levels of 17-Hydroxycorticosteroids Following Administration of Adrenal Steroids and Their Relation to Levels of Circulating Leukocytes. Don H. Nelson, Avery A. Sandberg, J. G. Palmer and Frank H. Tyler[4] (Univ. of Utah) determined the relationship of changes in blood steroid levels and changes in leukocytes after giving standard doses of vari-

(4) J. Clin. Invest. 31:843-849, September, 1952.

ous corticosteroids to normal subjects. Compound E (cortisone), compound F (hydrocortisone) and compound S were administered as free alcohols and as acetate esters.

After a test dose of 200 mg. compound F acetate orally, the peak plasma steroid level was reached within one hour and then fell rapidly. Lymphocytes and eosinophils showed negligible changes during peak steroid level, but fell markedly at four hours when the steroid levels had fallen sharply. The at four hours when the steroid levels had fallen sharply. The fall in lymphocytes and eosinophils was always accompanied by a pronounced rise in neutrophils and total white cell

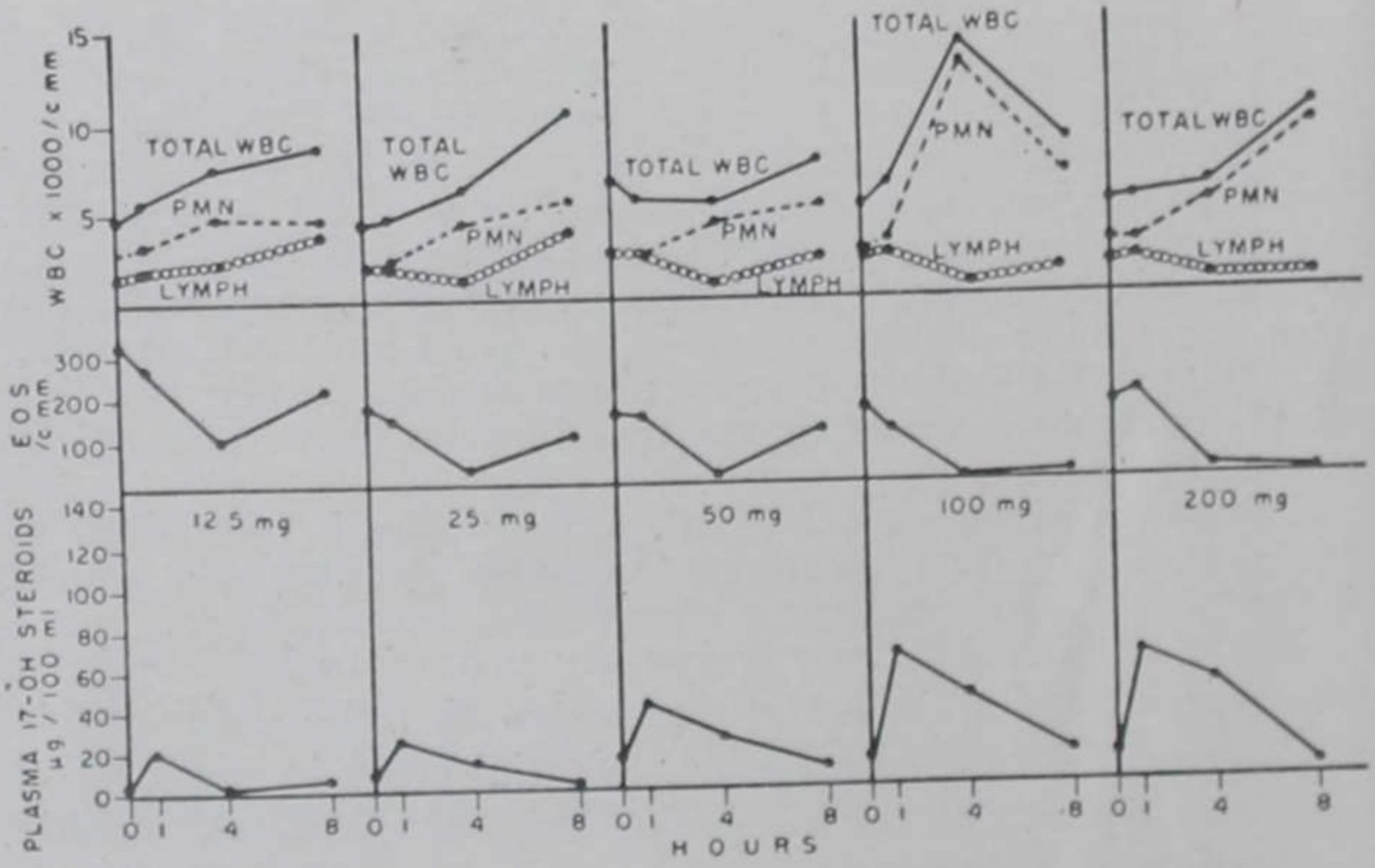

Fig. 35.—Effect of varying doses of compound F acetate given orally to a single subject. (Courtesy of Nelson, D. H., *et al.*: J. Clin. Invest. 31:843-849, September, 1952.)

count. A single intramuscular injection of 200 mg. compound F acetate produced no rise in blood steroid levels and no effect on the leukocytes, although these changes were noted after injection of the free alcohol. In one person given oral doses of compound F acetate ranging from 12.5 μ to 200 mg. to measure the relation between dose and response, the rise in blood steroid level was progressively greater and more prolonged as the dosage increased (Fig. 35). Eosinophil levels fell at all dosage levels, but with each increase they remained at low levels for longer periods. The decrease in lymphocytes was roughly correlated with dosage.

Cortisone orally, either as the acetate or as the free alco-

hol, also promptly raised plasma 17-hydroxycorticosteroid levels. The leukocyte changes appear to lag behind the steroid changes by 3-6 hours: after 24 hours both eosinophils and lymphocytes often rose higher than control levels. This may reflect a period of decreased adrenal activity or result from increased cell production after their destruction.

The mechanism producing the variable neutrophilia after steroid administration is obscure. Compound S given as the acetate or free alcohol either orally or intramuscularly produced no significant changes in either steroid levels or cells.

Statistical Analysis of "ACTH Test": Changes in Eosinophil Count in Normal and in Psychoneurotic Subjects. Renewed interest in relations between adrenocortical hormones and human behavior led Harley C. Shands and Frederic C. Bartter[5] (Massachusetts Gen'l Hosp.) to study the rate of disappearance of circulating eosinophils in 22 psychoneurotics and 18 normal subjects after intramuscular administration of 25 mg. ACTH. No differences were noted between the two groups. Although the rate of fall in males and females did not differ, counts for females were significantly lower. Statistical analysis of the data revealed that 95% of normal subjects may be expected to show 62-78% drop from the initial count.

Evaluation of Eosinophil Counts. J. Norrie Swanson, Walter Bauer and Marian Ropes[6] (Harvard Med. School) observed spontaneous diurnal variation in the number of circulating eosinophils in five healthy and eight arthritic subjects who received no medications during the study. Four examples

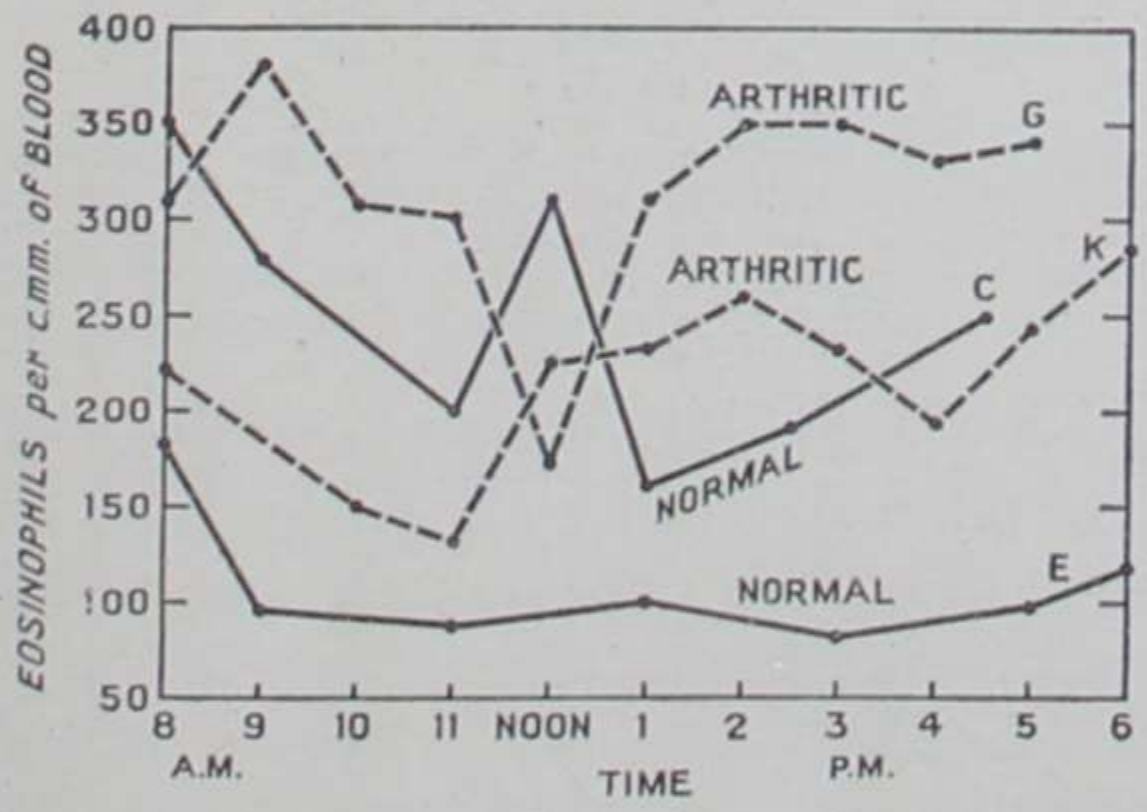

Fig. 36.—Examples of diurnal variation in number of circulating eosinophils. (Courtesy of Swanson, J. N., *et al.*: Lancet 1:129-132, Jan. 19, 1952.)

(5) J. Clin. Endocrinol. 12:178-183, February, 1952.
(6) Lancet 1:129-132, Jan. 19, 1952.

are shown in Figure 36. Usually there is a high morning count which falls until midday, then after a slight rise the count falls again in the early afternoon, finally rising toward evening. The percentage change in eosinophils that occurs spontaneously is shown in Figure 37. A morning four hour fall greater than 50% occurred eight times in 4 of the 13 subjects.

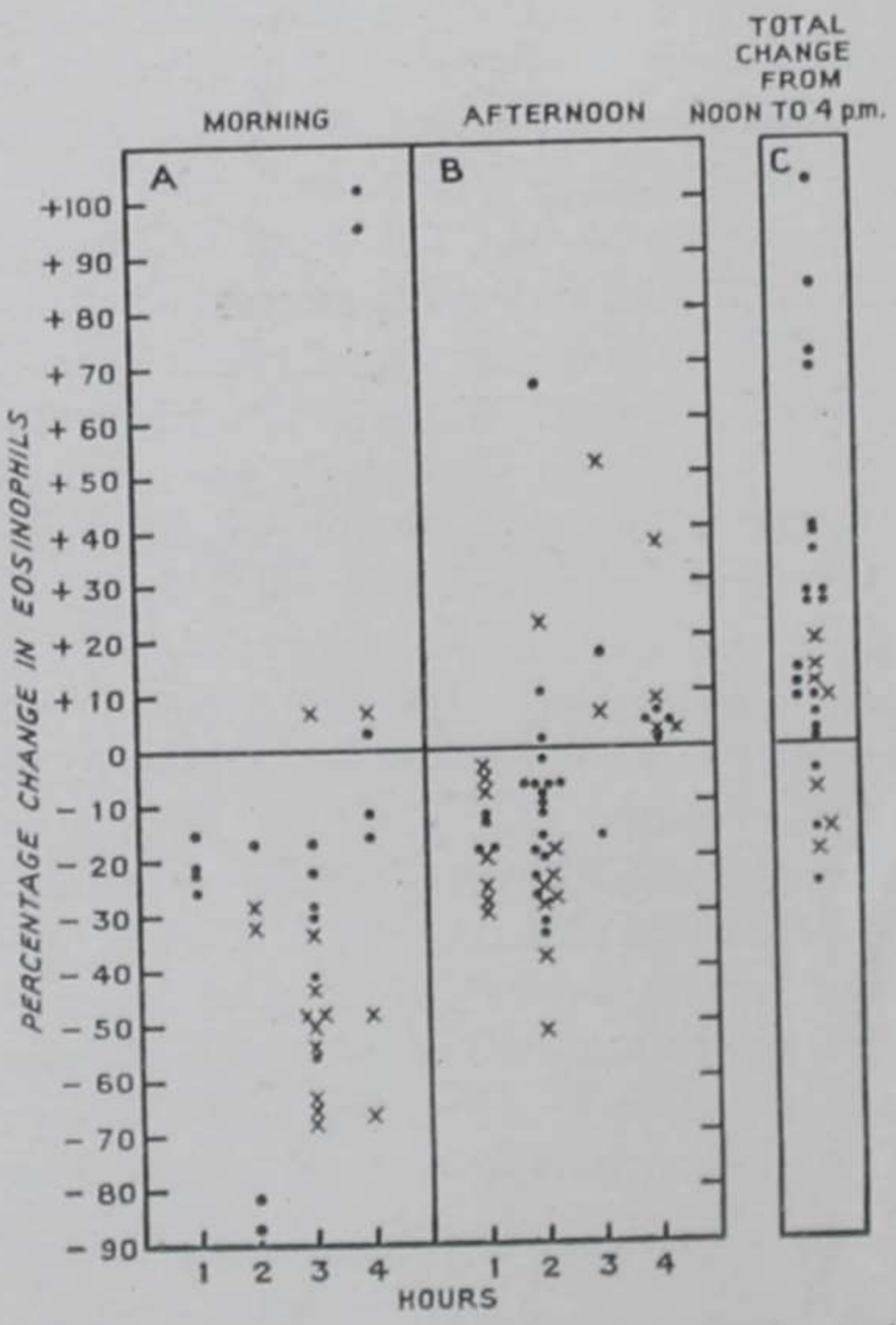

Fig. 37.—Comparison of spontaneous and uninterrupted morning and afternoon changes in eosinophil counts. Data for normal subjects is indicated by crosses; for arthritic subjects, by dots. *A* and *B* show rise or fall during period stated until terminated by clearage of direction. *C* shows total change (including both fall and rise) during four hours. (Courtesy of Swanson, J. N., *et al.*: Lancet 1:129-132, Jan. 19, 1952.)

Figure 37 also shows the total change from noon to 4 p.m.; the early afternoon fall was offset by a greater rise later.

On three occasions in one subject spontaneous morning falls were equal to, or greater than, those after administration of epinephrine or corticotrophin. These data must be considered in evaluating the ACTH test and in comparing solitary eosinophil counts. The morning is obviously an unsuitable time for measuring induced eosinophil falls, whereas the

afternoon is more reliable. The effect of meals may be disregarded, since eating or fasting does not alter the diurnal variation. Since the maximal effect can occur before the fourth hour, it is recommended that counts be done at the second or third hours if the fourth hour indicates a poor response.

[The preceding two reports fill an important gap in essential information, namely, the sensitivity of the circulating eosinophil count as an index of adrenal cortical function. Specificity of this index remains to be studied, particularly since it has been shown that epinephrine reduces the circulating eosinophil count in the absence of the adrenal gland. These studies also show that many results of Thorn tests done in the past were of doubtful value, since the tests were performed for the most part in the morning, at which time spontaneous falls of circulating eosinophil counts may occur. —Ed.]

Does Epinephrine Eosinopenia Reflect Pituitary-Adrenal Function in Man? Since first used by Recant, Hume, Forsham and Thorn (1950), the injection of 0.3 mg. epinephrine to cause a 50% fall in eosinophils was thought to measure pituitary-adrenal function. Statistical analyses of large numbers of such tests proved that they do not accurately assess adrenal function. To demonstrate the inadequacies of this test, Robert M. Kark and Robert C. Muehreke[7] (Univ. of Illinois) studied three patients with carcinoma of the prostate who had both adrenals and testes removed. They were maintained with cortisone orally. The injection of ACTH or saline alone failed to alter circulating eosinophils. However, four hours after 0.3 mg. epinephrine was injected, the patients had falls of 78, 54 and 36%. If the patient is not on maintenance cortisone therapy, the eosinopenia will not occur. Cortisone and epinephrine added to blood in vitro will not cause eosinopenia. It is suggested that the two hormones act on some organ such as the lung to cause it to trap and destroy eosinophils. Blood samples from pulmonary artery and vein during cardiac catheterization support this belief. It may be concluded that the epinephrine eosinopenia test cannot be used to test the integrity of the pituitary-adrenal system in man.

Stimulating Effect of Chorionic Gonadotrophin on the Adrenal Cortex. W. P. Plate[8] (Univ. of Utrecht) treated two castrated women and a eunuchoid man with severe genital atrophy with 60,000-70,000 I.U. chorionic gonadotrophin for three to five days. During therapy, 17-ketosteroid excretion rose in all patients (maximal rise from 7.7 mg./24 hours be-

(7) Lancet 1:1189-1190, June 14, 1952.
(8) Acta endocrinol. 11:119-126, 1952.

fore treatment to 15.3 mg.); in the man and one woman, estrogen excretion rose to over 50 I.U./24 hours. These changes can be attributed to stimulation of the adrenal cortex by chorionic gonadotrophin.

Role of Adrenal Glands in Glyconeogenesis was investigated by A. Góth, L. Lengyel and E. Bencze[9] (Budapest). The response of blood sugar to administration of 0.5 Gm. boiled egg white was determined in the following groups of rats which had fasted 16 hours before the experiments: normal rats, bilaterally adrenalectomized rats, adrenalectomized rats after transplantation of two functional rat adrenals and adrenalectomized rats after subcutaneous administration of 1 mg. cortisone and after subcutaneous administration of 0.5 mg. desoxycorticosterone acetate. Controls consisted of normal and adrenalectomized rats not fed protein and rats with a sham operation fed protein. The normal rats, rats with adrenal transplants and the cortisone-treated adrenalectomized rats showed a significant increase in blood sugar content after administration of protein, whereas there was a significant decrease in blood sugar in the adrenalectomized rats and DCA-treated adrenalectomized rats.

The authors concluded that adrenal function is necessary for the increase in the blood sugar content after oral administration of protein, that DCA does not stimulate glyconeogenesis from protein in adrenalectomized rats but that cortisone or transplanted adrenal glands are effective.

Further Studies on Properties of Highly Active Mineralocorticoid. H. M. Grundy, S. A. Simpson, J. F. Tait and M. Woodford[1] (Middlesex Hosp. Med. School) used paper chromatography fractionation to study various adrenal extracts; fractions were assayed for "mineral" activity by means of radioactive sodium-potassium ratios in the urine of adrenalectomized rats. A highly active mineralocorticoid was found in beef adrenal gland extract. This compound is not any of the known α-ketol steroids, either active or inactive, which have been isolated in crystalline form from adrenal gland extracts. It was also found in hog adrenal extract and in significant physiologic amounts in monkey and dog adrenal perfusate.

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(9) Acta med. scandinav. 142:102-107, 1952.
(1) Acta endocrinol. 11:199-220, 1952.

The mineralocorticoid proved to be extremely sensitive to heat, dilute mineral acid and weak alkali, ultraviolet light and acetylation. This property, together with the hydrophilic nature of the mineralocorticoid, agrees with that of the amorphous fraction of Wintersteiner and Pfiffner, and others. Neglect of this active fraction, particularly by chemical investigators, may have been due to its destruction by the more efficient methods for separation. The reaction with triphenyl tetrazolium chloride of a compound consistently associated with the biologic activity suggests that the mineralocorticoid is about 25 times more active than desoxycorticosterone acetate.

[The discovery of this compound has caused great excitement. It has revived the concept—formerly all but moribund—that the salt retention caused by the adrenal cortex is mediated by a particular specialized "salt" compound. In all fairness, I suppose the matter must be considered controversial.—Ed.]

Effect of Fractures on Urinary Electrolytes in Nonadrenalectomized Rats and in Adrenalectomized Rats Treated with Adrenal Cortex Extract. In a series of experiments which question the central role of the adrenal in the metabolic response to stress, Dwight J. Ingle, Robert C. Meeks and Kathryn E. Thomas[2] (Kalamazoo, Mich.) demonstrated that adrenalectomized animals given a uniform intake of adrenal cortical extract still show a normal metabolic response to injury. Retention of urinary sodium and chloride following fractures was studied in rats. Six sham operated rats, given control (saline) injections were compared with six adrenalectomized rats maintained on 4 cc. adrenal cortical extract each day. Both groups lived in otherwise similar circumstances and received a fracture of the tibia, knee and femur of both back legs while anesthetized. Both groups showed a similar post-injury rise in urinary nitrogen and potassium and a sharp decrease in urinary sodium and chloride followed by a compensatory rebound and return to normal values. It was concluded from these experiments that the observed responses to injury were not mediated by a change in the secretory activity of the adrenal cortex.

[Since adrenal corticoids cause retention of sodium and chloride and excretion of nitrogen and potassium, it would seem reasonable to assume that the occurrence of such changes after "stress" were possibly mediated by the adrenal cortex. This neat study shows clearly that these effects of "stress" are not mediated by the adrenal.—Ed.]

(2) Endocrinology 49:703-708, December, 1951.

Postoperative Potassium Deficit and Metabolic Alkalosis: Pathogenic Significance of Operative Trauma and of Potassium and Phosphorus Deprivation. Leonard P. Eliel, Olof H. Pearson and Frederick C. White[3] (Sloan-Kettering Inst.) studied two patients to evaluate the relative role of low potassium intake and operative trauma in the production of the syndrome characterized by apathy, lethargy, muscular weakness, abdominal distention and ileus, cardiac arrythmias and edema. This syndrome was noted in patients maintained postoperatively on parenteral fluids or on a dietary intake low or lacking in potassium and in whom hypopotassemia, hypochloremia and metabolic alkalosis and ECG changes consistent with potassium deficit were found. There was prompt reversal of clinical and blood chemical abnormalities on administration of adequate potassium.

One patient studied received no potassium or phosphorus postoperatively. The other received optimal amounts of both. Both patients underwent major operations for suspected or proved neoplasms and both were maintained on constant caloric and protein intakes. Metabolic changes were similar in both patients postoperatively, although they were more pronounced in the one who received no potassium or phosphorus. Both showed a loss of protoplasm as evidenced by negative balances of nitrogen, potassium and phosphorus and intracellular depletion of potassium and phosphorus. Metabolic alkalosis and hypochloremia and eosinopenia appeared and urinary excretion of uric acid, creatine, formaldehydogenic steroids and ketosteroids increased. These are changes that bear a striking resemblance to those seen in patients with hyperadrenocorticism, whether spontaneous or induced by ACTH or cortisone. Deprivation of potassium and phosphorus in one patient preoperatively resulted in intracellular losses of these elements but failed to increase nitrogen loss or produce any evidence of increased adrenal cortical function.

These findings suggest that a post-traumatic increase in adrenal cortical steroid production resulted in the metabolic changes observed. This is strengthened by the occurrence of such changes despite substantial and constant intakes of potassium and phosphorus. It has not been established whether similar changes with respect to nitrogen and the electrolytes

(3) Clin. Invest. 31:419-432, April, 1952.

would occur post-traumatically in the absence of a hyperadrenocortical state. On the other hand, provision of adequate potassium ion was accompanied by diminished losses of nitrogen, potassium and phosphorus and creatine, suggesting that potassium deprivation may have played an important role in these losses.

ADRENALECTOMY

Physiologic Effects of Bilateral Adrenalectomy in Man. Vincent P. Hollander, Charles D. West, Willet F. Whitmore, Jr., Henry T. Randall and Olof H. Pearson[4] (Memorial Cancer Center, New York City) report on 22 patients given cortisone as the only replacement therapy. The acute stress of surgery demands large quantities of cortical hormone. These needs were met with 300 mg. free cortisone intravenously on first day, with dosage gradually reduced thereafter, or by intramuscular injection of the much less soluble cortisone acetate in similar but divided dosage.

Starting a few days after operation, all patients were maintained on 37.5-75 mg. cortisone acetate by mouth daily in two to four divided doses. Patients on diets containing over 80 mEq. salt did not require supplementation. Maintenance dosage of cortisone was adjusted to individual needs. Most sensitive criterion for adequate replacement was the subjective state; patients on adequate therapy felt well and strong and had normal appetites; on inadequate therapy, they felt weak, lost the sense of well-being and soon had anorexia. Before there was laboratory evidence of adrenal insufficiency, patients began to look gaunt and haggard, in sharp contrast to their normal appearance. Other clinical criteria for adequate maintenance were constant daily body weight and normal blood pressure and temperature. Pigmentation was not noted. Pubic and axillary hair grew again in ovariectomized, adrenalectomized women who had adequate cortisone replacement.

Patients maintained on cortisone alone (average 50 mg./day) had normal serum electrolyte concentrations. Hypoglycemia did not appear during 24 hour fast; insulin and glucose tolerance either were normal or showed slightly diabetic curves. Most patients could respond to a water load by increased urinary volume and decreased urinary specific gravity.

Withdrawal of cortisone maintenance therapy in six pa-

(4) Cancer 5:1019-1024, September, 1952.

tients resulted in prompt symptoms and signs of adrenal insufficiency. Physiologic changes were characterized by prompt antidiuresis on cortisone withdrawal and prompt water diuresis on resumption of therapy. These observations indicate that water intoxication is an important feature of the physiologic effects of adrenal insufficiency in man.

These preliminary observations would indicate that cortisone may represent complete replacement for the normal adrenal cortex.

[A puzzling feature of this report is the fact that totally adrenalectomized patients, unlike patients with spontaneous or tuberculous Addison's disease, can be maintained by the administration of cortisone alone. It is also surprising that growth of pubic and axillary hair occurred in adrenalectomized women without administration of androgens.—Ed.]

Study of Bilateral Adrenalectomy in Malignant Hypertension and Chronic Nephritis: Preliminary Report. By total adrenalectomy, J. Hartwell Harrison, George W. Thorn and Modestino G. Criscitiello[5] (Harvard Med. School) planned to eliminate as far as possible the salt-retaining hypertensive factors of the adrenal, desoxycorticosterone-like substances, and to attempt to modify the cortisone-DCA substitution ratio thereafter for each patient in proportions compatible with an active sedentary existence, at the same time avoiding salt and water retention. Fourteen patients were selected (nine hypertensives and five nephritics with hypertension), all of whom had failed to respond to strict medical treatment and were considered too far advanced for sympathectomy. Bilateral total adrenalectomy was completed in 13 and unilateral adrenalectomy in 1. Hormonal substitution therapy consisted of 100 mg. cortisone given intramuscularly the night before operation and repeated the next morning before surgery. During operation, aqueous adrenal cortical extract, 100-200 cc., and neo-synephrine,® 20-50 mg., by intravenous drip were given as required for circulatory stability. Cortisone, 50 mg. every 6 hours, was given intramuscularly during the first 48 hours after operation and gradually reduced to 37-25 mg./day as a maintenance dose. Salt depletion was avoided in the late postoperative period by adding 3 + Gm. sodium chloride to the diet and/or DCA, 1 mg./day three to six times weekly.

Of the group with bilateral total adrenalectomy, two pa-

(5) J. Urol. 67:405-413, April, 1952.

tients died of renal failure and two of cardiac complications of vascular disease. Seven were definitely improved both subjectively and objectively. Specific symptoms relieved include headache, weakness, palpitation, substernal oppression, orthopnea, dyspnea, ascites and edema of the extremities. There was a notable disappearance of anxiety in most cases. Accompanying clinical signs were a striking decrease in heart size, clearing of lung fields, increase of vital capacity, diminution of hepatic enlargement, improved exercise tolerance and loss of edema. Concomitantly, there was an accompanying weight loss due to sustained diuresis of sodium chloride and water. Significant decrease in blood pressure with excellent toleration occurred in four; three others showed moderate improvement in blood pressure and two, no essential change. The authors attribute improvement to elimination of desoxycorticosterone-like factors and regulation of DCA and cortisone administration as necessary thereafter to avoid excessive retention of sodium and water as well as relative hypotension.

Clinical Studies on Bilateral Complete Adrenalectomy in Patients with Severe Hypertensive Vascular Disease. George W. Thorn, J. Hartwell Harrison, John P. Merrill, Modestino G. Criscitiello, Thomas F. Frawley and John T. Finkenstaedt[6] (Harvard Med. School) report on 15 patients with hypertension on whom bilateral complete adrenalectomy had been carried out more than one year previously. That adrenal cortical hormones are involved in the maintenance of hypertension has been suggested by aggravation of hypertension after ACTH therapy and by fall in blood pressure to normal or subnormal levels in hypertensive patients in whom Addison's disease develops. Such addisonian patients can be restored to a state of well-being without return of hypertension by treatment with cortisone combined with a minimal quantity of desoxycorticosterone.

The 15 hypertensive patients chosen for adrenalectomy were given a battery of cardiovascular, renal and endocrine tests. Advanced malignant hypertension was present in 11; advanced glomerulonephritis was the cause of hypertension in 3. Preoperative preparation included low salt diet, digitalis and diuretics to obtain maximal circulatory efficiency. Corti-

(6) Ann. Int. Med. 37:972-1005, November, 1952.

sone, 100 mg., was given the night before and repeated two hours before surgery. During the operation 100-200 ml. aqueous adrenal extract was administered intravenously with neosynephrine.® After surgery, 50 mg. cortisone was given every 6 hours for 48 hours, then gradually reduced to 25 mg. daily. Patients without congestive failure received 250-500 ml. NaCl

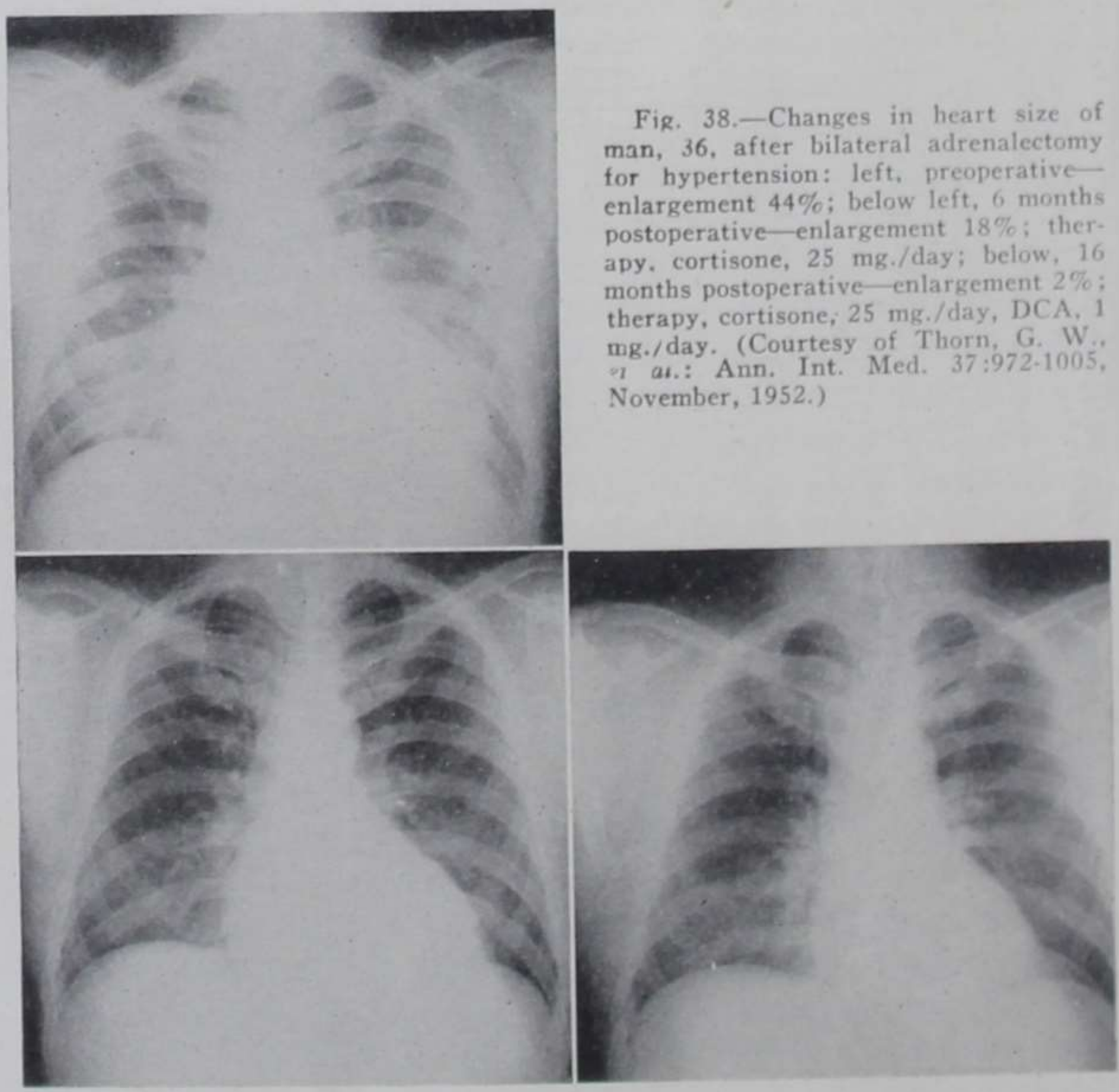

Fig. 38.—Changes in heart size of man, 36, after bilateral adrenalectomy for hypertension: left, preoperative—enlargement 44%; below left, 6 months postoperative—enlargement 18%; therapy, cortisone, 25 mg./day; below, 16 months postoperative—enlargement 2%; therapy, cortisone, 25 mg./day, DCA, 1 mg./day. (Courtesy of Thorn, G. W., *et al.*: Ann. Int. Med. 37:972-1005, November, 1952.)

intravenously in the first 24 hours if blood pressure and circulation warranted. All other fluid given parenterally was sodium chloride free. All but 3 of the 15 pairs of glands were grossly and histologically normal; one showed congestion, another hyalinization of capsular vessels and the third, degeneration of the zona fasciculata. Subsequent autopsy on nine showed no evidence of accessory adrenal tissue.

The nine patients who survived more than one month had

no evidence of any adrenal function. Although a darkening of skin pigmentation was indicated by spectrophotometric recordings, visual examination showed no change, with one exception. Apparently the maintenance of near-normal levels of circulating 11,17-oxysteroids inhibited development of severe pigmentation. Most patients had a surprising sense of well-being immediately after operation. A striking diuresis of sodium, as much as 400 mEq./day, was usually seen despite cortisone therapy in patients without renal failure. Edema, when present, disappeared and heart size was reduced appreciably. Desoxycorticosterone promptly stopped the sodium diuresis and restored cardiomegaly. Excessive sodium and chloride depletion required careful observation.

Of nine patients who survived more than 3 months, hypertension was definitely improved in two, one of whom was completely rehabilitated and returned to work until he died of acute coronary occlusion 11 months after operation. Three of the other six had symptomatic improvement without significant change in the basal blood pressure. Hypertensive patients in whom congestive failure is the chief cause of disability are likely to obtain considerable improvement. This is seen in the decrease in heart size after operation (Fig. 38). The blood urea nitrogen content rose 10-20 mg./100 ml. in 10 of 14 patients. In no case did renal function improve. Impaired renal function seems to be the most important single limiting factor. The susceptibility of the adrenalectomized patient to sudden withdrawal of maintenance hormonal therapy cannot be overemphasized. Fatal collapse was observed within a period as short as 48 hours.

It is concluded that bilateral adrenalectomy is feasible and possibly useful in patients with rapidly advancing malignant hypertension, without renal impairment and nitrogen retention, who have failed to respond to medical therapy.

[It is to be understood that this radical procedure was undertaken only when the prognosis was otherwise hopeless. The introduction of new antihypertensive drugs may alter the outlook for these patients. Meanwhile, valuable information has been provided by these investigations. —Ed.]

Addison's Disease

Addison's Disease Due to Chronic Disseminated Coccidioidomycosis. Patrick J. Maloney[7] (Springville, Calif.) reports

(7) A.M.A. Arch. Int. Med. 90:869-878, December, 1952.

a case and presents again the first reported case of Butt and Hoffman (1945). Possible reasons for the rarity of Addison's disease due to disseminated coccidioidomycosis may be early death from meningitis, extensive bronchopneumonia or cardiac failure or the rare occurrence of complete destruction of the adrenal glands by the disease. It is estimated that less than 5% intact residual adrenal tissue must be present for the typical clinical picture of Addison's disease to appear.

Primary idiopathic atrophy of the adrenals accounts for 50% of the cases of Addison's disease. Most of the others are due to bilateral caseous tuberculosis. The incidence of these is decreasing because there are fewer cases of tuberculosis. Rare causes include amyloid degeneration, metastasizing tumors of the lymphoma type, metastatic tumors from bronchogenic carcinoma, hemorrhage due to trauma or vascular disease, inflammatory changes associated with burns or sepsis, syphilis, adrenal tumors of androgenic type causing replacement of the normal hormone-producing cells of the adrenal cortex, and histoplasmosis.

In Butt and Hoffman's case a history of established coccidioidal disease of two years' duration was obtained. Signs and symptoms of Addison's disease were present ante mortem, and the diagnosis was suggested by an observer. The complete destruction of the adrenals by coccidioidal granulomas found at autopsy confirmed the diagnosis. The arrested primary pulmonary lesion was identified. The patient had failed to react on skin testing with a standard preparation of coccidioidin but did react positively with antigen prepared from his own organisms.

In Maloney's case, coccidioidal disease was of two years' duration. Initially, there was swelling over the right shoulder blade with intermittent purulent discharge. Fine granular infiltrates were present in both lungs. Skin tests and serologic study confirmed the coccidioidal origin of the pulmonary lesion. Slight fatigue and a 10 lb. weight loss in two years were the only constitutional symptoms. Six months later culture from a fluctuant swelling over the upper end of the sternum revealed mycelium of coccidioides. At the final hospitalization acute adrenal insufficiency was diagnosed. Despite therapy, death ensued. The adrenal glands weighed 20 Gm. and their normal architecture had been completely replaced. Final diag-

noses were: (1) disseminated coccidioidal granulomas, with involvement of lungs and adrenal glands, periaortic and hilar lymph nodes, and meninges; (2) extensive destruction of adrenal tissue by coccidioidal granulomas, and (3) subacute myocarditis.

Addison's Disease Secondary to Metastatic Carcinoma of Adrenal Glands. John M. Butterly, Louis Fishman, Jules Seckler and Herman Steinberg[8] (Queens Gen'l Hosp., Jamaica, N. Y.) report three proved and one probable case observed within two years. The condition is probably more common than usually realized, and diagnosis is often missed because of the resemblance of the addisonian picture to the cachectic state of advanced malignancy with widespread metastasis. Unless patients with increased pigmentation, cachexia, weight loss, asthenia, hypotension and cramplike pains are investigated for adrenal cortical hypofunction by electrolyte, endocrine and carbohydrate tolerance studies, the presence of a malignant condition may be used to explain the whole picture.

Man, 58, with weakness, anorexia and weight loss, was found to have an inguinal mass, which on biopsy proved to be a metastatic lesion of adenocarcinoma of undetermined site. A chest x-ray film showed a right hilar mass. The patient was emaciated and asthenic and appeared chronically ill. There were numerous deeply pigmented spots on the face, arms, chest and back. All blood studies gave normal results except for moderate anemia. After one month of hospitalization, generalized pigmentation was noted. The asthenia became worse, blood pressure fell, blood chlorides, sugar and sodium levels were low and the potassium level was high normal. Results with a Robinson-Power-Kepler water test were positive in parts I and II. Addison's disease secondary to bilateral adrenal destruction from metastasizing bronchogenic carcinoma was diagnosed after the urinary 17-ketosteroid excretion was found to be 4.3 mg./24 hr. The patient was treated with desoxycorticosterone acetate but died in three weeks.

Autopsy revealed a bronchogenic carcinoma, with gross metastatic involvement of the lymph nodes, both adrenals and the jejunum. Microscopic examination of the adrenals revealed complete replacement of the glandular structure by tumor with hyalinosis and fibrosis.

Addison's Disease Due to Metastatic Bronchogenic Carcinoma, reported by Jacques B. Wallach and William B. Scharfman[9] (Jamaica, N. Y.) is extremely rare, although adrenal involvement is not.

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(8) Ann. Int. Med. 37:930-939, November, 1952.
(9) J.A.M.A. 148:729-731, Mar. 1, 1952.

Man, 58, complaining of anorexia, weakness and weight loss for 12 months, presented a homogeneous density of the upper right lung on x-ray examination and an inguinal mass which biopsy showed to be adenocarcinoma. Blood pressure was normal and there was no abnormal pigmentation. Weakness and fatigue persisted, and six weeks later asthenia was marked, skin pigmentation was noted, blood pressure dropped to 85/60 and Addison's disease was suspected. A Robinson-Kepler-Power test gave positive results; serum chloride content was 96 mEq./L., potassium 20.5 mg./100 cc. and sodium 122 mEq./L. A glucose tolerance curve was of a mild diabetic type. Therapy with desoxycorticosterone and supplementary sodium chloride produced a rise in blood pressure and a gain of 5 lb. in 10 days. Sixteen days after institution of therapy, pulmonary edema suddenly developed and he died. Autopsy showed both adrenals completely replaced by metastases from a tumor of the right upper lobe bronchus.

[Although the adrenal gland is a common site of metastases from bronchogenic carcinoma, clinical Addison's disease is rarely so produced. When it does occur, the condition is often not diagnosed until the patient reacts unfavorably during administration of anesthesia for a thoracic operation.—Ed.]

Suprarenal Hemorrhage and Necrosis in Pregnancy. Margaret D. Crawford[1] (St. George's Hosp. Med. School) studied this type of lesion in autopsy material from 14 women who were pregnant or in the puerperium. All had had severe complications of pregnancy, and in no instance was the adrenal lesion diagnosed during life. Three patients had complained of transient severe backache and two of transient severe epigastric pain. The age of the adrenal lesion at death was such that the initial lesion could have occurred at the time of the pain. The absence of pain was not recorded for the other patients, but this may not be significant since backache is a common complaint of obstetric patients. Vomiting was noted in a number of cases, the vomitus sometimes being blood stained. In three, the symptoms came on suddenly during or immediately after a blood transfusion. No obvious local lesion was found to account for the initial adrenal lesion. Arterial lesions were not found, and venous thrombosis was discovered in only three cases.

The condition has no apparent relation to labor, since six patients were undelivered or had adrenal lesions which were clearly present before delivery. Toxemia of late pregnancy, particularly vomiting with consequent severe metabolic disturbance, and infection are of probable significance. It may

(1) J. Path. & Bact. 63:365-376, July, 1951.

be important that all but three patients were given intravenous infusions of glucose-saline and/or blood and that in some the transfusions were given when, as judged histologically, the adrenal lesions might have originated.

Two main histologic types of lesion were found: multiple hemorrhagic lesions and necrotic lesions. The type of lesion apparently depends on the length of survival after development of the initial lesion.

None of the patients had total destruction of the adrenal cortex, and none survived long enough for clinical signs of Addison's disease to develop. Nine patients died in sudden and unexpected collapse, similar to the type of death in the Waterhouse-Friderichsen syndrome. This suggests that the sudden death may be related to the adrenal lesions. Two patients died in severe and prolonged shock which did not respond to the usual treatment. Since three patients lived for many days after the initial lesion developed and died of an intercurrent condition, it seems reasonable to presume that there are patients with adrenal lesions of this type who do recover. Such patients may later have Addison's disease and presumably form part of the group previously described as having "primary contracted adrenals" or "adrenal atrophy," more appropriately called postnecrotic scarring.

Addison's Disease in the Negro. H. St. George Tucker, Jr., Isabel Taliaferro, Richard H. Kirkland and Robert Irby[2] (Med. College of Virginia) report six cases. Five of these were seen among 60,003 Negroes admitted to two hospitals during 10 years. In the same period 10 cases were seen among 94,106 white patients. On the basis of these figures and those reported by others, the disease appears to occur about as often in the Negro as in the white race. Tuberculosis was present in two cases and suspected in one; in one, hemorrhagic destruction of the adrenal glands at the time of a previous septicemia is thought to be a factor, and in two the cause is unknown. The clinical features of Addison's disease in the Negro differ in no way from those seen in white patients. However, pigmentary changes may be quite striking, although often overlooked in a race in which normal pigmentation may vary widely. Increased pigmentation may involve the entire integument, but usually involves the face, dorsum

(2) Am. J. M. Sc. 223:479-486, May, 1952.

of the hands and feet, elbows, knees, buccal mucosa, hard palate, gums and dorsum of the tongue (Fig. 39). The authors emphasize that every type of pigmentation described may occur in normal Negroes, that the changes produced by Addison's disease appear to be an intensification of melanin deposition along a racial pattern and that the changes are quantitative rather than qualitative. A history of deepening pigmentation is the most significant clinical sign. This change

Fig. 39.—Patient is on right. Note darker pigmentation on forehead and back of hand. Patient's wife selected man on left as most closely illustrating her husband's former skin color. (Courtesy of Tucker, H. St. G., Jr., *et al.*: Am. J. M. Sc. 223:479-486, May, 1952.)

antedated other symptoms of Addison's disease in three of the six patients. In one treated with cortisone for three months, a striking decrease in pigmentation has occurred.

[This report agrees with that of Bergner and Eisenstein (1951 YEAR BOOK, pp. 152-154), who noted that Addison's disease due to "atrophy" of the adrenal cortex had not been reported in the Negro.—Ed.]

Use of Electroconvulsive Therapy in Case of Addison's Disease, with complicating psychosis, is reported by Wallis L. Craddock and Nicholas H. Zeller[3] (V.A. Hosp., Jefferson Barracks, Mo.).

Man, 56, complained of weakness, which had been progressive for the past two years. Pulse rate, temperature and respiration were normal; blood pressure was 84/60. Physical examination revealed

(3) A.M.A. Arch. Int. Med. 90:392-394, September, 1952.

no abnormality except weakness and a diffuse tan on the unexposed as well as the exposed parts of the body. Mental status was normal. Routine studies were not remarkable except that a chest x-ray showed fibrocalcific tuberculosis of both apexes, although sputum was negative. The four hour corticotrophin test failed to show eosinophil depression, and the Kepler-Power-Robinson test confirmed the diagnosis of Addison's disease.

Substitution therapy was started (25 mg. cortisone daily and frequent implantation of desoxycorticosterone pellets). The patient did well for nine months, when he became depressed and self-accusatory. Hormone therapy was temporarily discontinued but was resumed as signs of addisonian crisis appeared. Although serum electrolytes returned to normal, the patient continued to be depressed and to have distressing hallucinations. Since he was considered a suicide risk, he was given four electric shock treatments, after which he became able to carry on normal activities. Although electric shock was given without an increase in hormone dosage, serum electrolytes did not change during this therapy, nor was there any sign of crisis.

[Mental symptoms are frequent in Addison's disease and may indeed dominate the clinical picture. In Cleghorn's review (J. Canad. M. A. 65:449-454, November, 1951), depression was reported to be one of the frequent psychologic symptoms. Usually administration of adequate doses of steroids, as in this case, reverses these symptoms. It is possible, however, that central nervous system changes may become irreversible in Addison's disease, just as in prolonged hypoglycemia, hypocalcemia or myxedema. The adequacy of steroid replacement therapy in this patient is eloquently attested by his ability to withstand electroconvulsion therapy.—Ed.]

Influence of Anesthesia, Operation and Obstetric Delivery on Patients with Adrenal Cortical Insufficiency. Herman Schwartz, William S. Derrick and E. M. Papper[4] evaluated the operative risk in addisonian patients. Between 1932 and 1952, 185 patients with adrenal insufficiency were treated at Presbyterian Hospital in New York. Of these only 11 had anesthesia for 14 operative or obstetric procedures. Eight additional patients received anesthesia for operation at the Peter Bent Brigham Hospital in Boston. An analysis of the 19 patients with 23 procedures reveals that no drug or method of anesthesia is without hazard. These patients respond to surgical stress with a narrow range of compensation. However, modern methods have greatly reduced earlier prohibitive mortality. Only 3 of the 19 patients died. All had received ether. None received hormone therapy before or during surgery. Hypotension occurred in 14 instances, usually without warning, and required prompt treatment as an impending adrenal crisis. Fluid retention and edema are also likely to occur due

(4) Surg., Gynec. & Obst. 94:455-463, April, 1952.

to excessive use of desoxycorticosterone acetate or fluids. The addisonian heart is small and lacks the normal reserve to cope with an increased load from parenterally administered fluids: Potassium deficiency is likely. It is clear that operations can be performed in addisonian patients if hormone and electrolyte therapy is managed intelligently.

Decompensated Hypertensive Heart Disease with Chronic Adrenal Insufficiency. Serious diagnostic and therapeutic problems arise when congestive heart failure and chronic adrenal insufficiency coexist. To establish and maintain a balance between the conditions is difficult because diuretics, especially if mercurial, and a low salt diet for the heart disease may lead to a sodium depletion syndrome simulating acute adrenal insufficiency, and desoxycorticosterone and salt for the adrenal insufficiency will be injurious to the heart. José Schermann, Nelson Botelho Reis, Renato Borges da Fonseca and M. Barretto Netto[5] (Rio de Janeiro) discuss three cases in which autopsy findings disclosed adrenal lesions; the first illustrates the diagnostic problem, the others, the difficulties encountered in treatment.

Case 1.—Mulatto man, 41, had ankle edema which rapidly became generalized a year before hospitalization. The urine became scanty and extremely dark. One month later, he was treated for an attack of nocturnal paroxysmal dyspnea. Three months later, moderate edema and exertional dyspnea reappeared, eventually requiring hospitalization. Physical examination showed cyanosis, small diffuse hyperchromic spots, more apparent over the jaws and auricular regions, and soft, painless ankle edema. He had a gallop rhythm; pulse rate was 102 and blood pressure 160/120. Moderate jugular distention was noted. There were pleural effusion on the right and a cough with abundant mucous expectoration. The liver, enlarged and palpable below the costal margin, was soft, smooth and painful. Diuresis produced 2 L. Strophanthin,® aminophylline, salt-free diet and later digitalis and aminophylline failed to improve cardiac symptoms. The edema, however, disappeared until the third month, when it reappeared in the legs to remain until death. Blood levels of urea and creatinine increased to 110 mg. and 3.6 mg./100 ml. In the terminal two months, there were daily abdominal colic, profound asthenia and intensification of the hyperchromic spots. The day after violent intractable retrosternal pain, he died in peripheral collapse.

This case will illustrate the diagnostic difficulties presented by this combination of diseases. The 1½ year course and picture of irreducible heart failure were not unusual; the hyper-

(5) Arq. brasil. med. 42:1-20, Jan.-Feb., 1952.

chromic spots, which became intensified with the appearance of abdominal colic and severe asthenia, however, suggested adrenal insufficiency. Extreme vacuolization in the fascicular zone of the adrenals and hemorrhagic areas found in the medullary layer at autopsy confirmed the diagnosis. This experience led to recognition of the combination and its detailed study in two subsequent patients.

Case 2.—Mulatto woman, 64, had had arterial hypertension and later exertional dyspnea; a respiratory infection culminated in bronchopneumonia, after which her condition deteriorated. Paroxysmal nocturnal dyspnea, then edema of the legs and oliguria appeared. On hospitalization confluent hyperchromic spots on the cheeks extended to the eyelids and mastoid region. She had anasarca and adopted an orthopneic position. Tachycardia (pulse 100), gallop rhythm and extrasystoles were found; blood pressure was 155/120, and respiration 40/minute. Radioscopy confirmed pleural effusion on the right. The liver was palpable below the costal margin, firm, smooth and painful on pressure. Digitalis, aminophylline, luminal® and oxygen, supplemented by a mercurial diuretic, brought striking improvement, but cough, hepatomegaly and exertional dyspnea persisted throughout the first month. Fatigue became so intense that she remained in bed without moving or speaking. The hyperchromic spots darkened and urinalysis revealed low density, albumin, pus and red blood cells and granular cylinders. Excretion of the follicle-stimulating hormone was 13 m.u. in 24 hours and of 17-ketosteroids, 417 mg.

Aqueous extract of adrenal cortex and desoxycorticosterone and small quantities of sodium occasionally added to the diet overcame the fatigue and she became ambulant despite moderate edema. A mercurial diuretic every four days maintained her for five months, when vague precordial pains, recurrent fatigue and anasarca appeared. Albuminuria increased to 12 Gm./100 ml.; blood urea was 100 mg. and creatinine 1.95 mg./100 ml. and leukocyte count rose to 9,500/cu. mm. Two days before death she had severe lumbar pain with abdominal radiation which was relieved by heat and antispasmodics; there was virtually no dyspnea, but edema was severe. Autopsy showed sarcoidosis of the heart, lymph nodes, lungs and kidneys; chronic adrenal inflammation, and a cardiac infarct.

Long-standing hypertension with myocardial lesions, culminated in congestive heart failure, accompanied in its advanced stages by signs of adrenal insufficiency. A low salt, low protein diet combined with a mercurial diuretic may precipitate latent adrenal insufficiency. Of interest is the alternation of mercurial diuretics and sodium chloride which kept this patient in fairly good condition for some months.

Case 3.—Negress, 50, had been treated for dyspnea, palpitation and edema for about five years. Early in 1950 she noticed darkening

of the skin on her face, hands and feet; she felt great fatigue. Dyspnea and edema, controlled by low salt diet and heart stimulants, recurred and necessitated hospitalization a month after severe pain in the left hemithorax, with cough and hemoptysis. She appeared chronically ill and was orthopneic. She had cutaneous hyperpigmentation, no pleural effusion or ascites, but grade 1 ankle edema. A gallop rhythm was noted; pulse was 112, blood pressure 140/105; some jugular distention and signs of pulmonary stasis were noted. The liver, sensitive to pressure, was palpable a little below the costal margin.

The six month hospital course was marked by profound asthenia and inability to secure cardiac compensation despite treatment. Desoxycorticosterone alternated with mercurial diuretics and a salt-free diet during the first month alleviated fatigue; later dyspnea diminished and edema disappeared. Meanwhile, severe diarrhea was relieved by sulfathalidine,® but recurred. Asthenia increased and blood pressure fell to 125/95. Follicle-stimulating hormone excretion was 13 m.u. in 24 hours. Pain in the left hemithorax recurred, with cough, hemoptysis and fever. Dyspnea became constant, pulse rose to 130/minute, and auricular fibrillation appeared. Violent pain in the right hypochondrium began four days before death and radiated to the lumbar and epigastric regions. Autopsy showed cardiac hypertrophy and dilatation, a small myocardial infarct, myocardial sclerosis and chronic adrenal inflammation.

Renal arteriosclerosis indicated that the hypertension was essential. Most striking, however, was the appearance of adrenal insufficiency. Color notwithstanding, hyperpigmentation of the face and extremities was obvious; hyperchromic spots on the gums had been noted for six months. Asthenia, cramps and abdominal pain completed the picture. Addison's disease was proved by the improvement with desoxycorticosterone therapy and by autopsy findings.

Because the salt depletion syndrome may simulate adrenal insufficiency, differential diagnosis is not easy in the face of concurrent hypertensive heart disease, especially in Negroes. Two important signs are permanent and progressive hyperpigmentation, and asthenia after use of mercurials and improving with desoxycorticosterone therapy. Extremely important also is increased electrolyte lability in Addison's disease, in which electrolyte balance can only be maintained by use of salt and desoxycorticosterone; withdrawal of these elements causes recurrence of symptoms. Treatment in such cases will undoubtedly be facilitated by cortisone, which causes only moderate sodium and water retention.

[Now that adrenalectomy is being utilized in the treatment of hypertension, this problem is likely to become more common. The use of cortisone has revolutionized the therapy of this combination of diseases. After the onset of hypocorticism, patients who were previously hypertensive often have to be given amounts of steroid which maintain their

blood pressure at higher than normal levels. The patient's sense of well-being is perhaps the best clinical indication of adequate dosage.—Ed.]

Some Biologic Properties of Different Esters of Desoxycorticosterone. Robert Gaunt, James H. Leathem, Constance Howell and Nancy Antonchak[6] (Summit, N. J.) compared the duration and effect of seven adrenal steroids using adrenalectomized rats. Desoxycorticosterone (DC), DC acetate, DC trimethylacetate, DC phenylacetate and DC β-cyclopentylpropionate failed to stimulate water diuresis or inhibit ACTH (as cortisone does), but all caused chloride retention. Compound S acetate was like a weak DC acetate. In either oil or aqueous solution, DC trimethylacetate was the most active compound in supporting life and growth. Of clinical interest is the fact that this steroid is also superior to all others in its length of action—a single injection of 5 mg. of oil suspension gave 55 days survival as against only 18 days for the same amount of DC acetate.

[The use of long-acting preparations of hormonal agents is becoming increasingly popular. In conditions in which a prolonged regimen and relatively stable dosage is indicated, as in Addison's disease, this form of therapy has distinct advantages. The best available information suggests that the number of milligrams of desoxycorticosterone acetate which constitute the daily intramuscular or sublingual dose, multiplied by 30, equals the number of milligrams of desoxycorticosterone trimethylacetate to be injected intramuscularly once a month.—Ed.]

Effect of Glycyrrhizinic Acid on Electrolyte Metabolism in Addison's Disease was investigated by J. Groen, H. Pelser, M. Frenkel, C. E. Kamminga and A. F. Willebrands[7] (Amsterdam).

Man, with established Addison's disease, had been maintained on ambulatory control with 3 mg. desoxycorticosterone acetate daily. He was hospitalized for further study and the dosage lowered to 2.5 mg. daily. An improved and normal electrolyte balance was maintained on this dose for six days. The dose was gradually reduced to zero over several days and ammonium glycyrrhizinate (precipitated from licorice extract) substituted until a dose of 4 Gm. daily was reached. The patient was maintained on this dose for 15 days with no other therapy. Electrolyte balance remained normal. The drug was then discontinued. Sodium excretion immediately increased; two days later the serum chloride level dropped, and on the third day potassium retention began. Body weight fell and the clinical condition deteriorated in the next five days.

Crude licorice extract, 40 Gm. daily, was started orally, and the sodium and chloride balance was restored on the second day. After

(6) Endocrinology 50:521-530, May, 1952
(7) J. Clin. Invest. 31:87-91, January, 1952.

three days the dose was lowered to 20 Gm. daily. The patient was able to return to work and has remained in good health.

Hormonal Treatment of Addison's Disease. Results of treatment in Addison's disease may be evaluated by increased body weight and blood pressure, improved clinical condition (increased appetite, gastrointestinal function and muscular strength) and a feeling of well-being. Variations in blood sodium chloride and potassium contents are indicative, but not conclusive. X-ray and ECG studies of the heart are useful, but inadequate for assessing results. Edema, signs of pulmonary stasis and hypopotassemia signify overdosage. Blood pressure rises above normal only with massive doses or if hypertension has preceded the disease. Sedimentation rate and eosinophil count fall with cortisone therapy, but usually only with large doses. These factors are therefore poor indexes of successful treatment.

Carl A. Hernberg[8] (Univ. of Helsinki) reports on three patients in whom 5 mg. desoxycorticosterone acetate (DCA) daily for three weeks raised blood pressure an average 25 mm. Hg, but doses increased to 25-30 mg. raised it only 13 mm. more. Blood pressure never became normal nor recovery complete. Body weight increased an average 2.5 kg. unless there was intercurrent infection. Results were better with cortisone, especially in large doses. Blood pressure rose an average of 38 mm. Improvement was retarded with doses under 25 mg., but if normal pressure had previously been attained, a small dose of cortisone, even without DCA added, was enough to keep the patient symptom-free for some time. Pigmentation faded appreciably during prolonged cortisone therapy, reaction to Kepler's test became negative and fasting hypoglycemia disappeared. With 50 mg. cortisone or more, sedimentation rate and eosinophil count decreased. With 25 mg. cortisone and 5 mg. DCA daily, blood pressure values became normal and body weight increased satisfactorily, but improvement was not as rapid as with large doses of cortisone alone. In prolonged treatment, 10-25 mg. cortisone and 3-5 mg. DCA a day sufficed. No signs of overdosage were noted. The patients' general condition was definitely better than on DCA alone. There were no signs of hypoglycemia.

In a woman, 24, with nearly nonexistent androgen production, general health improved greatly with at least 10 mg. methyltestos-

(8) Ann. med. int. Fenniae 41:244-257, 1952.

terone sublingually a day. When methyltestosterone was given during DCA-cortisone therapy, body weight, blood pressure and muscular strength increased even further. After treatment for approximately six weeks, axillary and pubic hair began to grow. Cortisone, 12.5 mg. a day, caused no complications or unfavorable reactions.

[I think it fair to say that the addition of cortisone to the maintenance dose of desoxycorticosterone acetate contributes to the well-being of a certain number of patients with Addison's disease. In my own experience, the percentage has been rather low, possibly because I like to use the largest amount of desoxycorticosterone acetate the patient can tolerate, e.g., 4-10 mg. once a day orally. Each of 20 patients under active treatment for hypocorticism has been given a trial on cortisone; only 4 feel sufficiently improved on the added medication to justify combined therapy. I believe most other workers in this field have felt, however, that a larger percentage of their patients were improved when cortisone was added.—Ed.]

Hyperfunction

CONGENITAL HYPERPLASIA

Waterhouse-Friderichsen Syndrome Treated with Cortisone: Report of Two Cases. Fulminating meningococcic infection with collapse and hemorrhages into the skin and adrenals is unique because no other infection is so consistently or quickly fatal. The patient, usually a child under 2, has often shared a family "cold," from which he appears to have recovered, when suddenly he becomes restless and fretful and refuses food. There may be vomiting or diarrhea, a rigor, a convulsion or rapidly developing delirium. Pronounced cyanosis appears and the respiratory rate often increases. Within a few hours purpura and ecchymoses appear and collapse rapidly supervenes. There may be no meningeal signs and pneumonia is often diagnosed. Death ensues before antibiotics have time to operate. Since acute adrenal failure may play a decisive role, cortisone should be administered. G. E. Breen, R. T. D. Emond and R. V. Walley[9] report on two patients, aged 1 and 2, hospitalized on the same day. Although the first was desperately ill for 48 hours before cortisone was administered, it undoubtedly prolonged life for several days and, but for cerebral hemorrhages found on autopsy, the child would have recovered. The second child promptly recovered with 0.5 Gm. sulfadiazine orally every four hours and 25 mg. cortisone every six hours for three doses. Chemotherapy alone cannot explain such prompt response. It is concluded that cortisone is of great value in treating this syndrome.

(9) Lancet 1:1140-1143, June 7, 1952.

Familial Congenital Adrenal Syndrome: Report of Two Cases and Review of Literature. Richard C. Bentinck, Frank Hinman, Sr., H. Lisser and Herbert F. Traut[1] (Univ. of California) review 100 reported instances of familial pseudohermaphroditism in 43 families. Although apparently infrequent, mild forms are probably unrecognized in many instances. The majority (83) were female pseudohermaphrodites.

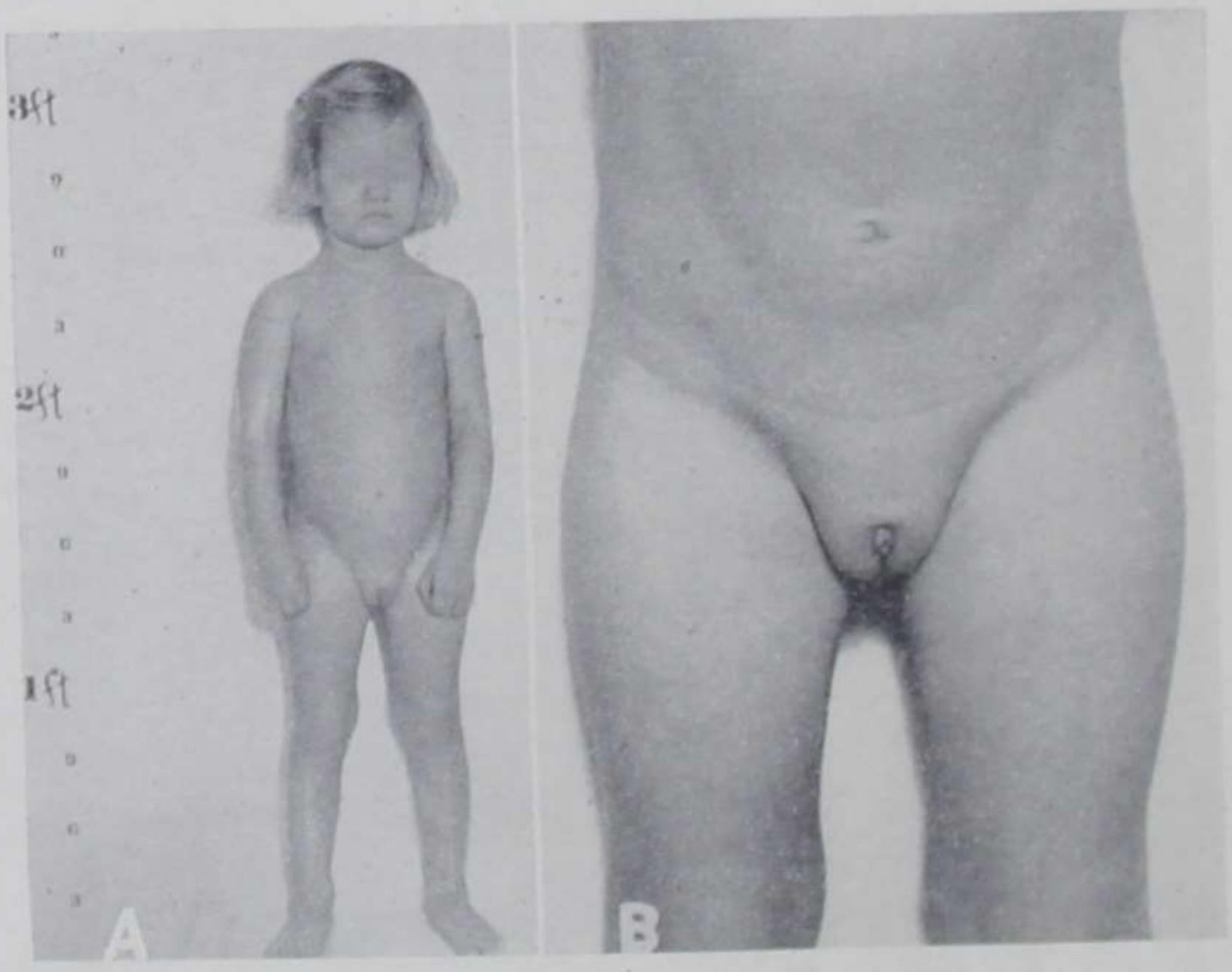

Fig. 40.—Case 1. *A*, at age 41 months. *B*, note prominent labia majora and protrusion of clitoris, even in erect posture. (Courtesy of Bentinck, R. C., *et al.*: Postgrad. Med. 11:301-312, April, 1952.)

The female pseudohermaphrodite possesses ovaries but, at birth, presents varying degrees of abnormality of wolffian and müllerian derivatives in the direction of the opposite sex. Secondary sexual attributes may vary in the same direction and may be precocious. Although certain rare instances of female pseudohermaphroditism may be "developmental" in contrast to endocrine in origin, more careful investigation may reveal a prenatal manifestation of the adrenogenital syndrome, and as such is analogous to virilism in the male. The authors report two examples occurring in the same family.

The two girls are the only children of normal parents with no family history of similar abnormality and not known to be con-

(1) Postgrad. Med. 11:301-312, April, 1952.

sanguineous. At birth the enlarged clitoris raised some doubts as to the true sex, but both children were reared as girls. Development was psychologically and socially normal.

Case 1.—At 41 months the older child presented bulging, wrinkled labioscrotal folds (Fig. 40). There were no labia minora; a phallus with well developed glans and prepuce was present. On the ventral aspect, the phallus bore a mucosa-lined urethral groove which terminated in a hypospadic orifice through which urine passed. A raphe, unbroken by a vaginal opening, extended to the anus. Cystoscopy of the urogenital sinus revealed a normal urethra and bladder anteriorly and a small vagina and infantile cervix posteriorly. Because legal definition of sex depends on the gonads, a laparotomy was performed and biopsy of both gonads revealed normal ovarian tissue.

Case 2.—The younger sibling, examined and explored at 3 months of age, was strikingly similar.

In the subsequent eight years, somatic development was precocious in both children. At ages 3 and 6 respectively, amputation of the clitoris and surgical construction of separate urethral and vaginal openings were performed. Deep voice, sparseness of axillary and pubic hair, acne and slight spontaneous vaginal bleeding were noted. No mammary development or adrenal insufficiency has been observed.

From the literature it is apparent that the genitalia are easily mistaken for perineal hypospadias in a male infant. Although pregnancy has never been reported in the female pseudohermaphrodite (nor in the true hermaphrodite), menstruation may occur. In no instance has the abnormality occurred in more than a single generation. Urinary 17-ketosteroids were elevated in 10 patients tested, but the level of elevation was unrelated to the degree of genital defect or virilization. In all of 32 instances in which definitive examination was made at operation or autopsy, the adrenals were grossly enlarged. This hyperplasia is believed to originate in the inner juxtaglomerular or reticular zone and may be associated with atrophy of the outer glomerular zone and symptoms of Addison's disease which may cause death. Thirty-three of the 100 reported patients died before the age of 6 months and 10 more in childhood. Twenty-nine were demonstrated to have adrenal insufficiency. This aspect of the syndrome deserves special consideration since proper treatment can now be life saving.

[As pointed out in the original article, the diagnosis may be very obvious in pronounced cases, but it may be most difficult in milder forms. Similarly, the difficulties which the patient endures may range from severe masculinization of some females to an insignificant degree of clitoridal hypertrophy in others. One of the most useful differential

points in the diagnosis of an androgenic state which developed before birth is the presence of a urogenital sinus. This anomaly differentiates the congenital syndrome from that produced by postnatal androgenic tumors.—Ed.]

Further Studies on Treatment of Congenital Adrenal Hyperplasia with Cortisone.—*I. Comparison of oral and intramuscular administration of cortisone, with note on suppressive action of compounds F and B on adrenal.*—Lawson Wilkins, Lytt I. Gardner, John F. Crigler, Jr., Samuel H. Silverman and Claude J. Migeon[2] (Johns Hopkins Hosp.) report observations based on the effects of cortisone administered to 11 patients with congenital adrenal hyperplasia. It is desirable to use the smallest dose which will be effective in suppressing as completely as possible the abnormal androgenic activity of the patient's adrenals. This minimal maintenance dose must be determined for each patient, using the urinary 17-ketosteroid level and the clinical picture as guides. In patients over age 8 the 17-ketosteroid excretion should be reduced at least to 8 mg./day. In patients under age 1, the normal level, usually less than 0.5 mg./day, is not achieved as a rule; an output below 1.7 mg. is considered satisfactory since therapeutic cortisone is metabolized and excreted in part in the 17-ketosteroid fraction. Presumably patients aged 1-8 are controlled when they excrete between 1.7 and 8 mg. of 17-ketosteroids daily. When excretion exceeds these levels, virilism may be expected to recur.

Initial treatment should be begun with relatively large doses of cortisone intramuscularly (50 mg./day for patients over age 8 and 25 mg./day for younger patients), because this insures more predictable results. In 5-10 days when the maximal suppression of 17-ketosteroid excretion has been obtained, the maintenance dose can be begun. This is usually 25 mg./day for the older patients. Treatment is equally effective if 75 mg. is injected every third day or 100 mg. every fourth day. If cortisone is given orally, 50-75 mg./day in divided doses may be required to equal the effect of only 25 mg./day by injection. For infants, maintenance doses of 5 mg./day or 25 mg. every fourth day by intramuscular injection are usually effective. Again two to three times as much is needed if the oral route is used. Thus, not only is oral cortisone therapy two to three times as expensive as intramuscular therapy, but

(2) J. Clin. Endocrinol. 12:257-276, March, 1952.

the annoyance of administering oral medication two to four times a day may be greater than the discomfort of a single injection every third or fourth day. Although the ultimate effects of cortisone suppression of the adrenals are not known, in a patient who had received 227 days of continuous therapy the activity of the glands, as measured by 17-ketosteroid excretion, returned promptly when the drug was discontinued. None of the 11 patients showed any evidence of irreversible adrenal damage.

In the one patient given compound F, doses of 25 mg./day seemed to have about the same effect as cortisone on suppression of adrenal activity. In an infant with the salt-losing type of adrenal hyperplasia, compound B appeared to have somewhat less suppressive action than cortisone, but doses of 12.5 mg./day had a definite sodium-retaining effect.

II. Effects of cortisone on sexual and somatic development, with hypothesis concerning mechanism of feminization.—The authors[3] report observations on six female pseudohermaphrodites, aged 8½-18½, treated continuously with cortisone for 5-17 months. In all, the breasts promptly developed, vaginal smears showed estrinization, hirsutism became less pronounced, and three patients began to menstruate regularly. Basal temperature curves of two patients became normal, thus suggesting that ovulation and progesterone secretion occurred.

Scalp hair became finer, more wavy and less oily and acne disappeared entirely in some patients. A painful clitoral stump became painless and was no longer palpable in one patient. No change in voice occurred, but body contours became more feminine, with fat deposition over the hips and buttocks, often associated with the appearance of gluteal striae (Figs. 41 and 42). Despite the weight gain, previously large appetites subsided. Three patients with considerable hypertension became normotensive. Rapid depigmentation was observed in two sisters with addisonian brownish discoloration. There was, of course, no effect on growth in the adults, but in three infants cortisone stopped abnormal growth and osseous development. In one of two boys with macrogenitosomia precox, phallic enlargement was not reversed, but further

(3) J. Clin. Endocrinol. 12:277-295, March, 1952.

growth was stopped and a remarkable growth in the size of the testes occurred.

Thus cortisone not only suppressed the excessive adrenal androgens responsible for rapid growth and virilization but led to normal adolescent development of the gonads, with

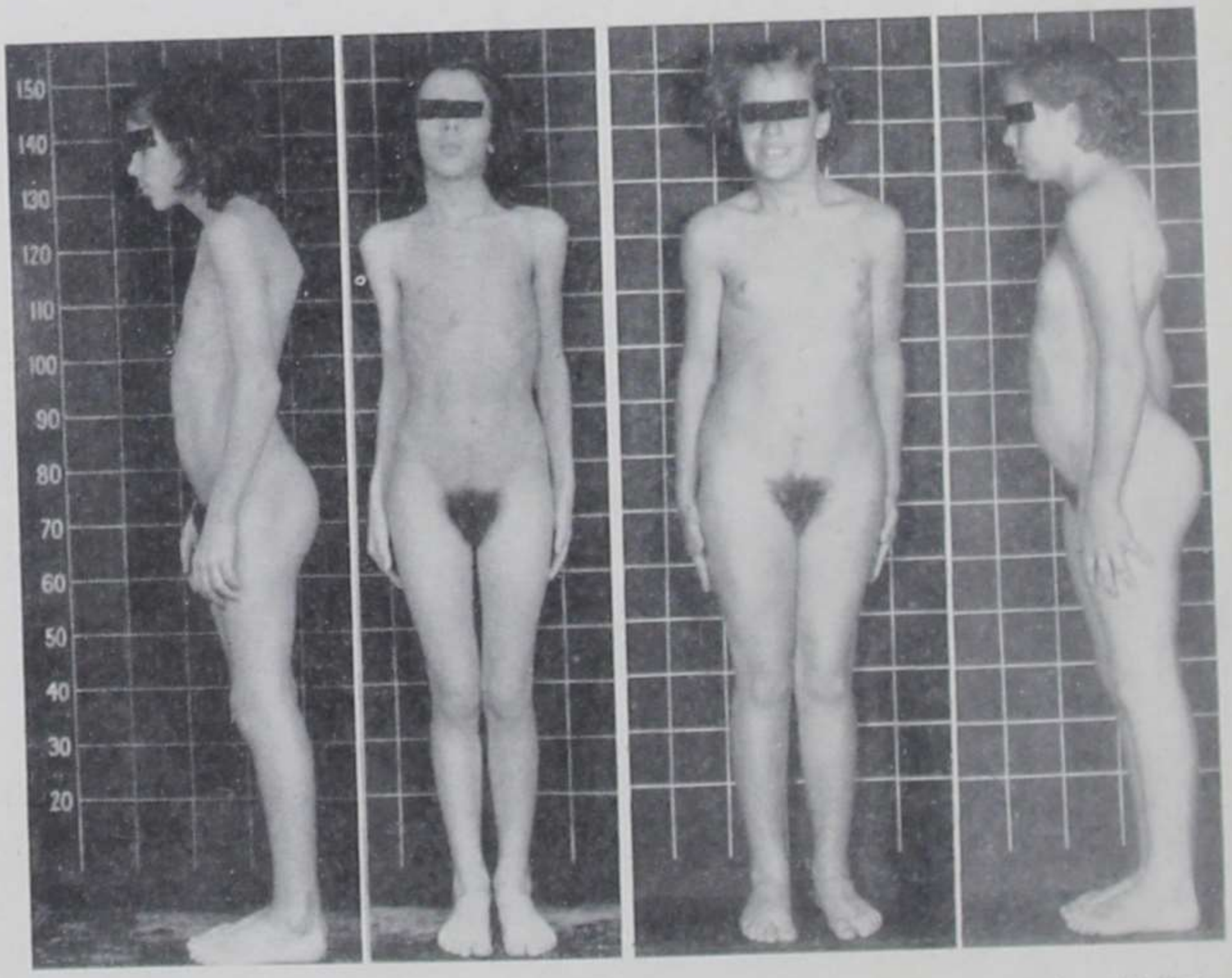

Fig. 41 (left).—Patient before treatment, at age 9 years 2 months. 17-Ketosteroid excretion was 30 mg./24 hours.

Fig. 42 (right).—Patient after eight months of cortisone treatment. 17-Ketosteroid excretion was 4 mg./24 hours. Breasts developed and vaginal smears became estrinized. Four menstrual periods occurred. Note changes of body contours due to deposition of fat over buttocks and hips. Gluteal striae developed. (Poor posture is due to paralysis of lumbodorsal muscles resulting from poliomyelitis.

(Courtesy of Wilkins, L., *et al.*: J. Clin. Endocrinol. 12:277-295, March, 1952.)

normal gonad function in males and normal feminization in females. A hypothesis is offered to explain this desirable effect, i.e., that cortisone suppresses adrenal function. This reduces excessive androgens and estrogens which have been suppressing pituitary gonadotrophin. In the absence of gonadotrophin, the ovaries or testes remain immature and do not secrete hormones. Cortisone therapy thus indirectly permits normal gonad function. The authors have confirmed this hypothesis in part by demonstrating the initial appearance of urinary gonadotrophins after cortisone therapy was begun.

[In the 1951 YEAR BOOK, pages 158-160, the preliminary observations of the early phases of this study were discussed. I am delighted to see that the feminization, which at that time was restricted to two patients, has now been achieved in the entire series. The described regimen is undoubtedly the best means of treating this condition thus far reported. —Ed.]

Further Studies on Treatment of Congenital Adrenal Hyperplasia with Cortisone: IV. Effect of Cortisone and Compound B in Infants with Disturbed Electrolyte Metabolism is discussed by John F. Crigler, Jr., Samuel H. Silverman and Lawson Wilkins[4] (Johns Hopkins Hosp.), who followed three infants with this disease for 14-20 months.

It has been recognized since 1939 that some infants with congenital adrenal hyperplasia have a disorder of electrolyte metabolism which, if untreated, may cause death from sodium loss and dehydration or from cardiac arrest with hyperkalemia. In the past, treatment with NaCl added to the diet and/or DCA was effective in correcting electrolyte abnormality and maintaining comparative health, but it did not alter the adrenal overactivity responsible for excessive growth and virilism. Cortisone and corticosterone both suppress adrenal overactivity and significantly improve electrolyte abnormality, but cortisone produces more marked suppression per milligram and less sodium retention than corticosterone.

When patients with congenital adrenal hyperplasia show clinical or laboratory evidence of disturbed electrolyte metabolism, the most useful therapy is NaCl given in large amounts (4-7 Gm. daily) by mouth or parenterally. This treatment does not, however, correct the abnormality of serum electrolytes. After the clinical manifestations are corrected, the minimal dose of cortisone required to bring about and maintain suppression of the hyperactive abnormal adrenals should be found. During adjustment of cortisone dosage, the high salt intake is continued. Urinary 17-ketosteroid excretion is a guide to the suppressive effect of cortisone. Excessive cortisone may cause symptoms of Cushing's syndrome. In infants, the addition of DCA is recommended in amount equivalent to only two-thirds the calculated intramuscular dose. The final combination of therapy must be decided for each patient individually.

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(4) Pediatrics 10:397-413, October, 1952.

Effect of Cortisone on Adrenogenital Syndrome: Temporarily Favorable Action is described by G. Laroche, J. Cheymol, J. Trémolières, M. Pellet and A. Corteel.[5]

Woman, born April 1929, had had an abnormally developed clitoris at age 5; pubic hair with beginning generalized hirsutism and pronounced libido at 7. By age 11, the picture was complete: the clitoris had attained maximal size; the vulva was small; the vaginal orifice barely admitted the little finger; pubic hair on the abdomen extended up to the umbilicus; she had axillary hair and a heavy growth on the legs, and facial hair (mustache and beard) was pronounced enough to require weekly shaving. Psychic condition was manifested by accentuated libido, voluptuous dreams and masturbation. This state continued with no signs of feminine puberty until age 16, when loss of hair began; at 17, a spontaneous hemorrhagic flow began and, although slight, was more or less continuous until October 1948. She was depressed and had feelings of shame and sexual dissatisfaction.

In December 1948, the first complete examination disclosed 17-ketosteroid level of 82 mg./24 hours. Psychiatric examination revealed an indisputably feminine psyche and a lively desire for normality. She was not obese and had no acne. Frontal and frontolateral alopecia were noted. Exploratory laparotomy revealed a small, rather soft uterus, normal tubes and, behind them, where the ovaries normally would be, two ovoid glands with smooth surfaces. Biopsy of these glands revealed normal ovarian tissue. The vaginal orifice was therefore enlarged and the clitoris amputated. Treatment with estrogens proved ineffective. In January 1950, quantitative measurements showed greatly elevated cortical steroid levels. Perirenal insufflation disclosed hypertrophy of the left adrenal gland. From January through October 1950, numerous hormone treatments failed to affect androgenic signs, and 17-ketosteroid excretion remained high. Radiotherapy (1,800 r in nine sessions) had no effect on the adrenals. On Feb. 15, 1951, the hypertrophied left adrenal was completely removed; the right one was macroscopically normal. Histologic examination of the removed gland showed simple reticulate hyperplasia. The postoperative course was uneventful.

The blood sugar content was always about 90 mg./100 ml. After a temporary decline, the 17-ketosteroid level again rose to 80 mg. On Apr. 25, 1951, 11-oxysteroid excretion was 2.4 mg. Cortisone therapy was then begun with 50 mg. daily for 20 days, then 100 mg. daily to a total 1,750 Gm. (28 days in all). The menses and breasts were unaffected, but the hair began to grow again after one month of treatment, and 17-ketosteroid excretion fell to 9.4 mg. in June. Some days after cortisone withdrawal, pronounced hypoglycemia was noted but caused no clinical disturbance.

The improvement resulting from cortisone therapy was temporary and was followed by a relapse marked clinically by renewed loss of hair and biologically by increase in output of 17-ketosteroids

(5) Ann. endocrinol. 13:62-70, 1952.

to 25 mg. and of 11-oxysteroids to 2 mg. on September 4. A second laparotomy was performed 20 days later to eliminate a possible intraovarian arrhenoblastoma. The right ovary was normal, the left one enlarged, but histologic examination of specimens removed from each proved that both were healthy. The uterus was small and the tubes were flexible. Careful search revealed no abnormal structures.

Of all treatments tried, cortisone alone affected the androgenic syndrome, reducing the steroids to normal levels. Cortisone withdrawal was followed by an increase in steroids and recurrent signs of virilism.

Further Studies on Treatment of Congenital Adrenal Hyperplasia with Cortisone: III. Control of Hypertension with Cortisone, with Discussion of Variations in Type of Congenital Adrenal Hyperplasia. Lawson Wilkins, John F. Crigler, Jr., Samuel H. Silverman, Lytt I. Gardner and Claude J. Migeon[6] (Johns Hopkins Univ.) report three cases with hypertension, in one of which there was a probable defect of the carbohydrate-regulating hormones of the adrenal.

Case 1.—Female pseudohermaphrodite, 18½, had pronounced pigmentation of addisonian type, persistent hypertension which was unresponsive to dietary salt restriction, and slight cardiomegaly. Daily intramuscular administration of 50 mg. cortisone without salt restriction resulted in feminization, regular menses, a decline in the 24 hour 17-ketosteroid excretion from an average of 53 to 4.5 mg. and an almost parallel reduction in blood pressure from between 140/100 and 150/105 to 100/76. Between the 200th and the 356th day of treatment, the dose of cortisone was reduced to an average of 16.6 mg./day; 17-ketosteroid excretion rose to an average of 9.6 mg./day and blood pressure rose to levels between 120/90 and 138/115. Subsequent increase of the dose to 75 mg. every third day resulted in suppression of urinary 17-ketosteroids to 3.8 mg./day and reduction of blood pressure to normal, which has been maintained. Cardiac enlargement was no longer present.

Case 2.—Female pseudohermaphrodite, 16¼, sister of the patient in Case 1, presented a practically identical condition. Oral administration of 50 mg. cortisone depressed the urinary 17-ketosteroid excretion from 62 mg. to 17 mg./day without, however, much effect on hypertension. On changing from oral to intramuscular administration, 17-ketosteroid excretion dropped sharply to 8 mg./day and blood pressure fell abruptly to 105/77. Eleven days later, the oral route was resumed; blood pressure remained depressed for 14 days, then rose to the previous hypertensive levels. Resumption of intramuscular therapy failed to reduce the blood pressure after 60 days, despite a 17-ketosteroid excretion level of 4.8 mg./day. Finally, a low sodium diet was instituted in conjunction with intramuscular cortisone therapy, and blood pressure fell to normal. Because the

(6) J. Clin. Endocrinol. 12:1015-1030, August, 1952.

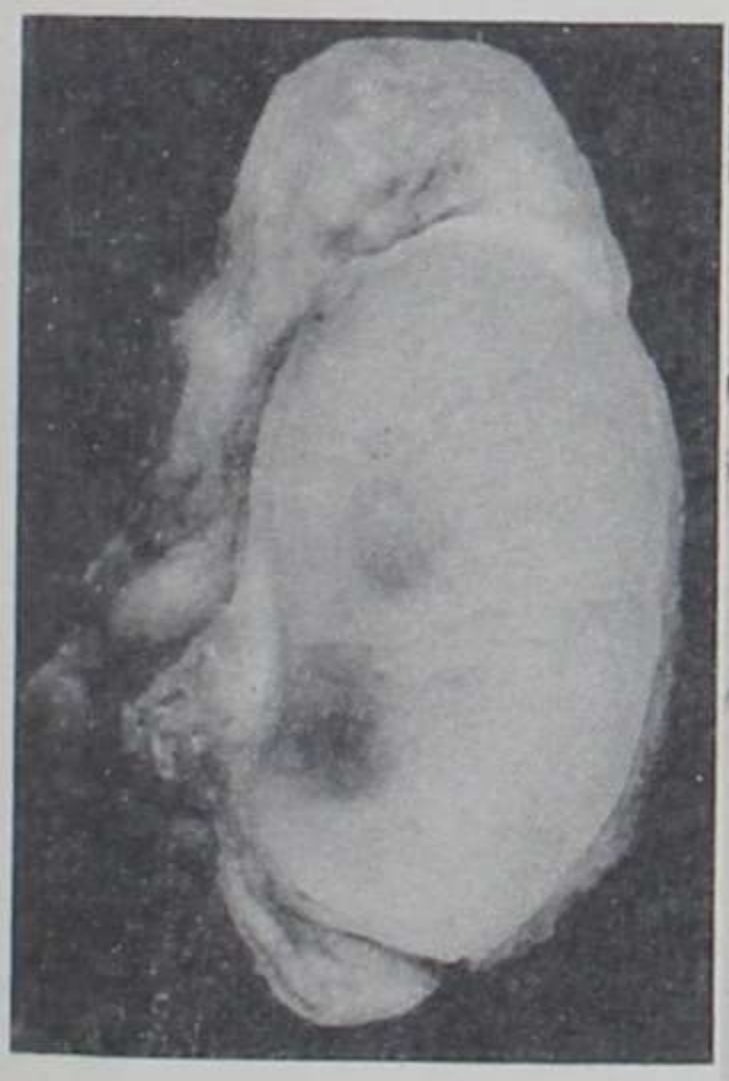
patient complained about the rigid salt restriction, this was discontinued with the admonition to use no more salt than palatability required. On continued treatment with 75 mg. cortisone intramuscularly every third day, blood pressure has remained normal.

Case 3.—Boy, aged 20 months, with sexual precocity of adrenal origin, was hospitalized in February 1949 with hypertension and cardiac decompensation. Cardiac failure was controlled with digitalis. Surgical exploration showed both adrenals to be greatly enlarged. The left adrenal was removed. Histologically, the cortex was composed largely of cells resembling the zona reticularis, and, in striking contrast to the adrenals of patients with congenital hyperplasia who have a defect of electrolyte regulation, there was also pronounced hyperplasia of the zona glomerulosa. The left testis was removed because of a nodule composed of hyperplastic adrenal tissue. Serum electrolytes and blood volume were normal. Desoxycorticosterone glucoside produced sodium retention without affecting hypertension. Neither estradiol dibenzoate nor ACTH affected hypertension, although both produced a paradoxical fall of urinary 17-ketosteroid excretion. There was no fall in circulating eosinophils. An episode of hypoglycemic convulsions in August 1949 stimulated investigations of carbohydrate metabolism. A deficiency of glycogenetic hormones of the adrenal cortex was suggested by the following: flat oral glucose tolerance curves, delayed rise in blood glucose concentration after fall induced in "response to hyperglycemia," degree of hypoglycemia and delayed recovery after intravenous injection of insulin, all of which became normal on treatment with cortisone; indefinite response of total circulating eosinophils during illness, infections, cardiac failure, injection of ACTH and epinephrine tests, with, however, response to cortisone.

Daily intramuscular administration of 50 mg. cortisone for 10 days in early 1950 resulted in reduction of 17-ketosteroid excretion from a daily average of 9.6 mg. to 1.4 mg. and elevation of blood pressure. Cortisone was discontinued, and the 17-ketosteroid excretion rose to the previous level. His condition deteriorated progressively over the next nine months; several episodes of circulatory collapse suggested adrenal insufficiency, although serum electrolytes remained normal and his condition seemed worse after infusions of aqueous adrenal extract. Edema developed on supplementary dietary sodium chloride, and diuretics were given. Treatment with lipoadrenal extract was not beneficial. Deterioration became more rapid, blood pressure fell to hypotensive levels, the heart became progressively larger and cardiac decompensation recurred despite continued digitalis therapy. In December 1950, death seemed imminent and the daily administration of 12.5 mg. cortisone was started. Improvement was rapid; blood pressure rose to normal levels and signs of cardiac failure disappeared. In February 1951, a cerebrovascular accident resulted in left hemiplegia, which persisted. Digitalis was discontinued in July and the patient subsequently led an active, unrestricted life.

[Present theory explains the virilism, salt loss, deficiency of normal carbohydrate metabolism and adrenal cortical hyperplasia; how hypertension is to be explained, I do not know. Some investigators believe that the zona glomerulosa produces a salt-retaining steroid similar to desoxycorticosterone or possibly to the more potent substance described by Grundy and his associates in this YEAR BOOK, p. 154.—Ed.]

Adrenal Cortical Hyperfunction in Childhood: Report of Case with Adrenocortical Hyperplasia and Testicular Adrenal Rests is presented by Elizabeth Kirk Rose, Horatio T. Enter-



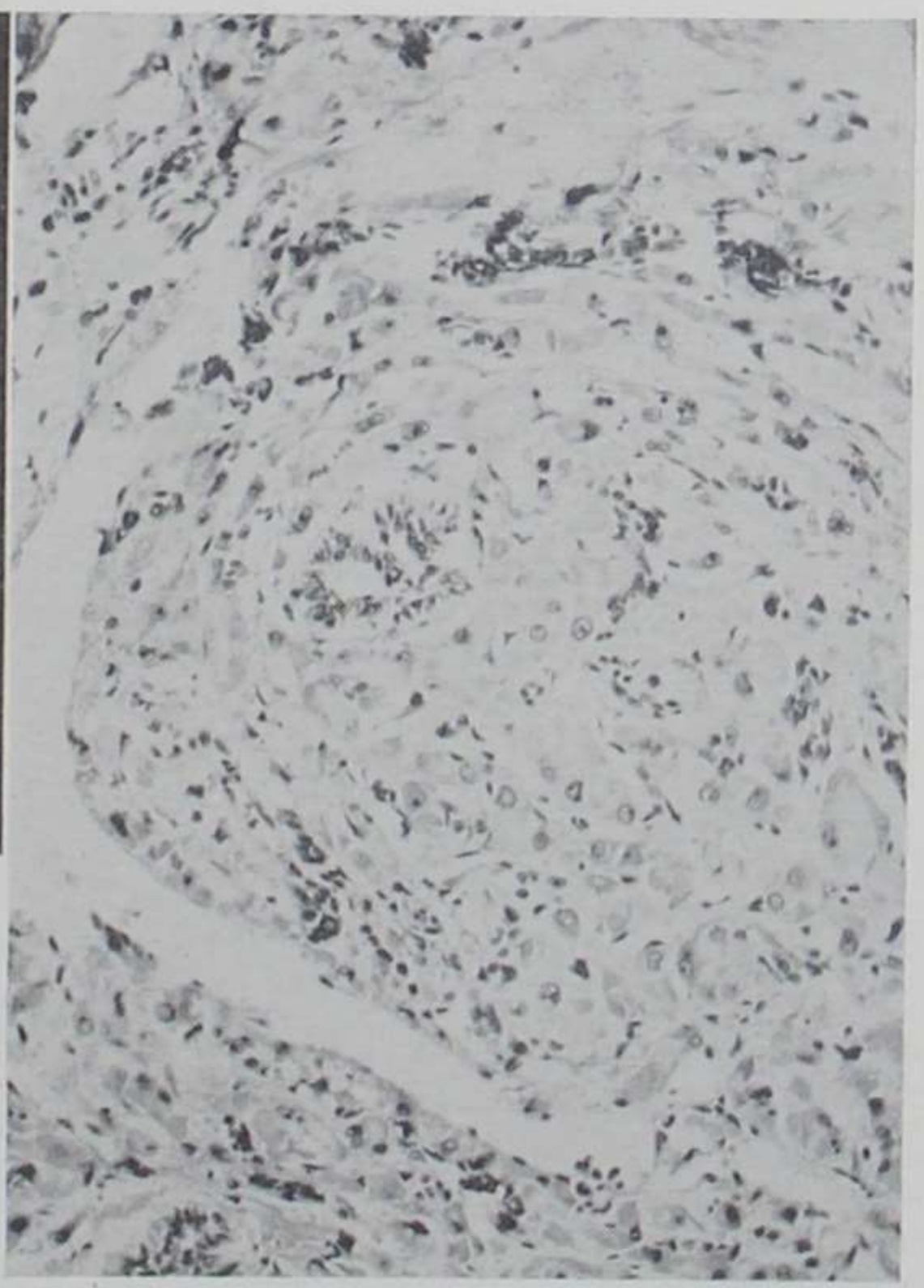


Fig. 43 (above).—Testis, showing nodule.

Fig. 44 (right).—Section showing adrenal rest cells above rete tubule; reduced from × 154.

(Courtesy of Rose, E. K., *et al.*: Pediatrics 9:475-484, April, 1952.)

line, Jonathan E. Rhoads and Edward Rose[7] (Hosp. of Univ. of Pennsylvania).

Boy, 3 years and 8 months, was normal until age 3, when lassitude was noted, with subsequent development of hirsutism, adult axillary odor, bulemia and rapid gain in weight. On examination, he appeared sluggish and strikingly obese, with a prominent abdomen, fat pads on the shoulders and hips, heavy eyebrows and fine hair over the shoulders, upper arms, axillae and pubic region. There were no striae. Blood pressure and genitalia were normal. Four months

(7) Pediatrics 9:475-484, April, 1952.

later, facial acne had appeared, and blood pressure was consistently elevated. Urinary neutral 17-ketosteroid and corticoid excretion were elevated. Glucose tolerance, serum sodium, potassium, calcium, inelevated. Glucose tolerance, serum sodium, potassium, calcium, inorganic phosphorus and cholesterol levels and plasma CO_2 and chloride levels were normal. Skeletal x-rays showed osteoporosis. On exploration, the adrenals were found to be enlarged, and about one fourth of the right and two thirds of the left adrenal were resected. After operation, gradual, but striking, improvement occurred. He became alert, hirsutism and acne disappeared and he lost weight, with a normalizing of body contour. Blood pressure became normal. X-rays showed skeletal recalcification, and the urinary corticoid excretion fell to essentially normal.

He died eight months after operation, following an episode characterized by headache, malaise, drowsiness, fever, generalized convulsions and vomiting, with massive hematemesis and melena. The immediate cause of death was massive hemorrhage from ulcerations of the esophagus and gastric mucosa, of uncertain origin, with aspiration of blood into the lungs.

The pituitary weighed 0.28 Gm. and was essentially normal histologically. The adrenals showed nodular hyperplasia, the nodules arising from the inner fascicular or reticular zones. The hyperplasia was not similar to the occasional nodulations found in infants with adrenal cortical hyperplasia associated with virilism. The testes were externally normal, but on section two small brown nodules were found in the left testis and one in the right (Fig. 43). Microscopically, these consisted of masses of cells, similar to those in the adrenal, which distorted the rete tubules (Fig. 44). The nodules were considered adrenal rests rather than interstitial cell tumor of the testes because: (1) cytologically the cells were similar to those of the adrenal and stained similarly with a variety of fat and other special stains; (2) crystalloids could not be identified; (3) the area of the rete is known as a frequent site of adrenal rests, and (4) virilism was not a prominent feature, as would be expected if the lesions represented an interstitial cell adenoma.

[It will be noted that one of the patients reported on by Wilkins and his associates on page 181 also had a testicular "adrenal rest." I wonder if these are not really enlarged Leydig cells, the growth of which was stimulated by the steroid secreted from the hyperplastic adrenal cortex. —Ed.]

Diagnosis of Intersex. D. Innes Williams[8] (London) reports six cases to illustrate the important and difficult problem presented by the newborn infant whose genitalia are of equivocal sexuality. The parents should not be told to wait and see how the child develops. To avoid anxiety and start proper treatment an early decision is necessary. A classification based on histology of gonads reveals three types: (1) intersex females (female pseudohermaphrodites), (2) intersex males, and

(8) Brit. M. J. 2:1264-1270, June 14, 1952.

(3) true hermaphrodites with gonadal tissue of both sexes. The anatomy of the genital passage may be identical in all three types and, except for unusual cases of corticoid deficiency, adrenal abnormalities are not manifest. The urethral orifice is usually wide enough to permit urethroscopy, but laparotomy is sometimes necessary.

Intersex females with hyperplasia of the adrenal cortex have normal female development until the twelfth fetal week when adrenal virilizing hormones halt vaginal growth and cause the phallus to grow and urethral folds to fuse, usually incompletely, leaving a hypospadias (Fig. 45). The adrenal

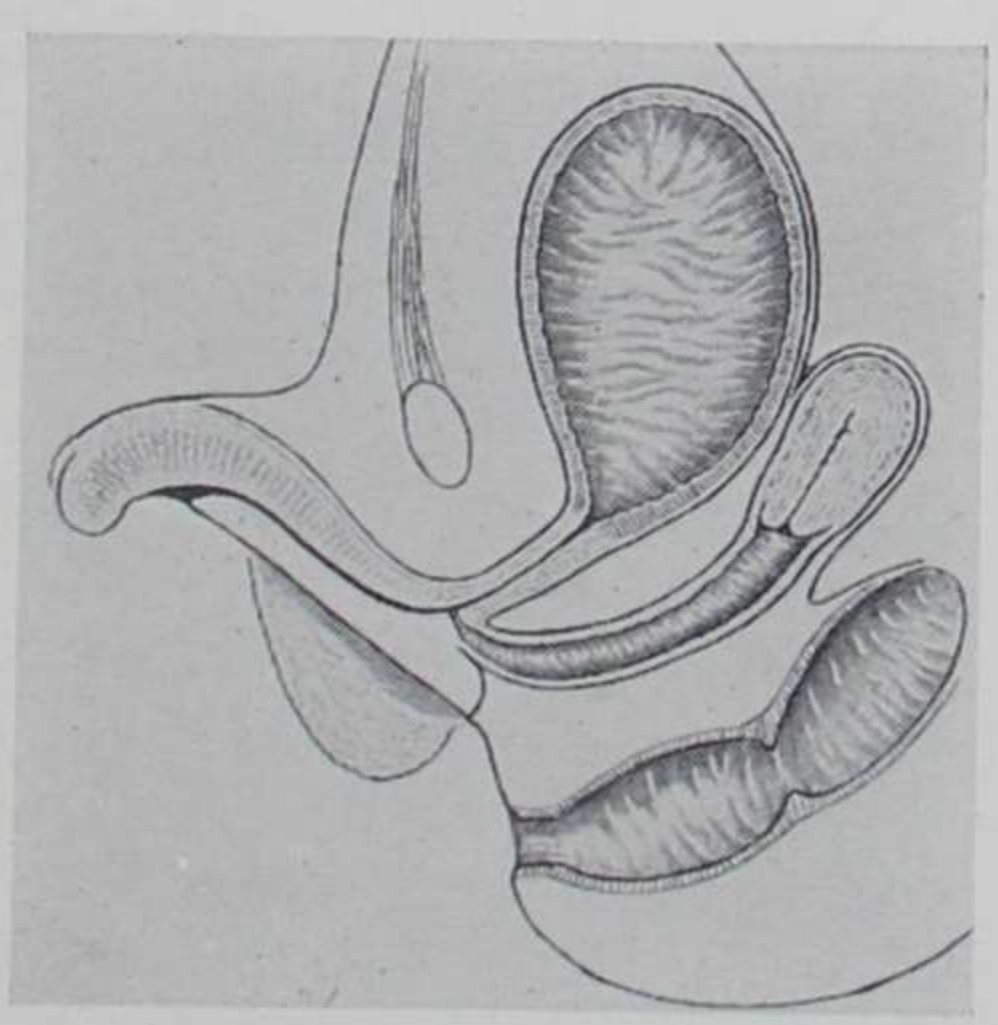


Fig. 45.—Anatomy of intersex female (hormonal type). Diagram shows vagina opening at the characteristic level—near the perineal membrane. Upper vagina, uterus and tubes are normally formed and symmetrical. The urethra is shown here opening well forward on the shaft of the penis, and the labioscrotal folds have united. (Courtesy of Williams, D. I.: Brit. M. J. 2:1264-1270, June 14, 1952.)

hormones continue to cause virilization after birth. Urethroscopy reveals absence of the verumontanum, and the vagina may be found. Laparotomy is usually unnecessary. Many intersex females are reared as boys and seem content with their lot, often being happily married to women. Surgical resection of the hypertrophied adrenals has not proved of great value, although there are exceptions, and cortisone treatment has been promising. However, it has proved tragic to attempt to feminize a patient hitherto regarded as male. Intersex females without adrenal disorder are extremely rare.

Intersex males with completely feminine genitalia are not rare and always regarded as girls. Amenorrhea at puberty

usually brings the patient to medical attention. The vagina is blind and exploration reveals atrophic testes which should be removed since there can be no change of sex. Other intersex males have equivocal sexuality. Unless a vaginal introitus is easily visible on inspection, all doubtful cases are better reared as boys.

[Because of the wide variability between the serious and the mild forms in this group of disorders, few generalizations can be made. Each case must be evaluated individually and, as early as possible, an attempt must be made to predict how the patient will look as an adult. If intense virilization is present in a child who has the gonads of a girl, one has the choice of transforming the child to a boy or of attempting to suppress the adrenal virilism by administration of cortisone. As noted in previous articles, suppression by cortisone must be continued, for the adrenal resumes production of androgens when the agent is withdrawn. In some cases it may, therefore, be more practical to transform the child to a boy before psychic trauma has been inflicted. This point of view was pleaded by Frank Hinman, Jr. (1951 YEAR BOOK, pp. 162 f.).—Ed.]

Problems of Human Intersexuality: Genetic and Endocrine Interaction. Julius Bauer[9] (College of Med. Evangelists) reviews the question of what hormones produce the remarkable physical and psychologic sexual changes in both the normal and the sexually abnormal individual. To understand this problem, consideration of genetic effects is essential. For example, pseudohermaphroditism is a condition of genetic origin, contrary to the opinion that it may be due to the hormonal influence of the embryonal adrenal cortex. For the following reasons, an endocrine origin is improbable. (1) There is no morphologic difference between pseudohermaphrodites with and those without adrenal cortical hyperplasia. Concomitant congenital adrenal hyperplasia is reported in about 15% of female pseudohermaphrodites but only in 0.7% of male pseudohermaphrodites. It has also been observed in persons without any abnormality of the genital organs. (2) The adrenal cortex develops from the mesothelium near the genital ridge about the same time as the gonads. It is hardly conceivable that in this period of embryonic development the adrenals should exert a hormonal influence of such potency as to modify the sexual differentiation of the gonads. (3) There is usually no premature sexual maturation in pseudohermaphroditism as should be expected if adrenal activity had started in embryonic life. (4) Surgical removal of the adrenal hyperplasia may fail to change the patient. (5) Pseudohermaphrodites with

(9) Acta med. scandinav. 142:162-176, 1952.

and without adrenocortical hyperplasia exhibit a great variety of malformations of the urogenital tract. The combination of pseudohermaphroditism with malformations and genetic defects of organs other than the genitalia (syndactyly, clubfoot, duodenal atresia, hemangiomas, etc.) also points to a genetic abnormality. (6) The condition may be familial. A more satisfactory hypothesis is that an abnormality of the sex genes produces abnormalities in the gonads with impaired dominance of either sex. The adrenal hyperplasia unsuccessfully attempts to overcome this deficiency. This is not to argue that adrenogenital syndromes may not be endocrine in nature. But even here the adrenal tumors may have different genic structures which determine whether they produce predominantly estrogens or androgens. Also, the same hormone may act differently on target organs of different genic structure, and the intermediary metabolism of the sex steroid may be altered according to genic pattern so that hormones are transformed and excreted in the urine as steroids of the "opposite" sex.

It is concluded that human intersexuality, hermaphroditism and pseudohermaphroditism, may result from lack of sufficient prevalence of one genic sex determiner over the other. If associated with functionally active tumors, the intersexuality may be reversible by resecting the tumor.

[It is well to remember that not all cases of intersexuality are endocrine in origin; some are genetic.—Ed.]

CUSHING'S SYNDROME

Natural History of Cushing's Syndrome. Charles M. Plotz, Abbie I. Knowlton and Charles Ragan[1] (Columbia Univ.-Presbyterian Med. Center) report data on 33 patients.

The pituitary of 19 was irradiated. Complete remission occurred in three, one of whom had also received methyltestosterone and adrenal irradiation. Six others showed some degree of improvement. The adrenals of three patients were irradiated, without effect in two. Androgens were given for prolonged periods to two patients, but evaluation was complicated because of previous and subsequent irradiation. No patients received prolonged estrogen therapy. In 17 patients the adrenal areas were explored. A unilateral benign tumor was removed from five patients; two had complete remissions and three died postoperatively. Removal of an adrenal carcinoma caused

(1) Am. J. Med. 13:597-614, November, 1952.

temporary improvement, but death from metastases occurred. Cortical hyperplasia was found in 11 patients. Biopsy specimens were obtained from nine of these; one had unilateral subtotal resection and the other had bilateral partial resection. The clinical course was unchanged in 10, and the other patient died of wound infection. One of the 11 improved after bilateral hemiadrenalectomy was done later.

All 33 patients had the classic physical characteristics of Cushing's syndrome. Of 32 followed continuously, 17 died within an average of five years of onset of symptoms. The disease followed a progressive downhill course in those who died. Poor wound healing or inability to localize simple infection was exhibited by 7 of the 19 who underwent surgery. Psychosis or neurosis occurred in eight patients. Two had myocardial infarctions and three pulmonary infarctions.

A review of 114 cases in which autopsy was done—7 from this series and 107 from the literature—revealed the major causes of death to be infection, complications of cardiovascular disease and neoplastic disease. An extremely high incidence of arteriosclerosis and osteoporosis was noted.

The close parallelism of spontaneous and induced forms of hyperadrenalism suggests potential hazards of long term therapy with ACTH or cortisone.

[When irradiation of the pituitary is effective, the results may be truly dramatic. The best results reported by this technic were those of M. C. Sosman (Am. J. Roentgenol. 62:1-32, July, 1949). It is to be emphasized that this form of treatment is reserved for patients without adrenal cortical tumors. The rationale of therapy is to inhibit the excess production of corticotrophin which is thought to be responsible for bilateral adrenal cortical hyperplasia.—Ed.]

Mortality in Surgically Treated Adrenocortical Tumors: I. Minnie B. Goldberg, Gilbert S. Gordan, William C. Deamer and Frank Hinman, Jr.[2] (Univ. of California) report three cases of Cushing's syndrome due to adrenocortical tumors. Resection of the tumor resulted in two deaths and one eight year survival, the longest period on record. The case report of one patient who was treated unsuccessfully with adrenal cortical extract alone follows.

Woman, 39, with a complaint of weak legs for four years, especially on boarding streetcars, had been considered psychoneurotic. She had amenorrhea, hirsutism (concealed by epilation), palpitations, urinary frequency, ankle edema and a "ferocious appetite." Striae and obesity were absent, although the skin was thin and dry

(2) Postgrad. Med. 11:313-324, April, 1952.

and presented numerous ecchymoses. Laboratory tests revealed hemoconcentration, leukocytosis, lymphopenia, eosinopenia, diabetic glucose tolerance and greatly increased excretion of 17-ketosteroids and 11-oxysteroids in the urine. Roentgenograms showed osteoporosis of the skull and spine with fractures of four ribs. Intravenous pyelograms on two occasions failed to reveal an adrenal mass, but on injection of 600 cc. carbon monoxide gas into the left perirenal space a large tumor was evident (Fig. 46). The tumor (9 cm. in diameter) was removed, together with seven eighths of the left adrenal. The patient did well until the second day, when intractable congestive failure with pulmonary edema developed. Death occurred

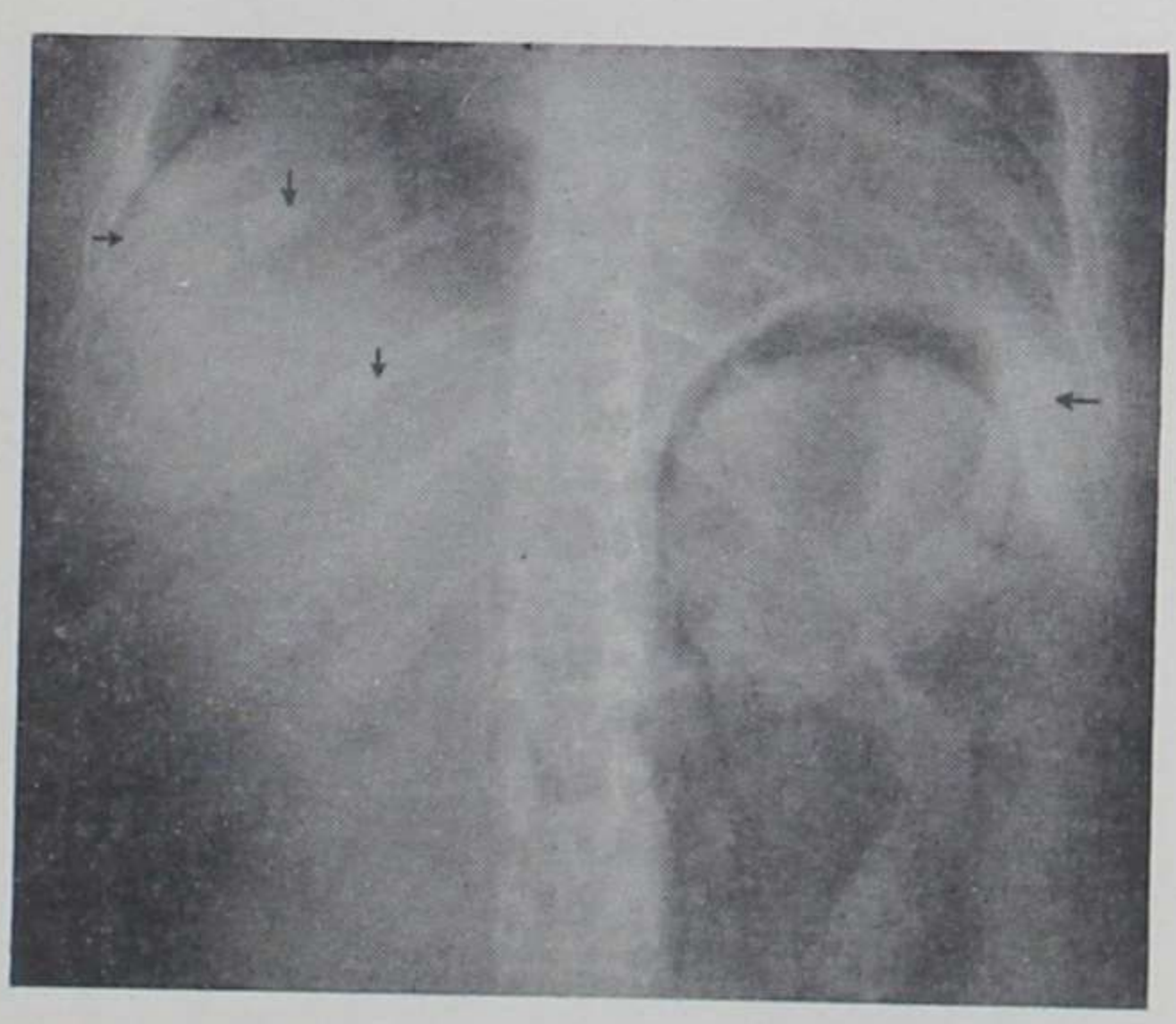


Fig. 46.—Large spherical tumor above left kidney, demonstrated by perirenal insufflation. Note also callus formation at site of fractured ribs. (Courtesy of Goldberg, M. B., *et al.*: Postgrad. Med. 11:313-324, April, 1952.)

on the fifth postoperative day. At no time was there evidence of adrenal failure or of potassium deficit, although no desoxycorticosterone was used for fear of causing fluid retention.

[Since this report was published, three more patients with Cushing's syndrome due to adrenal cortical tumors have been successfully operated on at the University of California Hospital.—Ed.]

Coexistence of Cushing's Syndrome and Internal Hydrocephalus Produced by Cerebellar Tumor is reported by K. R. Crispell and William Parson[3] (Univ. of Virginia).

Man, 35, semistuporous on hospitalization, had had sick headaches for 20 years and had for two years noted progressive weakness, facial rounding and reddening; weight had risen from 155-190 lb. Increasing weakness, unsteady gait, decreasing vision, vertigo and more severe headache for seven months had prompted seeking

(3) Am. J. Med. 13:247-250, August, 1952.

medical attention; "high blood pressure and too many red blood cells" had been found and a low sodium reduction diet, on which he lost 20 lb., had been prescribed. Symptoms increased and two days before hospitalization he had a generalized convulsion. Physical examination revealed Cushing's body contour and striae (Fig. 47), cardiac enlargement, sluggish pupillary reactions to light, bilateral choked disks with hemorrhage and exudate, central paresis of the

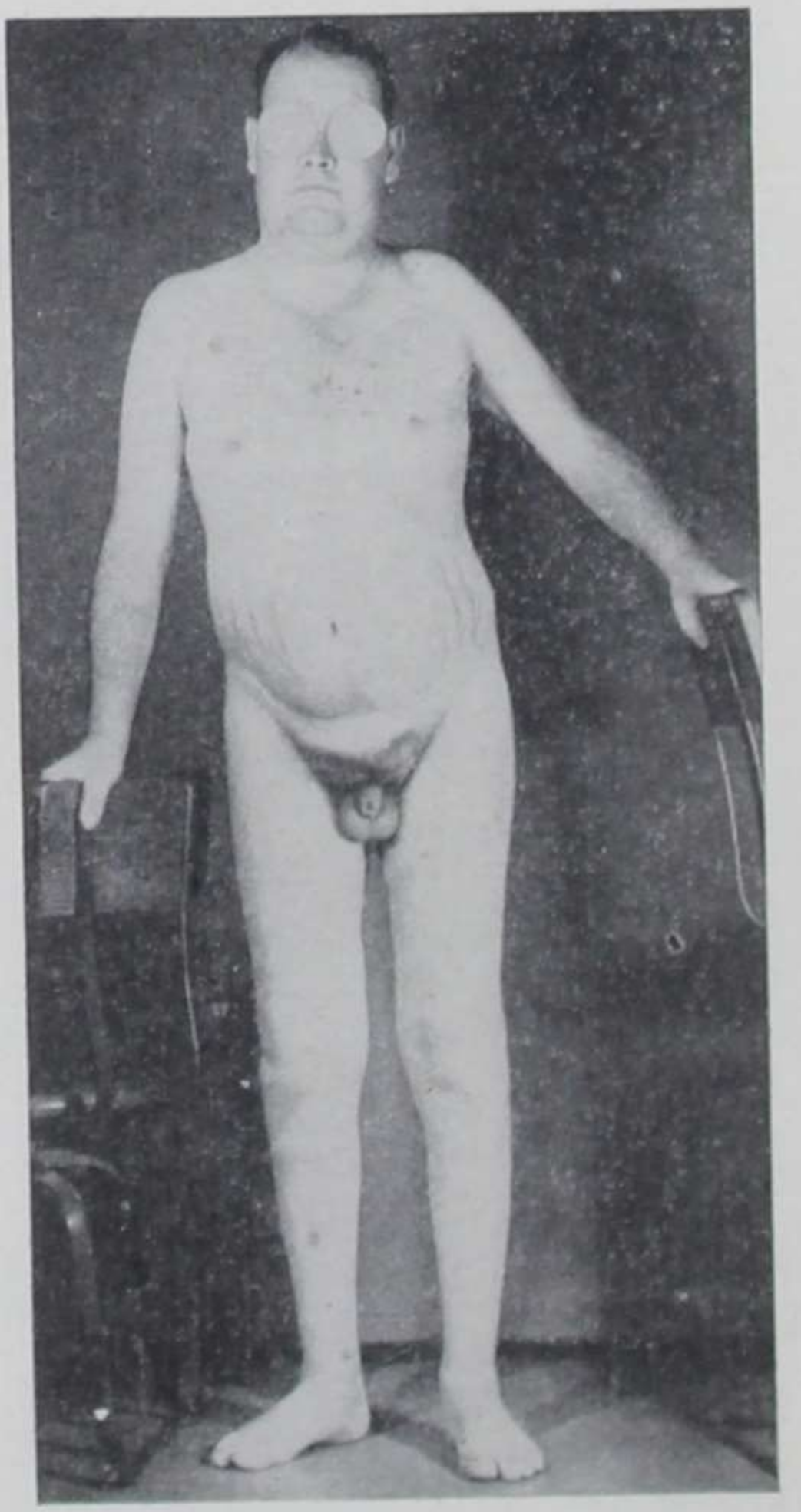


Fig. 47.—Body contour and striae of Cushing's syndrome. (Courtesy of Crispell, K. R., and Parson, W.: Am. J. Med. 13:247-250, August, 1952.)

right seventh nerve and bilateral lateral nystagmus. Erythrocytes numbered 5,200,000 with 15.5 Gm. hemoglobin and 49% hematocrit reading. Ventriculograms revealed "enormous symmetrical dilatation of the ventricular system; no air in the fourth ventricle." The posterior fossa was explored and a large amount of tumor was removed by suction from the left cerebellar hemisphere; microscopy revealed an astrocytoma.

Postoperatively he was free from headache and alert, although somewhat confused, but otherwise unchanged. Blood pressure was 140/120. Additional studies revealed normal serum electrolyte balance. A glucose tolerance test showed hyperglycemia until the third hour; total eosinophil count was 9/cu. mm.; 17-ketosteroid excretion was 21.6 and 19.2 mg./24 hours; urinary excretion of "cortins" was 7.6 mg./24 hours. Intravenous urograms revealed normal renal shadows and x-rays showed no osteoporosis. Four months after operation the Cushing syndrome remained unchanged. Pressure in the third ventricle may have caused hypothalamic stimulation releasing ACTH from the pituitary.

[Peter Heinbecker of St. Louis reported the production of some of the features of Cushing's syndrome in dogs by injury to the hypothalamus (Medicine 23:225, 1944).—Ed.]

Personality Changes in Cushing's Syndrome are analyzed by Albert M. Starr[5] (Yale Univ.) on the basis of 53 proved cases, 39 of pituitary adenoma, 7 of adrenal tumor, 6 showing hyalinization of anterior lobe basophils (Crooke's change) without tumor and 1 of arrhenoblastoma with Crooke's change. Specific mention of the patient's emotional status was made in all. Personality changes were noted in 60%. Severe depression, the most common finding, was seen in 25%; 15% had frank psychosis. Other personality changes included unusual nervousness and irritability in 15%, mental retardation and dulness in 11%, attempted suicide in 10%, anxiety and insomnia in 10%, chronic confusion in 4%, convulsions in 4% and euphoria, the rarest manifestation, in only 2%.

Although many of the nonpsychotic personality alterations may be secondary to the weakness and to the often grotesque appearance produced by the disease, it is suggested that the frequency and severity of psychosis point to it as a significant part of the syndrome. Simple behavior disturbances may often also be primary manifestations of the syndrome. It is unlikely that ACTH is the responsible factor, since euphoria, the commonest mental change induced by exogenous ACTH, is rare in Cushing's syndrome.

Adrenocortical Tumor Arising in Liver of 3 Year Old Boy with Signs of Virilism and Cushing's Syndrome: Report of Case with Cure after Partial Resection of Right Lobe of Liver. Lawson Wilkins and Mark M. Ravitch[4] (Johns Hopkins Univ.) report a unique case.

Boy, 2 years and 9 months, began to have pubic hair three months

(5) J. Clin. Endocrinol. 12:502-505, May, 1952.
(4) Pediatrics 9:671-681, June, 1952.

before hospitalization. The penis and scrotum were larger than normal, but he appeared healthy and lacked other evidence of virilism (Fig. 48, *A*). X-ray of the abdomen (Fig. 49) revealed a rounded, 6.5 cm., mottled calcified mass. Urinary 17-ketosteroid excretion was 11.2 and 9.8 mg./24 hour on two occasions. Adrenogenital syndrome was diagnosed and operation performed. No adrenal gland

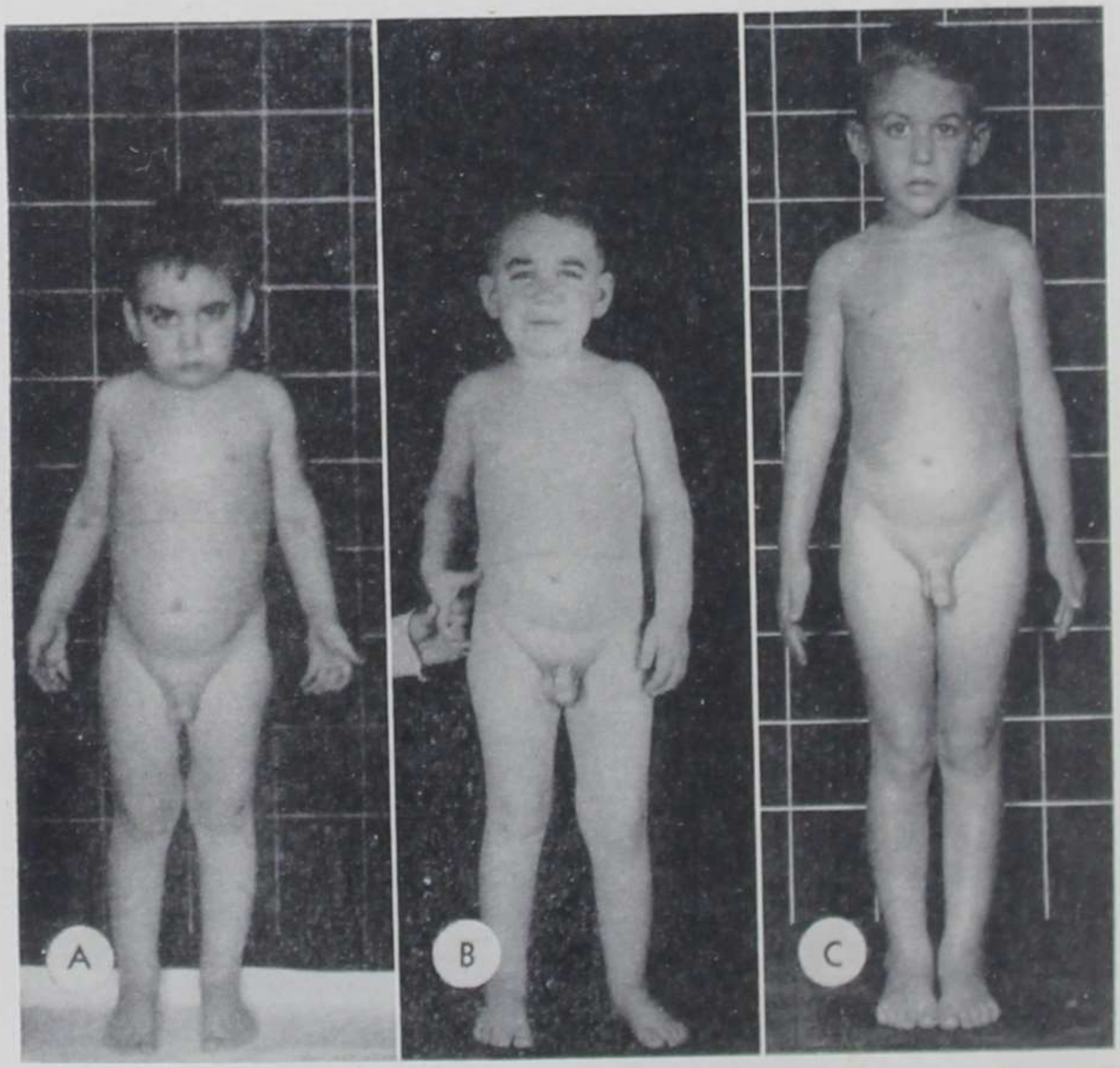


Fig. 48.—*A*, age 2¾. Growth of pubic hair and enlargement of penis noted three months previously; 17-ketosteroid excretion, 10 mg. *B*, age 3¾, shortly after removal of right lobe of liver containing adrenocortical tumor. Patient has not grown rapidly and face has become rounder. *C*, age 4¾, 11 months after operation. Growth normal and pubic hair has disappeared; 17-ketosteroid excretion, 0.8 mg. (Courtesy of Wilkins, L., and Ravitch, M. M.: Pediatrics 9:671-681, June, 1952.)

could be found on the right, but an 8 cm. mass in the right lobe of the liver was noted. This was thought to be an adrenal metastasis, so the incision was closed and he was discharged as incurable. He remained well and vigorous for 11 months without significant change. Epiphyseal development was normal. Facial appearance began to suggest Cushing's syndrome (Fig. 48, *B*). Since no metastases were found, a second operation was performed with removal of the entire right lobe of the liver containing the tumor. The tumor was

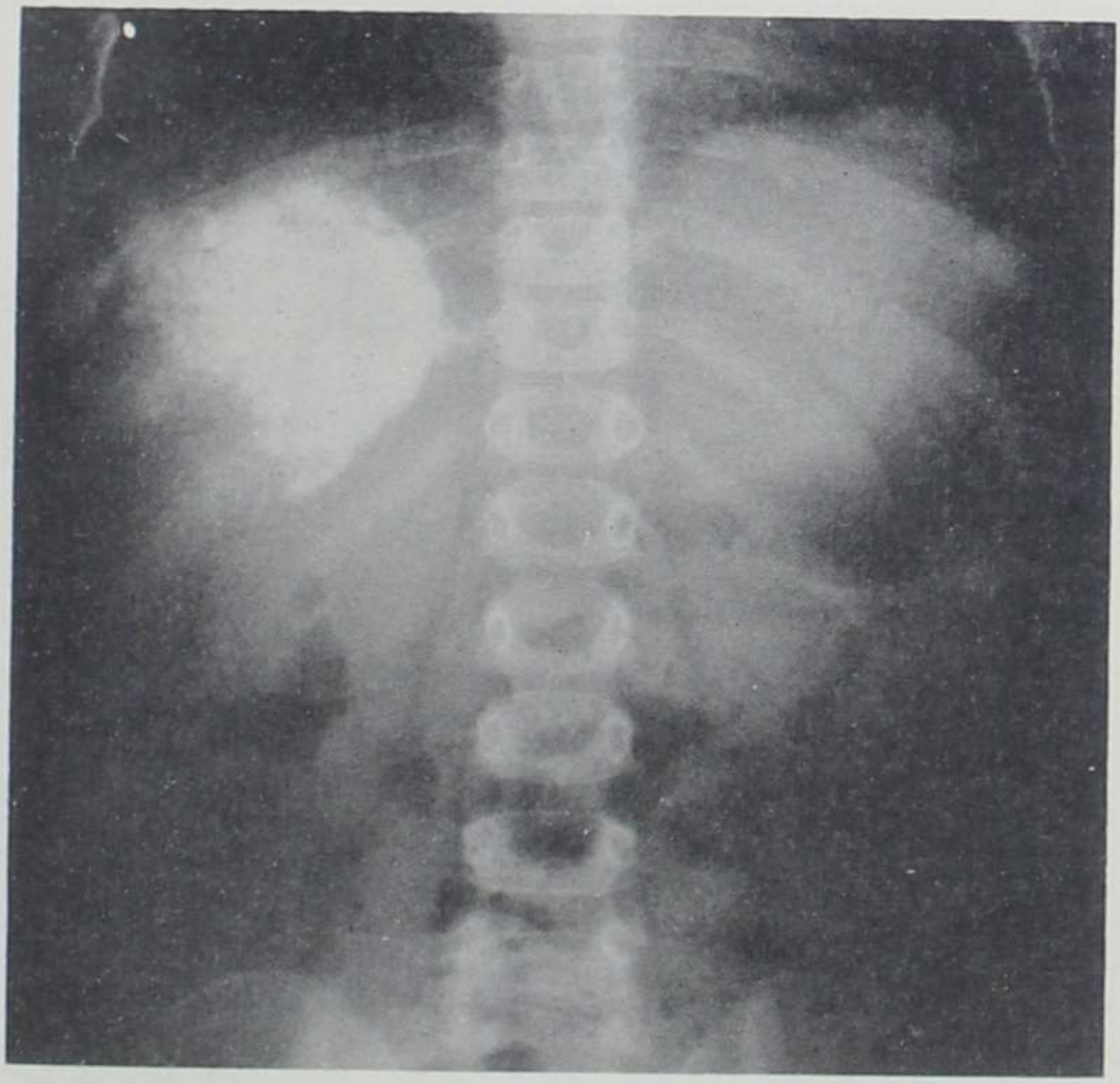


Fig. 49.—X-ray of abdomen showing large calcified mass in position of right lobe of liver. (Courtesy of Wilkins, L., and Ravitch, M. M.: Pediatrics 9:671-681, June, 1952.)

completely embedded in the liver and derived its blood flow entirely from the liver. Postoperatively he went into shock and required adrenal hormone therapy for 13 days. Later hepatitis was encountered and treated, and two years later he was well and developing normally (*C*).

It is theorized that as the liver developed as a budding of the gut, it enveloped the posterior adrenogenital ridge enough to enclose the anlage of the right adrenal gland.

Neuropsychiatric Aspects of Cushing's Syndrome. A conservative estimate of the total incidence of mental disturbance in this disorder has been placed at 20.5%. Contributing to these disturbances may possibly be any or all of the following: (1) psychologic trauma imposed by the accompanying disfiguring physical changes, (2) alterations in the metabolism of sugar, protein and electrolytes, which may be intimately related to the changes noted occasionally during replacement therapy in various diseases with (3) cortisone and ACTH in relative excess and (4) organic changes in the central nerv-

ous system. William H. Trethowan and Stanley Cobb[6] (Harvard Med. School) studied the records of 25 patients seen at Massachusetts General Hospital in 16 years and were able to list the following symptoms: depression, tiredness, pressure headaches, emotional instability, hysteria, fine hand tremors, decreased libido, palpitations, apprehensiveness, apathy, trouble with memory, trembling, dizzy spells and numbness and tingling.

Case 2.—Woman, 31, with a nonsignificant previous history, had gain in weight for one year. Shortly after onset, she noted abdominal enlargement, generalized weakness, particularly of the legs, amenorrhea and foggy vision. For seven months before admission, she had shown a change in personality marked by hyperactivity, disorientation and negativism for which she received electric shock therapy with some calming effect. Cushing's disease was suspected about three months later, and she received irradiation to the pituitary with an increase in mental symptoms. An adrenal adenoma was resected, after which the mental symptoms completely receded as did the characteristics of Cushing's syndrome

Case 3.—Woman, 37, was hospitalized with characteristic clinical picture of Cushing's syndrome. Eighteen months earlier while in Ireland, she had had backache and limb and joint pains. Within three months, menstrual periods had ceased and she had hot flushes. After her return to America, her family noted changes in physical appearance and personality. Previously sociable, she now was seclusive and depressed. However, the week before hospitalization, she had expressed concern about her appearance. One month after admission, during which her mental condition worsened, a cortical adenoma of the left adrenal was removed. There were no significant changes in her mental state for over a month, but after about two months she had apparently returned to normal, both mentally and physically, and remained so during the 2½ year follow-up.

Case 4.—Woman, 25, in 1943 was discharged from the military service with a diagnosis of hysteria. She tired easily, was unable to concentrate and had two "breakdowns" in the ensuing year. These symptoms continued and were accompanied by temporal headaches, back pains, amenorrhea, acne and hirsutism. In 1948, both adrenals were explored and the left one was removed without improving physical or mental condition. In 1949, a pellet of desoxycorticosterone acetate was implanted. She continued to be depressed and complained of deterioration of memory and thought processes. She also had more nervous spells, in which she shook all over and felt a desire to scream. Objectively, she was noted as depressed and retarded; speech was slow, and she answered questions only after long pauses. She expressed agitation, said that she felt she must scream at times and was concerned that her heart was stopping. The right adrenal was again explored and found to be enlarged

(6) A.M.A. Arch. Neurol. & Psychiat. 67:283-309, March, 1952.

several times; about one-half was resected. After some initial improvement, there was a return of all the complaints, and again a portion of the right adrenal (5.5 Gm.) was resected. She again improved and, for the first time, voiced the opinion that she felt better. However, in several months, hypoadrenalism was evident and mental symptoms recurred. She responded to replacement therapy, but follow-up studies now indicated some degree of mental impairment. Her mental state, although much improved, was not altogether normal. She was still easily upset by the comments of others, was inclined to be restless and irritable, became depressed at times and was generally less interested in her environment than she felt she should be.

[The two preceding reports properly emphasize the serious nature of the central nervous system manifestations of hypercorticism. Other endocrine excesses or deficiencies, such as Addison's disease, myxedema, thyrotoxicosis, Simmonds' disease, hypoparathyroidism and hypoglycemia, may likewise produce profound symptoms relating to this system. These changes, however, are somewhat specific for the type of endocrine disease; for instance, apathy characterizes myxedema; excitement, thyrotoxicosis; neuromuscular irritability, hypoparathyroidism; and convulsions or bizarre behavior characterize hypoglycemia. One of the important observations arising from the widespread use of cortisone and corticotrophin has been that patients react very differently to the same compound. Cortisone may produce euphoria in one patient, depression in another and psychoses or convulsions in still another. From the central nervous system symptoms which have been recorded, one might guess that the steroid elaborated in excess in Cushing's syndrome due to adrenal cortical tumor is not cortisone.—Ed.]

ANDROGENIC EXCESS

Successful Removal of Benign Androgenic Adrenal Tumor from Diabetic Woman is reported by C. I. Hamilton, Jr., and H. C. Shepardson[7] (Univ. of California). This patient had all features of the adrenogenital syndrome and obesity and diabetes mellitus as well. Since the diabetes was easily controlled and unaffected by tumor removal, it was considered an incidental finding. Virilization seemed to be the sole effect attributable to the hormone produced by the adrenal tumor.

Woman, 44, was hospitalized in 1949 for obesity, amenorrhea, hypertrichosis and diabetes mellitus. When first seen at age 21 because of obesity (weight 213 lb.), she had normal hair distribution and BMR was +2%. She was next seen in 1945 for amenorrhea which she had had since 1937 and for alopecia which was recent. She weighed 240 lb., had masculine hair distribution and a BMR of +16%. In 1946 skull and abdomen appeared normal in x-rays. Glucose tolerance was borderline. She was rehospitalized in 1949 because of increasing baldness, polyuria and polydipsia. She then weighed 205 lb., had a deep masculine voice, moderate alopecia, a

(7) Postgrad. Med. 11:284-287, April, 1952.

heavy beard that had to be shaved daily and enlarged clitoris. Laboratory tests revealed decreased glucose tolerance and 17-ketosteroid excretion of 59 mg./24 hours. Intravenous pyelograms suggested a mass above the right kidney, confirmed by perirenal gas insufflation. Diabetes was well controlled with 25 units of protamine zinc insulin daily. She was prepared for operation with desoxycorticosterone acetate and whole adrenal extract. Operative and postoperative courses were uneventful. An 8 cm. mass was removed from the right adrenal region. The cells resembled normal zona fasciculata and reticularis. Ten days later 17-ketosteroid excretion was 9.7 mg./24 hours. After a few irregular menses, regular monthly bleeding began; the voice became less masculine and scalp hair more luxuriant. Facial hair remained unchanged and still required daily shaving. The diabetes was controlled with the same diet and insulin as before operation. Weight did not appreciably change.

Adrenal Cortical Carcinoma with Excess Androgen Production in Adult Man is reported by William J. Kerr and Gilbert S. Gordan[8] (Univ. of California), who stress that whereas excessive androgen production results in well recognized syndromes in the female of any age and in the preadolescent male, androgenic tumors in the adult male are extremely rare.

Man, 44, was hospitalized for x-radiation of a right upper quadrant abdominal mass diagnosed by biopsy as carcinoma of uncertain origin. Examination results were essentially normal except for the mass and for enlarged tender breasts from which no secretion could be expressed. Laboratory tests revealed only a low hemoglobin content and x-ray films showed downward displacement of the right kidney. The mass decreased in size after x-ray therapy and he felt well for five years. Libido, potentia and shaving habits remained normal despite enlarging breasts. Weight remained normal despite numerous pulmonary metastases that continued to enlarge after x-ray therapy to the chest. Mild polycythemia and hypertension appeared. A 17-ketosteroid assay revealed an output of 224.5 mg./24 hours. He died six years later of hypertension (220/120). Autopsy showed normal spermatogenesis, normal prostate, gynecomastia due to ductal and stromal hyperplasia, normal left adrenal and an ischemic right kidney. The tumor had originated in the right adrenal gland and metastasized to liver, diaphragm and lung.

The anatomic findings in the glandular organs with clinical features of high 17-ketosteroid output, normal potentia and weight maintenance and well-being despite carcinomatosis indicate that this was an androgen-producing tumor of the adrenal cortex and not estrogenic, as might have been concluded from the breast growth.

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(8) Postgrad. Med. 11:278-283, April, 1952.

Successful Surgical Removal of Adrenal Cortical Adenoma Causing Virilism for 30 Years is reported by Roberto F. Escamilla and Stanley G. Johnson[9] (Univ. of California).

In woman, 63, amenorrhea and gradually increasing hirsutism had appeared after her third pregnancy at age 33. She had to shave daily and was bald; blood pressure rose to 165/90, and the clitoris was three times normal size. Skull and chest films and intravenous pyelograms revealed no abnormalities. Sugar tolerance decreased; BMR was + 19%; 17-ketosteroid excretion ranged from 456 to 741 mg./24 hours. Presumptive diagnosis was adrenal cortical tumor; site was not apparent.

She was prepared for operation with 5 cc. lipoadrenal extract the night before and the morning of laparotomy. Transperitoneal abdominal exploration revealed a normal pelvis; a solid mass (17.5 × 12 × 8.5 cm.) was found above the right kidney. The abdominal wound was closed and the tumor removed by lateral thoracoretroperitoneal approach. Medication during operation consisted of 5 cc. lipoadrenal extract, 500 cc. whole blood and 500 cc. plasma. Postoperatively she received lipoadrenal extract, whole blood, glucose solution and aqueous adrenocortical extract in amounts necessary to maintain adequate blood pressure and hydration. Dosage of lipoadrenal extract was gradually diminished daily and by the eighth postoperative day it had been withdrawn. Recovery was uneventful except for one episode of pulmonary embolism after which the superficial femoral veins were ligated. One week after operation 17-ketosteroid excretion was 15.8 mg./24 hours and for 38 months after operation it ranged from 5.6 to 16 mg./24 hours. Glucose tolerance was greatly improved and blood pressure reduced to 120/70. The pattern of hair growth, however, remained virtually unchanged.

It is stressed that a large adrenal tumor can exist without being evident in intravenous pyelograms and that long-standing patterns of hair growth may not change despite removal of the stimulus for the pattern.

[There is a legitimate difference of opinion as to how far one should go in attempts to localize a presumed adrenal cortical tumor before operation. The authors of this report preferred exploratory laparotomy to illumination of the adrenals by insufflation of gas. My own preference would have been for localization before operation.—Ed.]

Effect of Cortisone on Excretion of 17-Ketosteroids in Adrenal Tumor. Wilkins and others have successfully used cortisone therapy to suppress adrenal hyperactivity in patients with the androgenital syndrome. Hyperfunction was associated with adrenal hyperplasia, and administration of cortisone resulted in a striking decrease in urinary 17-ketosteroid output. Since then, it has been debated whether cortisone would suppress the

(9) Postgrad. Med. 11:272-277, April, 1952.

activity of an adrenal tumor. Eleanor H. Venning, C. J. Pattee, Frances McCall and J. S. L. Browne[1] (Montreal) report on results of therapy in four cases of adrenal hyperfunction, three due to adrenal tumors.

Girl, 5, was hospitalized in 1951 because of progressive masculinization and deepening of the voice, which began two years previously. Pubic, axillary, labial and thigh hair, clitoral enlargement, broadening of the shoulders and increasing muscular development

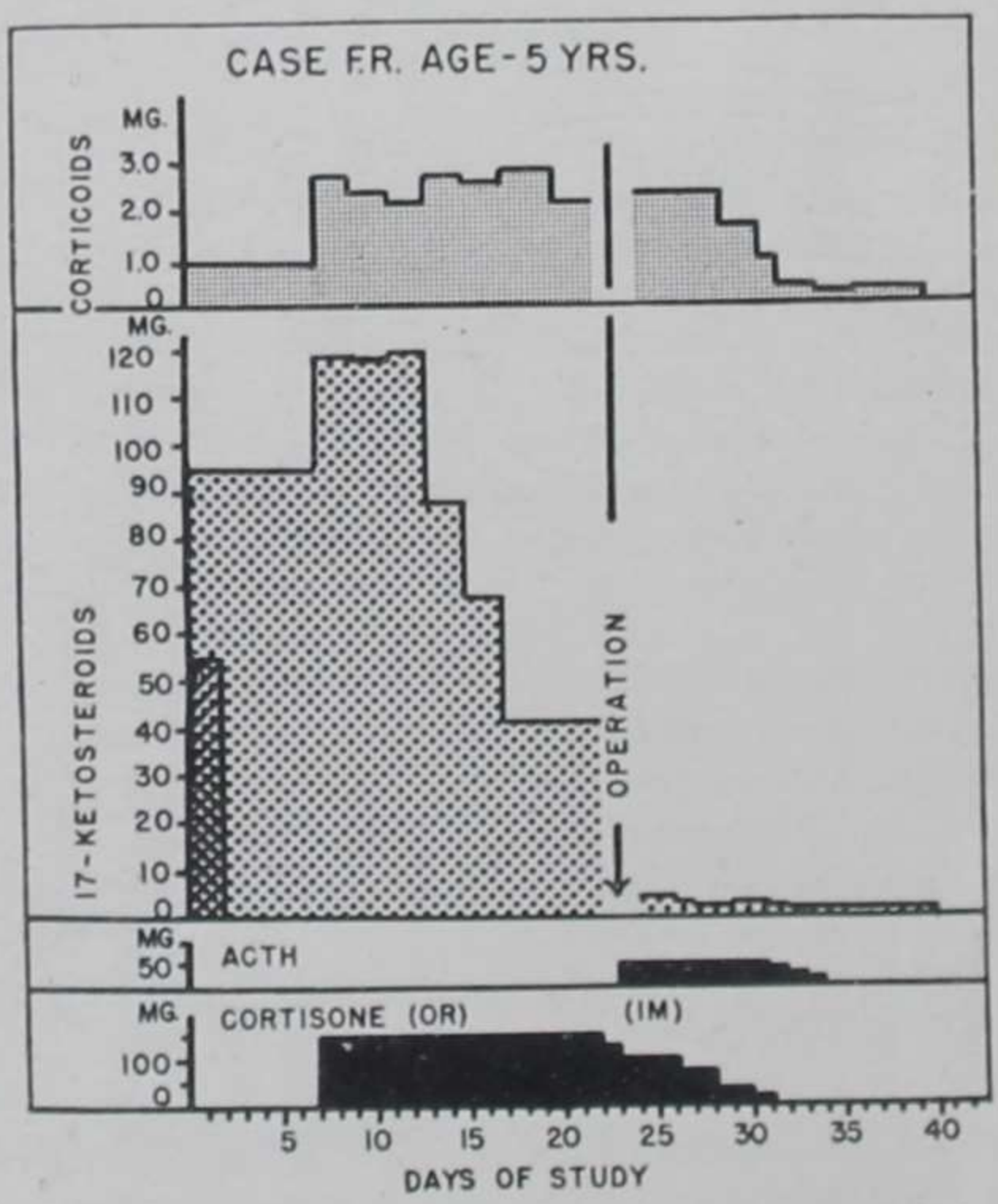


Fig. 50.—17-Ketosteroid and corticoid excretion after administration of cortisone and ACTH in case of adrenal tumor. Dark column represents beta-hydroxyketosteroids. (Courtesy of Venning, E. H., *et al.*: J. Clin. Endocrinol. 12:1409-1425, November, 1952.)

were noted. The white blood cell count was 14,100, with 500 eosinophils/cu. mm. Other laboratory data were normal. Bone age was advanced to between 11 and 15 years. An intravenous pyelogram revealed a soft tissue shadow immediately above the upper pole of the right kidney. Urinary 17-ketosteroid excretion varied between 70 and 95 mg./24 hours; urinary corticoid excretion was 40 μg./24 hours by bioassay and 0.86 mg. by chemical assay. Estrogens were not detected. Cortisone, 150 mg., was given daily for 13 days, followed by smaller doses. There was an initial rise in 17-ketosteroid excretion, followed by a decrease to about half the initial value, where it remained until the tumorous right adrenal gland

(1) J. Clin. Endocrinol. 12:1409-1425, November, 1952.

was removed (Fig. 50). Preoperatively she received 150 mg. cortisone intramuscularly and was maintained on penicillin, and ACTH and cortisone in decreasing doses postoperatively, during which time she was in excellent condition. The 17-ketosteroid excretion rapidly decreased to 3.7 mg. and then more gradually fell to normal levels of about 1 mg. The right adrenal gland weighed 25 Gm. and bore a striking histologic resemblance to normal tissue, except for the lack of organized structure. The capsule was not invaded. Some of the cells resembled those of the zona fasiculata. The adenoma was considered possibly benign.

The other three patients had hirsutism and virilism or amenorrhea. In none of the three with tumor was it possible to decrease the 17-ketosteroid excretion to normal levels with cortisone therapy, although some reduction was obtained. The β-hydroxy fraction was not influenced in one patient. Cortisone also failed to decrease the 17-ketosteroid output significantly in the case of unilateral adrenal hyperplasia. When ACTH, 100 mg. daily, was administered for five days to a patient with adrenal tumor, only small increases in corticoid and 17-ketosteroid excretion occurred, whereas in the case of hyperplasia there was a significant increase in corticoid excretion, with a delayed 17-ketosteroid response. Further investigations concerning the possibility of using the response to cortisone and ACTH as a means of differentiating adrenal hyperplasia and tumor would be of value.

[Another method of differentiating between the high steroid output caused by hyperplasia and that caused by tumor is the simple Allen sulfuric acid test, which can be applied to the same urinary extracts used for the ketosteroid analysis.—Ed.]

Feminizing Adrenocortical Carcinoma and Carcinoma of Prostate. Jon Myhre[2] (Bergen, Norway) reports a case.

Man, 35, married, with three children, the youngest born in 1944, in 1942 noted diminishing libido, gradually increasing impotence and swelling and tenderness of both breasts. When he was hospitalized in 1946, considerable symmetrical swelling of both breasts was found, but no fluid could be pressed out. Abdominal palpation and x-rays revealed nothing abnormal. Results of the Friedman test were negative, and quantitative estimation of gonadotrophin gave normal low values. Androgen excretion was below average but within normal limits. Diagnosis was gynecomastia of unknown origin. In 1948 he had a feeling of fulness in the epigastrium, at times even oppressive pains, and was hospitalized with a diagnosis of splenomegaly. Under the left costal margin, a large mass with uneven surface, reaching down as far as the navel, could be palpated in the abdomen. X-rays of the lungs revealed numerous,

(2) Acta endocrinol. 10:233-242, 1952.

evenly spread densities. Results of the Friedman test and frog test for urinary gonadotrophin were negative, but excretion of 17-ketosteroids was greatly increased—256 mg./24 hours. He was discharged with a diagnosis of adrenal cortical carcinoma with metastases. Before discharge he received an intramuscular implantation of 300 mg. testosterone propionate. In March 1949 the abdominal mass was further enlarged and lung infiltrates increased. Urinary excretion of 17-ketosteroids was 262 mg./24 hours. Again 300 mg. testosterone propionate was implanted. The patient died in May 1949. Autopsy revealed a left adrenal tumor weighing 2,090 Gm. Although the gross appearance of the prostate was normal, microscopic examination revealed a carcinoma of this organ too; its appearance and mode of growth differed completely from that found in the adrenal gland.

Feminizing adrenal cortical tumor has previously been reported in at least 15 cases. The disease often develops slowly, leaving a chance for effective therapy if hormone estimations and exploratory laparotomy are used as aids to early diagnosis. Estrogen excretion, investigated in four of the earlier cases, was greatly increased in two; results of the Friedman test were positive in one of three. Urinary excretion of 17-ketosteroids was increased in two of four cases; in one, it was 190 mg./24 hours, even on first examination, and in another it increased from 34 to 108 mg./24 hours within 4 months. In the present case the disease was sufficiently advanced even on first admission that an estimation of 17-ketosteroids would probably have been of great diagnostic value. However, it was impossible to perform this test in Norway in 1946. In previously reported autopsies in such cases, the prostate seems to have been normal. The surprising discovery of a prostatic carcinoma in the present case is not considered important in the development of the patient's symptoms and signs.

Urinary excretion of estrogens and 17-ketosteroids should be determined in all cases of gynecomastia. Exploration of the adrenals should be done in all cases of unknown etiology if excretion of these substances is even moderately increased.

[This syndrome has been called "feminization" because of the presence of gynecomastia. Since gynecomastia is also produced by the administration of testosterone compounds and since the author's patient had a daily 17-ketosteroid excretion of 256 mg., I think it more likely that the syndrome results from an excess of androgens rather than of estrogens. I do not agree with the conclusion that exploration of the adrenals is indicated in all cases of gynecomastia of unknown etiology in which urinary excretion of estrogens or 17-ketosteroids is even *moderately* increased. This is one condition in which I believe all of the simpler measures for recognition of an adrenal cortical mass, as outlined in the introduction to the section on Adrenal Medulla (p. 131) should be performed before operation is considered.—Ed.]

CORTISONE, CORTICOTROPHIN AND ALLIED COMPOUNDS

The passage of adequate time and the reports of additional numbers of clinical studies now make it possible to venture an evaluation of the place of cortisone, hydrocortisone and corticotrophin in practice. When these compounds were first introduced, the most enthusiastic observers hailed the dawn of a new day in medicine, an era in which the deleterious effects of profound toxins could be averted and surgeons could, with impunity, transplant tissues and organs from one individual to another, perhaps even from one species to another. Other workers, better versed in the known effects of cortical hormones from long study of the natural condition of hypercorticism as found in Cushing's disease and Cushing's syndrome, urged caution, fearing that the pronounced metabolic effects of these agents rendered them too dangerous for practical therapeutics. The truth seems to lie somewhere between these extremes. The fact that a goodly number of patients with rheumatoid arthritis derive sufficient benefit from these drugs to enable them to carry on a fruitful life without undue suffering from the expected metabolic effects certainly cannot be ignored. Moderate doses of cortisone, partially suppress rheumatic activity and have only minimal undesired effects, leaving the patient with "arthritis in miniature" and the least degree of hypercorticism possible. The over-optimistic hope that adrenal corticoids would permit the flaunting of the laws of immunity has not been realized. In short, these are highly potent, useful compounds with a recognized sphere of activity, capable of producing much good and also much harm, and their use is properly indicated when simpler measures are exhausted or ineffectual.

A distinction must be drawn between the use of these compounds as replacement therapy in pituitary and adrenal insufficiency and their pharmacodynamic use in much larger doses to suppress activity of rheumatoid arthritis, acute rheumatic fever, disseminated lupus erythematosus, early periarteritis nodosa, acute drug sensitivity, contact dermatitis, exfoliative dermatitis, serum sickness, acute hemolytic icterus, various types of uveitis and keratitis, intractable asthma, refractory gout, severe ulcerative colitis, sarcoidosis, nephrosis and pemphigus. In most of these conditions, relief is obtained only with doses of cortisone or corticotrophin that result in some degree of hypercorticism.

The usefulness of these compounds in hypopituitarism and Addison's disease is discussed in the sections on the Pituitary Gland and the Adrenal Cortex respectively. One particular disorder of the adrenal gland, congenital androgenic hyperplasia, which in girls is associated with pseudohermaphroditism and in boys with macrogenitosomia precox, is treated much more effectively by the administration of cortisone than by any previously described form of treatment. The use of these compounds in the maintenance of patients undergoing adrenal surgery for hypertension or various neoplastic diseases is described in the sections on the Adrenal Cortex and the Endocrine Treatment of Neoplastic Diseases respectively. —Ed.

Chemistry and Physiology

Enhanced Clinical Effectiveness of Purified Corticotrophin. M. S. Raben, I. N. Rosenberg, V. W. Westermeyer and E. B. Astwood[3] (New England Center Hosp., Boston) used ma-

(3) J.A.M.A. 148:844-845, Mar. 8, 1952.

terial which had been purified by the oxycellulose method and contained 80 units/mg. by bioassay. It was given subcutaneously every 8 hours in aqueous solution or every 24 or 48 hours in gelatin solution or as a suspension in sesame oil. The gelatin solution prolonged the action of corticotrophin best and reduced the daily dose below that required for injections of aqueous solution at eight hour intervals. Before the augmented clinical potency of this material was realized, evidence of excessive dosage was easily obtained. There was no qualitative difference between the therapeutic or overdosage effects of the pure and the impure preparations. The fall of erythrocyte sedimentation rate and rise in 17-ketosteroid excretion were consistent with the therapeutic efficiency of the doses used.

Purified corticotrophin appeared to be about twice as effective clinically as would be expected from the animal assay. This is probably related to the increased stability of purified corticotrophin in body fluids. This preparation is 150 times as effective clinically as standard corticotrophin and at least 250 times as effective (on a weight basis) as cortisone. Experience with it indicates that newer preparations of corticotrophin will require clinical evaluation to determine dosage and frequency of administration.

[The new highly purified extract is so much more potent than the earlier preparations that doses of corticotrophin should no longer be measured in milligrams but in biologic units. Although the results of the bioassay of the potency of corticotrophin vary according to the test used (depletion of adrenal ascorbic acid, eosinopenic activity, augmentation of 17-ketosteroid or 11-oxysteroid output, suppression of rheumatic activity, adrenal weight maintenance or restoration in the hypophysectomized rat), the biologic assays measure the active principle rather than the amount of contaminating protein in the preparation.—Ed.]

Comparison of Duration of Action of Various Long-Acting ACTH Preparations in Human Subjects was made by William Q. Wolfson and Stefan S. Fajans[4] (Univ. of Michigan). The criterion for comparison was ability of the products to induce a decrease in blood eosinophils that persists for 24 hours after a single 100 unit dose. Normal subjects and patients with rheumatoid arthritis, eye disease, gouty arthritis or mild diabetes mellitus were studied. Duration of action of adactar and adactar tannate was clearly superior to that of either acthar-in-oil (adactar-0-40) or ACTH in heavy gelatin. Re-

(4) New England J. Med. 246:1000-1004, June 26, 1952.

sults with adactar were almost identical to those with adactar tannate. Results with ACTH in gelatin were slightly superior to those with acthar-in-oil. These results are consistent with those previously obtained by semiquantitative metabolic bioassay in man.

Long-acting ACTH preparations may be used to decrease the frequency of injections of this hormone and the cost of ACTH treatment. A preparation for general clinical use cannot be selected by duration of action alone. Temperature stability, ease of administration, tendency to cause local or systemic reactions and several other factors must also be considered.

An addendum indicates that results of further studies with the long-acting crude ACTH-corticotrophins described and with related materials confirm the more prolonged action of the adactar type materials.

The length of action of long-acting crude ACTH-corticotrophins has also been compared with that of the newer "high-potency" purified ACTX-corticotrophins. Each USP unit of "high-potency" purified ACTX-corticotrophin is apparently about as effective as 3 USP units of crude ACTH-corticotrophin given subcutaneously or intramuscularly in identical menstrua. A comparable superiority of the ACTX-corticotrophin has been demonstrated in its ability to produce metabolic and therapeutic effects.

Identification of ACTH in Human Placental Tissue was attempted by Jeanette C. Opsahl and C. N. H. Long[5] (Yale Univ.) to determine whether this tissue was a source of the corticotrophin activity in pregnancy urine after inactivation of gonadotrophins. Two fractions were separated from ground fresh, warm placental tissue and blood. Fraction I was derived from successive acetone extractions of the precipitate. Fraction II was derived from acetone extraction of the tissue residue remaining after the original acetone extraction in the preparation of fraction I. More than twice as large a yield of dried powder was obtained in fraction II.

The presence of corticotrophin activity was detected by inhibition of hyaluronidase-enhanced spreading. Administration of various fractions of crude placental extracts to normal or

(5) Yale J. Biol. & Med. 24:199-209, December, 1951.

hypophysectomized mice produced marked inhibition of hyaluronidase-enhanced spreading with essentially complete inhibition of exogenously added enzyme. These fractions have no effect in adrenalectomized mice and are without effect when injected intradermally at the site of the hyaluronidase injection. Fraction II consistently showed greater activity than fraction I.

The fractions extracted from fresh placental tissue were not only extremely large for the crude procedures employed in extraction but also possessed corticotrophin activity in dosage ranges comparable to those for pituitary preparations. However, placental tissues that had been frozen and stored before extraction did not yield fractions comparable in activity or quantity to those obtained with the use of fresh placentas. Thus, a destruction of corticotrophin activity is indicated, even though the tissue remained in the frozen state. There is indication that this lability of corticotrophin has been observed in the isolation of corticotrophin from pituitary tissue. The inhibitory effect of placental extracts is not due to the presence in them of measurable quantities of steroids of the adrenal cortical type (cortisone or compound F). There is a similarity between the inhibitory effects produced by the placental fractions and the results following administration of pituitary corticotrophin, chorionic gonadotrophins and heat-inactivated chorionic gonadotrophins. Presence of corticotrophin activity in placental extracts is also shown by the depletion of adrenal ascorbic acid and fall in circulating eosinophils after injection into hypophysectomized rats and mice.

[The number of hormones known to be elaborated by the human placenta is rapidly becoming equal to the number of hormones derived from all the ductless glands. For this reason, it is difficult to know which phenomena of pregnancy can be ascribed to the effects of any specific hormones. Indeed, it is important to recall that many changes in pregnancy are not caused by hormones at all.—Ed.]

Electrolyte Changes Produced by ACTH, Cortisone and Doca® in Cirrhosis of Liver were measured by William H. Blahd, William S. Adams, Alan Leslie, Ralph Goldman and Samuel H. Bassett[6] (Univ. of California, Los Angeles). Six patients with proved cirrhosis with ascites and three normal persons, all on low sodium intake, were given the following medication intramuscularly daily for 10 days with a 10 day

(6) J. Lab. & Clin. Med. 39:393-403, March, 1952.

rest between courses: (1) doca® 25 mg.; (2) cortisone 200 mg.; (3) doca® 25 mg. and cortisone 200 mg., and (4) ACTH 100 mg. In four patients and in normal subjects, doca,® cortisone or ACTH caused pronounced diminution of urine and sweat sodium and urinary volume. Withdrawal caused sodium and water diuresis, in some cases so pronounced that it caused loss of all edema and ascites. With doca® and cortisone given together the effects were the same except that on withdrawal the diuresis was usually more pronounced than with either agent alone. Sometimes there appeared to be a gradual escape from the salt-and-water-retaining effects of the hormones, more commonly when doca® and cortisone were given simultaneously. Two patients with far advanced cirrhosis did not respond to the medication but instead showed an invariable sodium and water retention that eventually required paracentesis. Although it has been proved that edema and ascites formation in cirrhosis are related to sodium retention, it cannot be said that this is due to adrenocortical overactivity.

Protective Effect of Adrenal Steroid Administration on Irradiated Mice. E. A. Mirand, M. C. Reinhard and H. L. Goltz[7] (Buffalo, N. Y.) exposed young male and female DBA mice to 500 r head or whole body radiation. Both groups had 100% mortality, but mice given whole body radiation died sooner. Mice given 500 r head radiation and primed before or after irradiation with cortisone (1 mg. daily for three days) or with desoxycorticosterone (0.5 mg. daily for three days) showed evidence that either compound afforded protection from the lethal effect of ionizing radiation. Those given hormones after irradiation had less protection than those given hormones before.

Adverse Effect of Cortisone on Marrow Regeneration Following Irradiation. John B. Thiersch, Loretta Conroy, Alexander R. Stevens and Clement A. Finch[8] (Univ. of Washington) found that cortisone impaired recovery of hemopoietic tissues of rats after irradiation. Effects of cortisone in normal rats included weight loss, decrease in size of spleen and adrenal glands, eosinopenia and mild bone marrow depression. X-radiation alone caused weight loss and marrow damage, followed by repair in three to four weeks. Cortisone given to

(7) Proc. Soc. Exper. Biol. & Med. 81:397-400, November, 1952.
(8) J. Lab. & Clin. Med. 41:174-181, August, 1952.

irradiated rats caused a cumulative harmful effect of radiation and of the hormone as well; their weight loss and blood and bone marrow depression were more severe than with either agent alone. Histologic study revealed much slower marrow regeneration, and radioiron uptake studies indicated a lower level of erythropoiesis in animals treated with cortisone.

The mechanism of cortisone effect is unknown. Depletion of sulfhydryl groups and lymphoid tissue injury may both be important in potentiating radiation damage. Although cortisone may produce both effects, in this experiment cortisone was given several days after irradiation, when these mechanisms were not demonstrably effective.

[It is not clear whether the contrasting results described in the two preceding papers are due to species difference (the first report involved mice; the second, rats) or to varying amounts of radiation or to differences in dose of hormones.—Ed.]

Effect of ACTH, Cortisone and Doca® on Survival of Burned Rat. William B. Neal, Jr., Edward R. Woodward, Allen E. Kark, José M. Zubiran and J. Antonio Montalbetti[9] (Univ. of Chicago) produced a 30% body surface burn in male rats by immersion in water at 85 C. for 30 seconds. Mortality after various treatments was calculated after 72 hours. Cortisone, 5 mg. every 24 hours, after burning did not increase survival rate, but mortality after burning was reduced by subcutaneous infusion of isotonic sodium chloride solution equal to 10% of the animal's body weight immediately after burning. Pretreatment with cortisone (5 mg. every 24 hours for four days) lowered the survival rate of burned rats. Survival rate was not significantly altered by 2.5 mg. corticotrophin every 12 hours for seven doses before, nor by 2.5 mg. every 12 hours for seven doses before and every 12 hours after burning.

Desoxycorticosterone acetate given before burning protected the rats against burn shock, but did not profoundly enhance the protective effect of isotonic sodium chloride solution given in amounts equal to 10% of body weight.

Role of ACTH and Cortisone in Treatment of Shock. Oliver Cope[1] (Harvard Med. School) divides the development of our understanding of the role of the adrenal gland in shock

(9) A.M.A. Arch. Surg. 65:774-782, November, 1952.
(1) J. Indiana M. A. 45:485-492, June, 1952.

into four periods: (1) the adrenaline-autonomic alarm period of Cannoh (1915), (2) the similarity between shock and adrenal cortical insufficiency in the dog, noted by Swingle (1934), (3) the pituitary-adrenal alarm mechanism of Vogt and Long (1945), and now (4) the advent of ACTH and cortisone. The status of these hormones in the treatment of shock is confusing. In many instances enthusiasm seems to have overrun sound criticism.

It is clear that trauma normally causes an increased output of adrenal cortical hormones in the blood and urine with a drop in eosinophils, sweat sodium, adrenal vitamin C, etc. Patients with Addison's disease need extra hormone during any stress. Should the spontaneous adrenal response in a normal person undergoing injury be fortified with ACTH or cortisone? To answer this question it is necessary to define the normal response, learn its purpose and know whether it is adequate to meet the need. A review of all data, including data from histologic examination of the adrenals of severely burned patients, shows no evidence of any patient failing to make a normal and adequate adrenal response except those with Addison's disease, hypopituitarism and perhaps myxedema. An attempt to answer the question by the clinical trial of hormones in the prevention or therapy of shock in burns or trauma is inconclusive since there are too many variables. It is unfortunate that the medical public has already plunged into this approach with so little hope for a conclusive outcome. The experimental examination of claims that ACTH dries burns and diminishes the need for plasma fails to confirm that swelling or bleb formation is influenced in any way; two patients with Cushing's syndrome who voluntarily submitted to burns had the usual edema and blebbing response. Dog experiments show that neither ACTH nor cortisone influences the rate and volume of edema formation or the rise in flow and protein concentration of lymph at a burned area. Capillary permeability is not influenced, and plasma needs are not reduced.

It may be concluded that the physiologic purpose of adrenal hormones in trauma is not known. The hazards of using

ACTH or cortisone include potassium depletion, spread of infection, psychoses, perforated ulcer, endocrine imbalance, and substitution of doubtful for proved methods of therapy. There is no proved role for ACTH or cortisone in the therapy of shock in patients who were well before a burn or other trauma.

Eosinophilia Occurring during Administration of ACTH. Aage Videbaek[2] (Univ. Hosp., Copenhagen) reports that two of four different commercial preparations of ACTH may induce eosinophilia after one to three weeks of daily administration even though the expected eosinopenia occurred initially. Eosinopenia could be induced at any time by the use of other preparations, such as whale or sheep ACTH. In some cases the eosinophilia persisted for weeks after ACTH was discontinued although it usually subsided promptly. This rise in eosinophils was considered to be a species protein sensitivity reaction independent of the physiologic effects of ACTH.

Adverse Effects

Osteoporosis and Pathologic Fractures Following Treatment with ACTH and Cortisone. Increased urinary and fecal excretion of calcium and phosphorus, as well as a fall in serum concentrations of these substances, have been noted during ACTH and cortisone therapy. Osteoporosis and fractures, characteristic of Cushing's syndrome, should be expected in patients taking the hormones for prolonged periods. Ralph Teicher and Carl T. Nelson[3] (Columbia Univ.) present a case.

Man, 48, with pemphigus vulgaris, had a skeletal survey which was normal (Fig. 51). ACTH or cortisone was started in July 1949. Hyperadrenalism in the form of increased pigmentation, moon face, poikilodermia, gynecomastia, hypertension and buffalo hump obesity were first noted in May 1950. In May 1951, after 41,650 mg. cortisone and 4,135 mg. ACTH, x-rays revealed some demineralization of the vertebrae. An explosive outbreak of bullae necessitated simultaneous administration of 22,325 mg. cortisone and 1,100 mg. ACTH. During the next three months an additional 19,000 mg. corti-

(2) Acta endocrinol. 9:37-47, 1952.
(3) J. Invest. Dermat. 19:205-210, September, 1952.

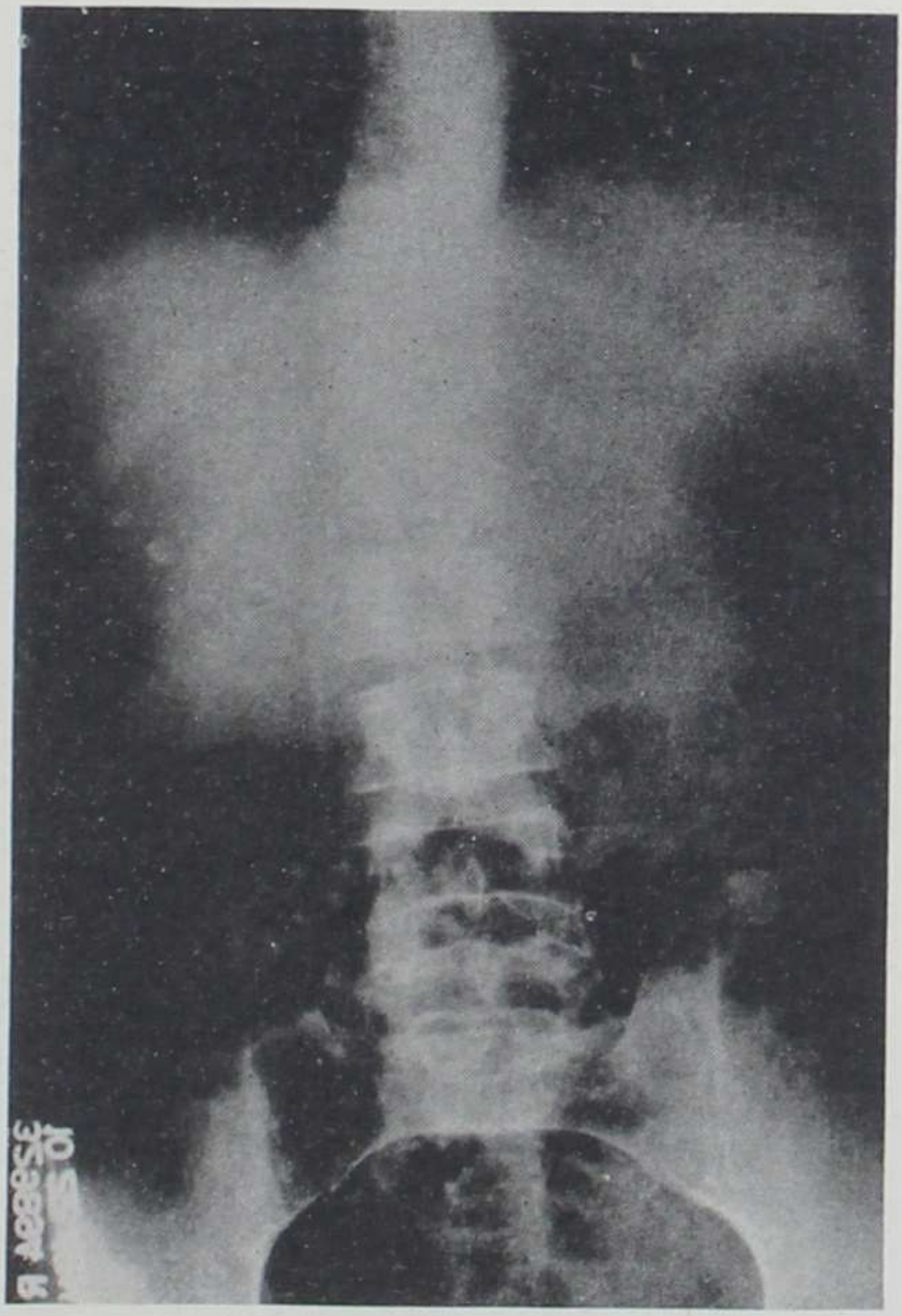


Fig. 51.—Osteoporosis without bony abnormalities of vertebral bodies. (Courtesy of Teicher, R., and Nelson, C. T.: J. Invest. Dermat. 19:205-210, September, 1952.)

sone was given. In December, severe low back pain prevented standing or straightening of the back. Two months later x-rays showed extension of the previously noted osteoporosis with collapse and "codfishing" of all vertebral bodies from the 9th thoracic to 5th lumbar (Fig. 52). Serum calcium level was 8.8 mg., phosphorus 3.7 mg. and alkaline phosphatase 4.3 Bodansky units.

Since the basic mechanism appears related to protein breakdown with release of protein-bound calcium, attempts to correct the negative nitrogen balance and, thereby, the calcium disturbance by the use of androgens and estrogens were tried, but without success. Calcium was also given without change in the x-ray findings although the serum calcium level rose.

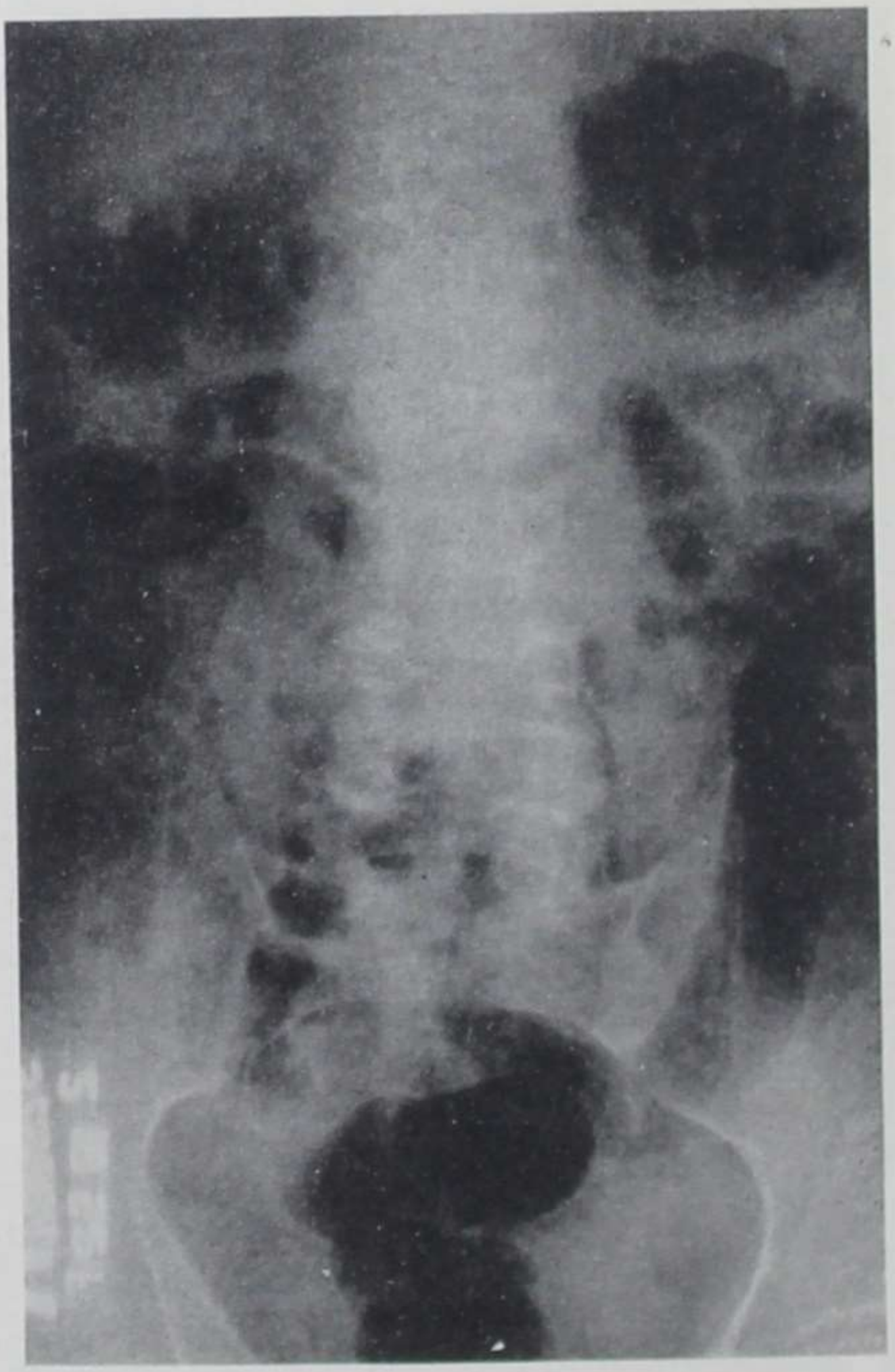
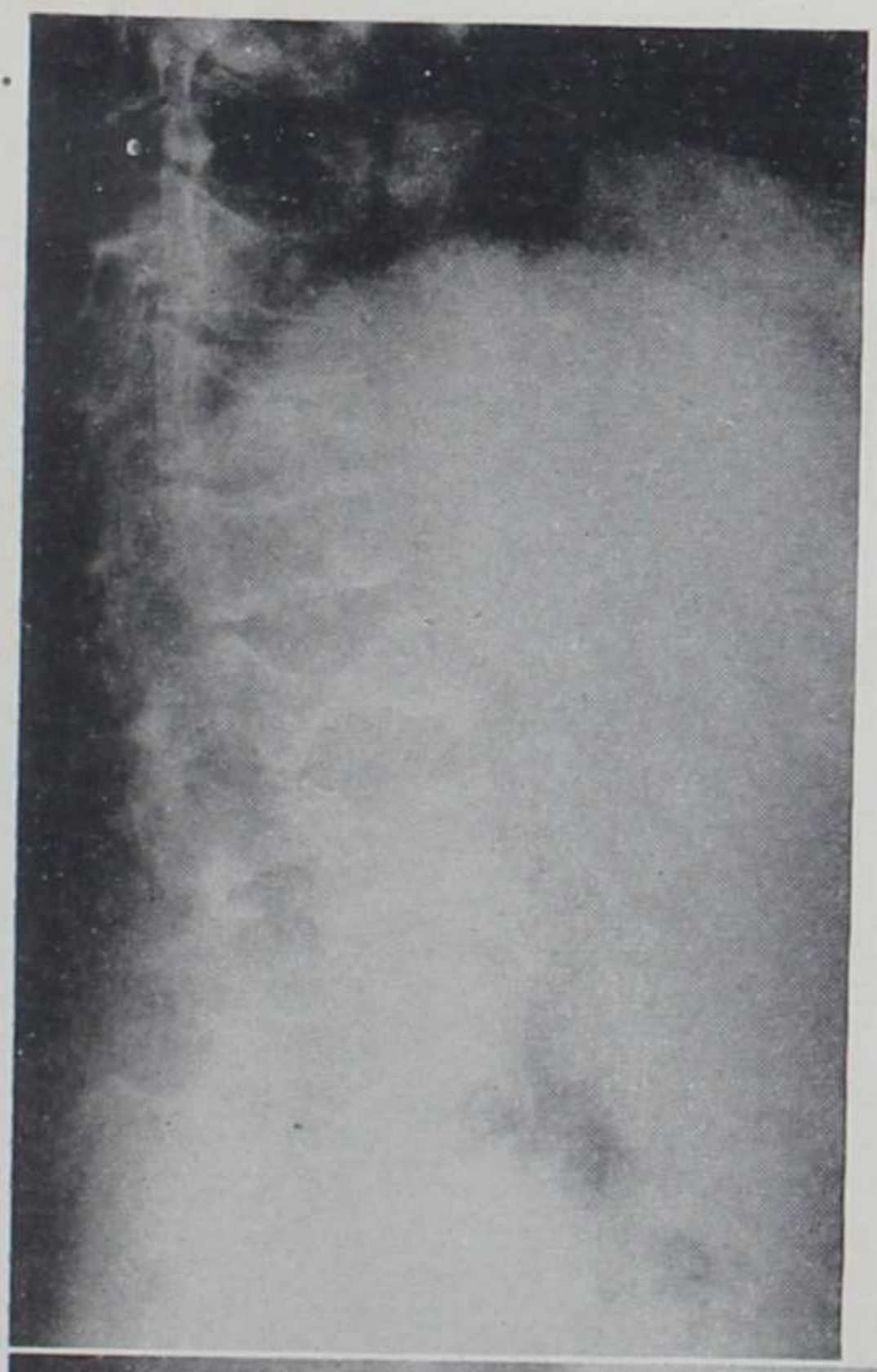


Fig. 52.—Same patient 31 months after ACTH and cortisone therapy. Note multiple compression defects and "codfishing" of vertebral bodies. (Courtesy of Teicher, R., and Nelson, C. T.: J. Invest. Dermat. 19:205-210, September, 1952.)

Pathologic Fractures in Patients with Rheumatoid Arthritis Treated with Cortisone. Felix Demartini, Albert W. Grokoest and Charles Ragan[4] (Columbia Univ.) point out that since pathologic fractures are rare complications of rheumatoid arthritis, their appearance in five women after 2-20 months of hormonal therapy emphasizes that significant decalcification is an additional serious complication of prolonged treatment with corticotrophin or cortisone. One or more factors predisposing to osteoporosis were noted in all five, four of

(4) J.A.M.A. 149:750-752, June 21, 1952.



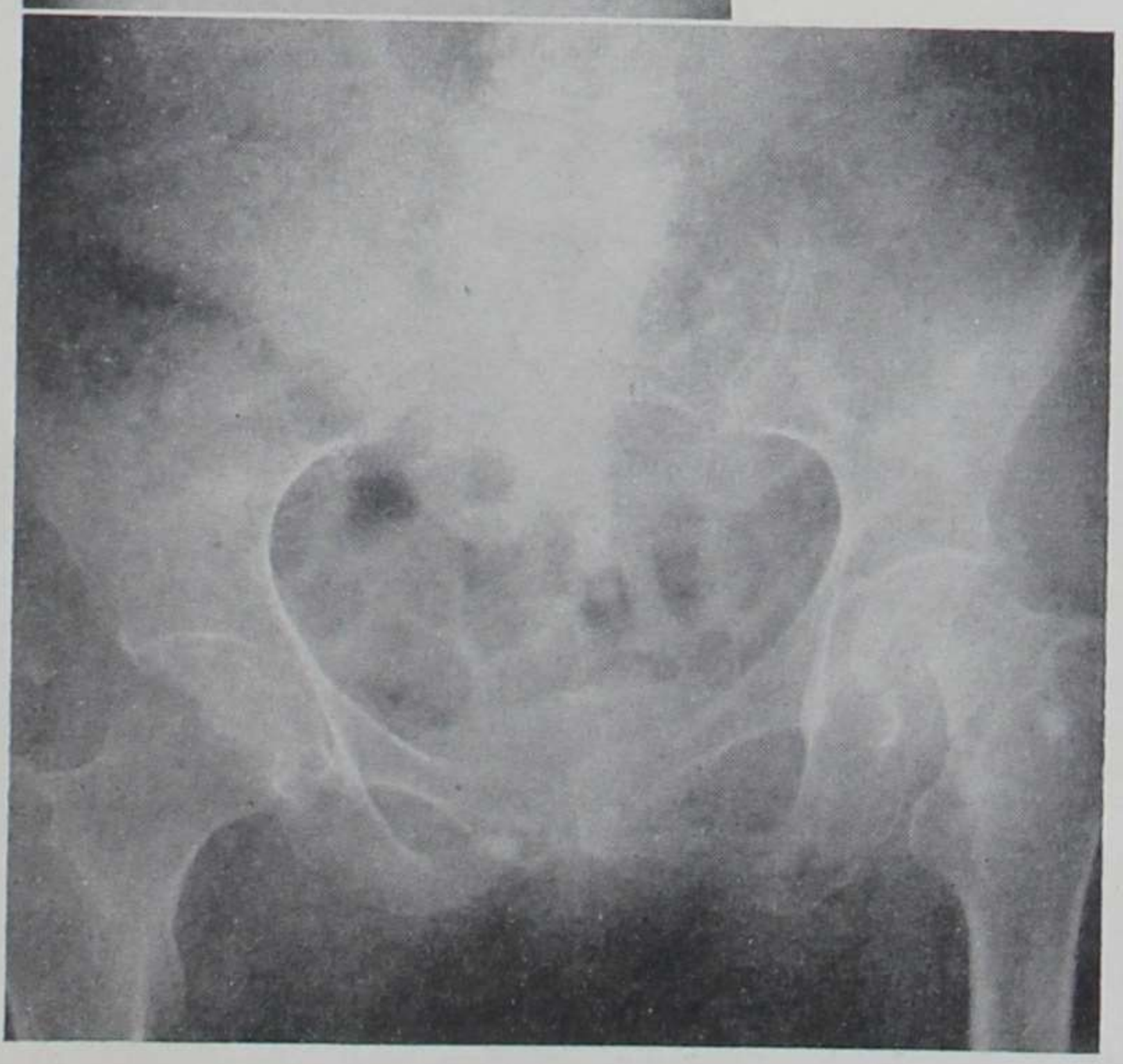


Fig. 53 (left).—Spine with "codfish deformity" after 15 months of cortisone therapy.

Fig. 54 (below).—Fracture of left femur, sustained after grand mal seizure, after 15 months of cortisone therapy.

(Courtesy of Demartini, F., *et al.*: J.A.M.A. 149:750-752, June 21, 1952.)

whom were postmenopausal. Rheumatoid arthritis was so severe in three that physical activity was minimal; each also required at least 500 mg. cortisone weekly. Each had vertebral fractures. Typical "codfish deformity" of the vertebrae was noted in one patient (Fig. 53) after 15 months of cortisone therapy. One patient also had fractures of both femora (Fig. 54) and of the left humeral head. In only one patient was compression fracture closely related temporally to start of ambulation after long bed rest. Several factors probably contribute to osteoporosis in rheumatoid arthritis: cortisone undoubtedly potentiates the tendency to lose calcium; the antianabolic effect of cortisone may involve the nonutilization of ingested amino acids; the need to give sufficient corticotrophin or cortisone to produce "hyperadrenalism"; and, since experimental fractures heal poorly during cortisone therapy, the activity of cells concerned with bone deposition may lessen during cortisone administration.

[The production of osteoporosis by administration of cortisone and corticotrophin was predictable on the basis of the known catabolic activity of these compounds (see the 1951 YEAR BOOK, p. 178). No crystal ball was required to make this prophecy; osteoporosis is a cardinal feature of Cushing's syndrome, and the amounts of cortisone or of corticotrophin ordinarily needed to suppress activity in rheumatoid arthritis usually produce Cushing's syndrome medicamentosa. Concurrent administration of estrogens or androgens may be expected to obviate this complication, especially in postmenopausal women.—Ed.]

Adrenal Atrophy and Irreversible Shock Associated with Cortisone Therapy is reported by Charles G. Fraser, Fred S. Preuss and Walter D. Bigford[5] (V.A. Hosp., Tucson, Ariz.).

Man, 34, with severe generalized rheumatoid arthritis and flexion contracture of the hips, had taken cortisone for eight months, first 1,200 mg. in 10 days, then 100 mg. three times a week, then 25 mg. twice daily for two months. Except for striking evidence of rheumatoid arthritis, physical and laboratory findings were essentially normal. A cup arthroplasty of the hip was undertaken. During the 1½ hour operation, blood pressure which was 140/80 never fell below 110/80 nor did pulse rate, 72, rise above 80. Blood loss was estimated at 500 ml.; during the operation, he received 550 ml. whole blood, which was discontinued because of muscular twitching. Shortly after he was transferred from the operating table to bed, blood pressure fell to about 40 systolic and the pulse became almost imperceptible. Epinephrine by intravenous and intracardiac routes had no effect. Instead of the usual signs of shock, the patient appeared flushed; respiration was labored and there were signs of air

(5) J.A.M.A. 149:1542-1543, Aug. 23, 1952.

Fig. 55 (top).—Cross section of entire adrenal gland, showing pronounced adrenal atrophy; enlarged from × 10.
Fig. 56 (bottom).—Cross section of normal adrenal gland; enlarged from × 10. (Courtesy of Fraser, C. G., *et al.*: J.A.M.A. 149:1542-1543, Aug. 23, 1952.)

hunger. The axillary temperature rose to 102 F.; he lost consciousness and died three hours after surgery.

Autopsy revealed a moderate, not excessive hemorrhage at the operative site, multiple small parenchymatous hemorrhages in the lungs, a small subendocardial hematoma, congestion in the abdominal viscera and severe atrophy of both adrenals (Figs. 55 and 56). Microscopically, the three layers of the adrenal cortex were narrowed; the cortical cells had not appreciably changed; the adrenal medulla was also atrophic. The kidneys gave no evidence of transfusion reaction. There was no evidence of fat embolism.

[Adrenal cortical atrophy is to be expected in patients who have received large doses of cortisone over long periods. This article points out two extremely important considerations: namely, patients who have this type of adrenal cortical atrophy are not good candidates for surgery, and this type of adrenal cortical insufficiency is best combated by administration of corticotrophin. Actually, at times, administration of cortisone to reduce the function of the adrenal cortex is desirable, e.g., in congenital adrenal cortical hyperplasia with pseudohermaphroditism or macrogenitosomia precox. "One man's meat is another man's poison." —Ed.]

Perforation of Bowel during Treatment of Ulcerative Colitis with Corticotrophin: Report of Three Cases. Maurice Tulin, Fred Kern, Jr., and Thomas P. Almy[6] (Cornell Med. Center) report peritonitis in 17 patients treated for ulcerative colitis with ACTH.

Case 1.—Man, 23, after repeated bouts of bloody bowel movements, weight loss, abdominal pain and occasional vomiting for a year, had a fever of 104 F., mild abdominal tenderness and proctoscopic evidence of diffuse ulcerative colitis. He was given 20 mg. corticotrophin in 1,000 cc. of 5% glucose intravenously during eight hours on two separate days; on the third day, he complained of abdominal pain. The abdomen was tender and had rebound tenderness. X-rays showed air under the diaphragm. Laparotomy revealed diffuse peritonitis and culture disclosed Escherichia coli. The site of perforation was not visualized. The patient improved after ileostomy.

Case 2.—Woman, 36, after prolonged ulcerative colitis was treated with antibiotics and 25 mg. corticotrophin intramuscularly every 6 hours for 2½ weeks. Tachycardia, low grade fever, bloody diarrhea and abdominal pain continued without any clinical improvement. The abdomen was tense and distended and slightly tender in the lower left quadrant. Ileostomy, done because of her poor condition, revealed diffuse peritonitis with thick adhesions and two separate perforations of the transverse colon. She eventually had a total colectomy.

Case 3.—Girl, 20, after severe ulcerative colitis for three weeks, was treated with antibiotics and whole blood with no change in the downhill course. She was given 20 mg. corticotrophin in an intravenous infusion of 5% glucose in eight hours but congestive heart failure required withdrawal of corticotrophin therapy for five days, after which it was resumed. She received 25 mg. intravenously daily for four days, then 40 mg. daily for two days. The abdomen became rigid, distended and silent; no pulse or blood pressure could be detected. She began to pass gross blood through the rectum and, despite infusion of whole blood, died. Autopsy revealed acute fibrinous peritonitis and a small perforation in the pelvic colon, probably a postmortem occurrence.

Because of the pathologic changes in the colon in ulcerative colitis and because of the known retardation of healing

(6) J.A.M.A. 150:559-562, Oct. 11, 1952.

processes by corticotrophin therapy, it is reasonable to assume that the hormone contributed to perforation and peritonitis in these cases. Corticotrophin should never be used in acute fulminating colitis if onset of fever is sudden, prostration severe, if differential white cell count shifts to the left and if there is a poorly organized exudative inflammatory reaction in the colon.

[Although peptic ulcers frequently develop during the administration of cortisone or corticotrophin, perforation of the lesions of ulcerative colitis is less often reported. The diagnosis of perforation may be extremely difficult, inasmuch as these hormones may mask the usual signs of peritonitis.—Ed.]

Disseminated Lupus Erythematosus Complicated by Miliary Tuberculosis during Cortisone Therapy is reported by J. N. Harris-Jones and N. K. Pein[7] (Royal Hosp., Sheffield).

Woman, 36, after four years of disseminated lupus erythematosus, was hospitalized for cortisone treatment during her third relapse. Clinical manifestations included reappearance of a maculopapular

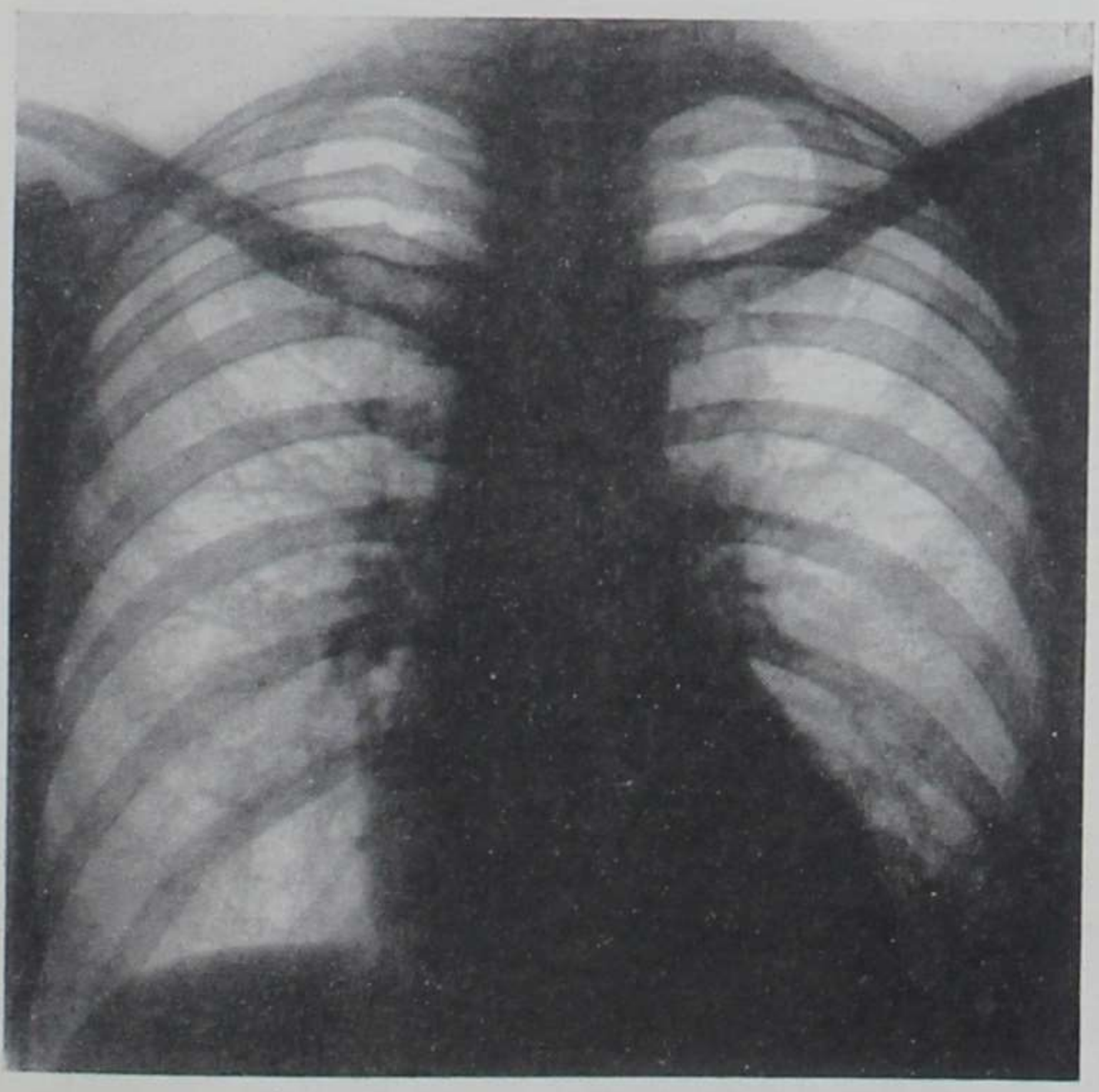


Fig. 57.—View of chest, before cortisone therapy, showing increased vascular markings only. (Courtesy of Harris-Jones, J. N., and Pein, N. K.: Lancet 2:115-117, July 19, 1952.)

(7) Lancet 2:115-117, July 19, 1952.

rash, fever, tachycardia, and peripheral arthritis. Lupus erythematosus cells were found. The albumin-globulin ratio was reversed. The urine repeatedly contained protein, granular casts, and erythrocytes. Chest x-ray showed increased vascular markings at the left base, but no other abnormality (Fig. 57). She was given a total of 2.35 Gm. cortisone acetate intramuscularly in 21 days; the rash and arthralgia disappeared within 3 days and the fever after 8 days. On the 17th day, when she was receiving 100 mg. cortisone every

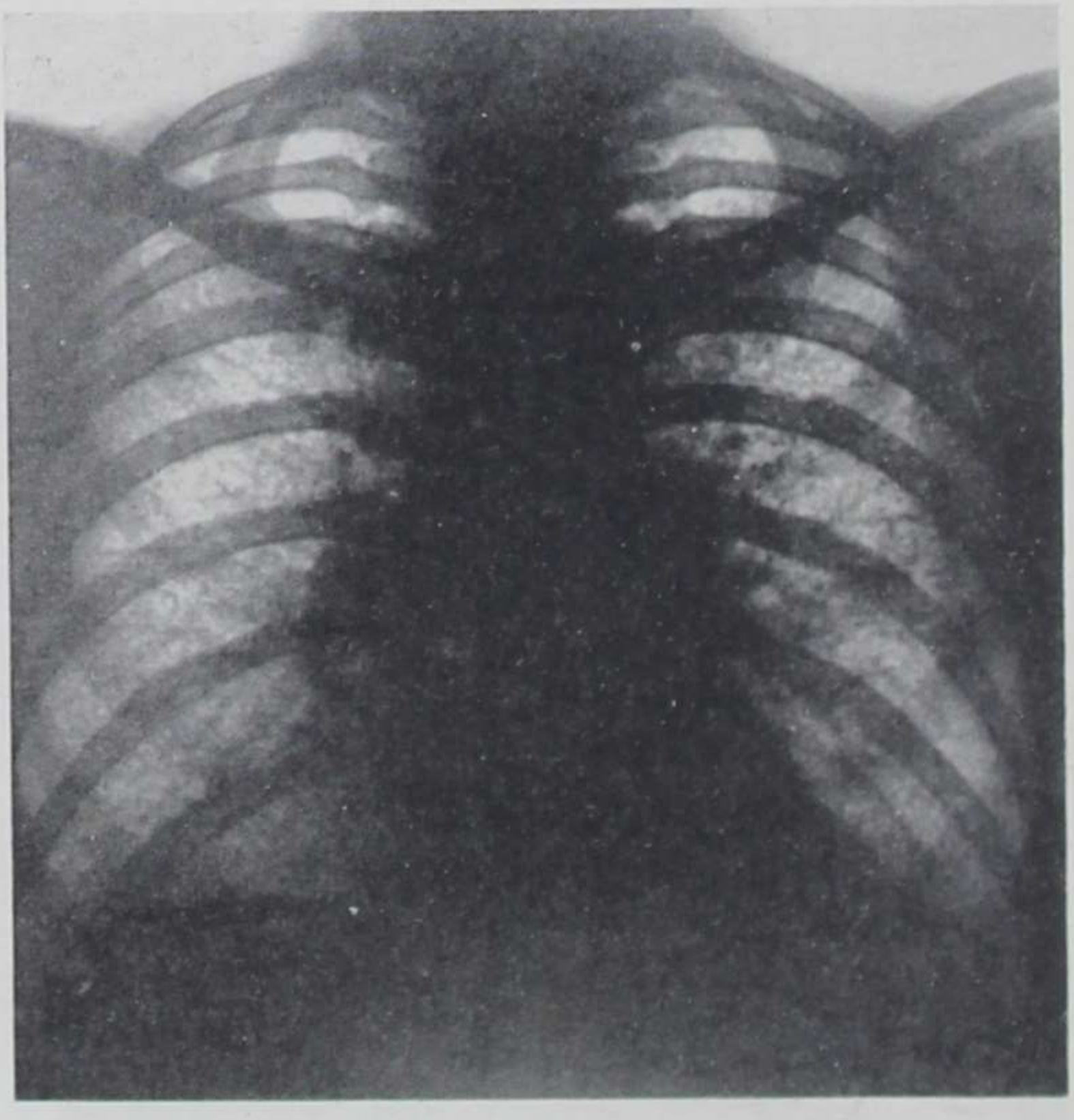


Fig. 58.—View of chest, after cortisone therapy, showing miliary infiltration. (Courtesy of Harris-Jones, J. N., and Pein, N. K.: Lancet 2:115-117, July 19, 1952.)

other day, arthralgia, tachycardia, and fever returned; when increasing the cortisone dosage to 100 mg. daily increased the fever, cortisone was withdrawn. Although she looked and felt well, fever continued and she had a slight, almost nonproductive cough. Fine scattered crepitations were heard over both lung fields and x-ray examination revealed miliary infiltration throughout both lungs (Fig. 58). Guinea pig inoculation gave positive results and tubercle bacilli were cultured from gastric washings. With streptomycin and p-aminosalicylic acid therapy for three months, fever disappeared. She gained weight and became well. There was no appreciable change in the x-ray appearance of the lungs.

The authors note that the disease may have spread from a latent and unsuspected focus directly activated by cortisone and that this case indicated the affinity of disseminated lupus erythematosus and tuberculosis.

[Administration of cortisone or of corticotrophin distinctly increases the possibility of a spread of tuberculosis. This undesirable complication probably results from the catabolic action of these compounds, which inhibits healing and localization. The occurrence of this problem is becoming increasingly frequent, as shown by this report and subsequent articles. The incidence is particularly noticeable in patients with sarcoidosis who are treated with cortisone or corticotrophin.—Ed.]

Cortisone-Induced Metastases of Adenocarcinoma in Mice. M. Agosin, R. Christen, O. Badinez, G. Gasic, A. Neghme, O. Pizarro and A. Jarpa[8] injected adenocarcinoma K7 in C3H mice and eight or nine days after inoculation gave 0.5 mg. cortisone intramuscularly daily to some of them. Others served as controls. Local tumor growth was arrested when cortisone was given. Metastases were never observed in untreated animals. However, they appeared about five to six weeks after transplantation in cortisone-treated animals. The longer the animals survived, the greater was the incidence. The axillary, inguinal, mesenteric and retroperitoneal nodes and mediastinum, peritoneum, pleura, liver, spleen, kidney, lung, diaphragm and muscles of the thigh were involved. Cortisone-induced metastases also were transplantable and produced local growth, but the growth in turn did not produce metastases unless cortisone was given to the new host.

There were notable histologic differences between untreated and treated tumors. The former consisted of polyhedric epithelial cells of great size; their nuclei were globular and rich in chromatin, with a great number of atypical forms and mitoses. The cells were gathered in irregular nodules, separated by a small amount of stroma. There were zones of central necrosis. In the treated tumors central necrosis was much more extensive. The cells were dissociated and showed degenerative changes, and it was difficult to recognize them as epithelial because of loss of normal relationship and their histiocyte-like appearance. In the periphery the cells showed nuclear abnormalities. Mitoses appeared much less frequently. The histologic picture of the metastases was similar to that of local growth in the treated animals.

(8) Proc. Soc. Exper. Biol. & Med. 80:128-131, May, 1952.

Lipid Deposition in Aortas in Younger Age Groups Following Cortisone and Adrenocorticotrophic Hormone was found by Eugenia M. Etheridge and Cornelia Hoch-Ligeti[9] (Univ. of Virginia). All specimens were from patients under 21. Aortas from 34 patients treated with cortisone or ACTH were compared with those from 43 random-picked controls. In the 1-10 age group, of 26 treated cases, lipid deposition was found in the intima of 24 and in the media of 12, whereas among 28 controls, only 11 had intimal and 2 had medial lipid deposits. Degree of deposition was more pronounced in those treated and seemed related to length of treatment. After age 11, lipid was so common in the controls that any differences from the treated group were equivocal.

Rheumatic Diseases

Antirheumatic Effects of Hydrocortisone (Free Alcohol), Hydrocortisone Acetate and Cortisone (Free Alcohol) as Compared with Cortisone Acetate: Results from Oral Administration in Patients with Rheumatoid Arthritis are compared by Edward W. Boland[1] (Los Angeles). In 150 patients treated with cortisone orally, 47% with severe, 70% with moderately severe and 92% with mild cases improved. The cost and complications of prolonged therapy have led to tests of many other compounds: substance S of Reichstein (11-desoxycorticosterone), compound A of Kendall (11-dehydrocorticosterone), 21-desoxycortisone, 21-desoxy-11-dehydrocorticosterone, desoxycorticosterone acetate (alone or with ascorbic acid), 17-hydroxyprogesterone, pregnenethiolone acetate, delta-5-pregnenolone and 21-acetoxypregnenolone. All but cortisone and the other 11-oxysteroid, Kendall's compound F (17-hydroxycorticosterone; hydrocortisone), were devoid of antirheumatic effect. Either hormone may be administered as the free alcohol or as the acetate, which is much less soluble and probably less well absorbed.

Five patients seemed to respond to hydrocortisone (free alcohol) orally more rapidly than to cortisone. Ten patients with stable maintenance requirements for cortisone acetate orally were uniformly maintained on smaller doses of hydrocortisone (free alcohol) with an average cortisone acetate-

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(9) Am. J. Path. 28:315-319, Mar.-Apr., 1952.
(1) Brit. M. J. 1:559-564, Mar. 15, 1952.

hydrocortisone ratio of 1.56:1. By contrast, comparison of cortisone acetate and hydrocortisone acetate in nine patients revealed that cortisone was more effective by a ratio of 1:1.37. This is confirmed in a comparison between hydrocortisone (free alcohol) and hydrocortisone acetate in nine patients. The free alcohol was almost twice as potent with a ratio of 1:1.97. Cortisone (free alcohol) and hydrocortisone (free alcohol) were equally effective orally. Of 10 patients receiving cortisone acetate, 2 had signs of hormonal excess (including edema and moon face) which disappeared with transfer to therapeutically equivalent doses of hydrocortisone (free alcohol). The free alcohol of either hormone apparently has nearly twice the antirheumatic activity with fewer adverse effects; their commercial production may therefore be desirable.

Comparative Effects of Cortisone, ACTH and Doca® in Case of Rheumatoid Arthritis with Addison's Disease are reported by Philip Ellman and Leon Cudkowicz[2] (St. Stephen's Hosp., London). The adrenal insufficiency was believed to have occurred incidentally after the rheumatoid arthritis was established. Kendall and others contend that there is no real evidence that rheumatoid disease is an endocrine disorder.

With a daily dose of 45 mg. ACTH, the patient obtained relief from rheumatoid arthritis, but the symptoms referable to adrenal insufficiency were not altered. Cortisone, 75 mg. daily, controlled both the joint lesions and adrenal insufficiency. Owing to the difficulty of maintaining the patient indefinitely on cortisone, 5 mg. doca® daily was given orally, followed by implantation of 300 mg. on the 13th day, to furnish 1.5 mg. daily. Relief from symptoms of Addison's disease occurred, but rheumatoid symptoms were not affected. When cortisone was added in about two weeks, 25 mg. by injection for 11 days, followed by oral therapy not exceeding 50 mg. daily, the patient improved. Daily maintenance dose was fixed at 25 mg.

[As noted in this report, corticotrophin will not suppress rheumatoid arthritis in a patient whose adrenals are incapable of responding to the hormone. In a beautifully designed and carefully reported study, Haynes, Savard and Dorfman (Science 116:690, 1952) showed that the elaboration of corticoids from adrenal slices in vitro depends on the presence of corticotrophin. Similar studies by Hechter and his colleagues on perfused adrenal glands of cattle have confirmed the observation that corticotrophin directly stimulates the adrenal.—Ed.]

(2) Ann. Rheumat. Dis. 11:225-229, September, 1952.

Absence of Response to Cortisone is reported by G. D. Kersley, L. Mandel and M. H. L. Desmarais.[3]

Man, 38, with typical active rheumatoid arthritis confirmed by synovial biopsy, who failed to show any clinical improvement after several daily doses of 400 mg. ACTH intramuscularly and 100 mg. intravenously in an eight hour drip. Thyroid and ascorbic acid failed to potentiate the ACTH. Response to 1.5 mg. doses every eight hours of Astwood's purified corticotrophin or 500 mg. cortisone intramuscularly a day was not evident. No clinical improvement was seen when cortisone was combined with tolazoline, used to produce vasodilatation to aid cortisone distribution in the effective tissues. Equally ineffective were cortisone and hydrocortisone applied directly to diseased tissues by intra-articular injection. There was no clinical or biochemical evidence of adrenocortical insufficiency and eosinopenic response was normal to ACTH and cortisone systemically. The failure to respond to therapy cannot be explained by inadequate dosage, inadequate absorption from site of administration, failure to stimulate the adrenal gland or the type of medication used. The fault must lie in the end organ or affected tissues.

With 200 mg. cortisone daily and 50 mg. tolazoline hydrochloride orally for 30 days, there was no sign of improvement or toxicity. Rheumatic activity did not increase on withdrawal of the cortisone. Improvement was, however, striking in a swollen knee after an injection of hydrocortisone.

Use of Massive Dose Cortisone in Treatment of Rheumatoid Arthritis. Since in most cases, cortisone and ACTH improve rheumatoid arthritis only during their administration, John D. Chase and James J. Lightbody[4] (Wayne Univ.) used massive doses in seven patients with the hope of prolonging remission. Cortisone was given parenterally in divided doses to a total of 500 mg. or more daily. When toxic symptoms appeared, cortisone was stopped abruptly in six cases. All patients received a low sodium diet with potassium supplements. In three patients a grade I therapeutic response (American Rheumatism Ass'n criteria) was achieved and in four a grade II response. Neither the total dose of cortisone administered nor duration of treatment was correlated to the response, but pretreatment severity of the arthritis was. Total cortisone dosage ranged from 6.1 to 26.6 Gm., emphasizing the wide variation in tolerance before signs of toxicity appeared.

All seven patients experienced reversible toxicity which persisted less than three months. A fall in weight and rise in blood pressure with pronounced dyspnea and bronchospasm

(3) Brit. M. J. 2:540-541, Sept. 6, 1952.
(4) J. Michigan M. Soc. 51:1167-1175, September, 1952.

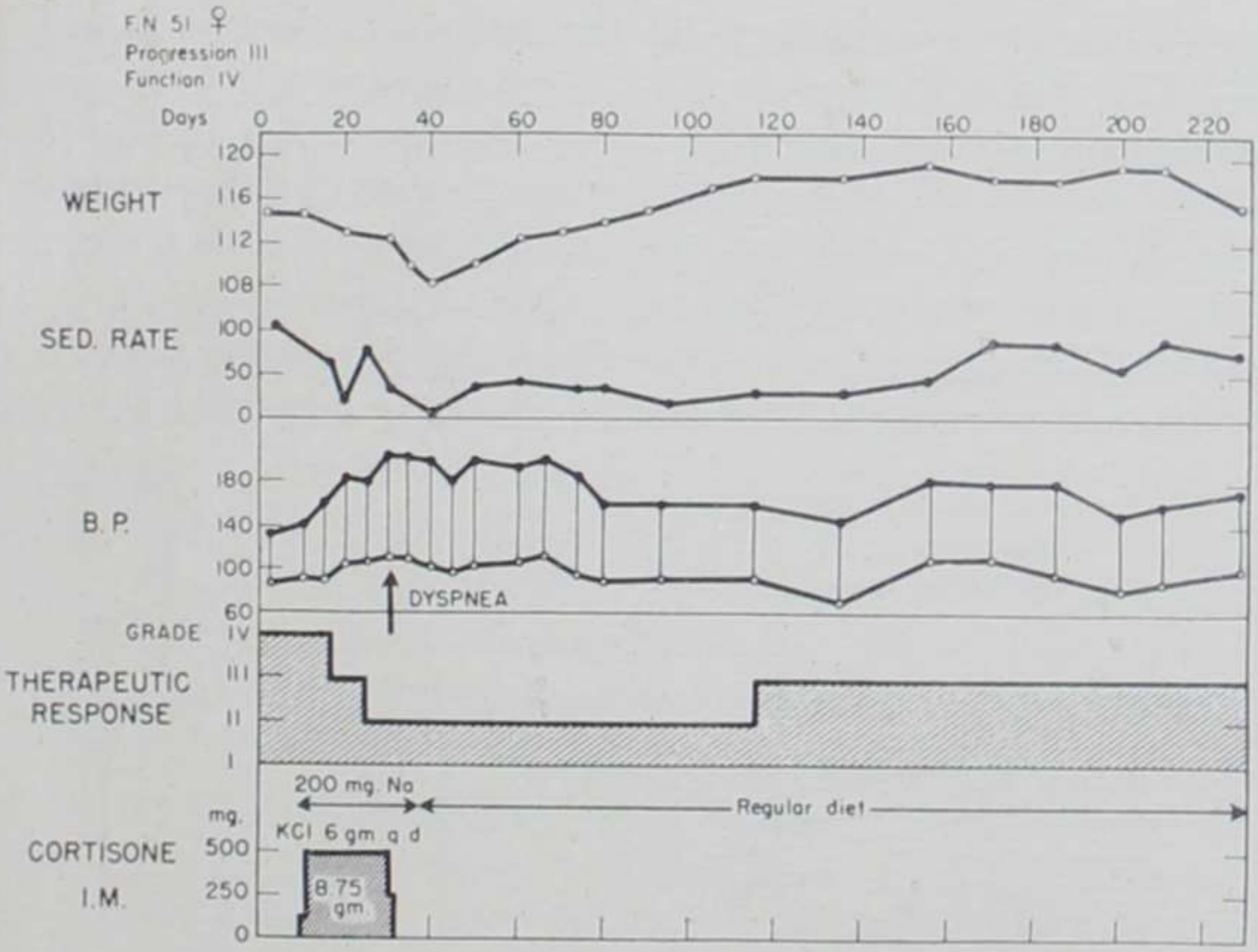


Fig. 59.—Decrease in weight and sedimentation rate with coincident rise in blood pressure with cortisone therapy. (Courtesy of Chase, J. D., and Lightbody, J. J.: J. Michigan M. Soc. 51:1167-1175, September, 1952.)

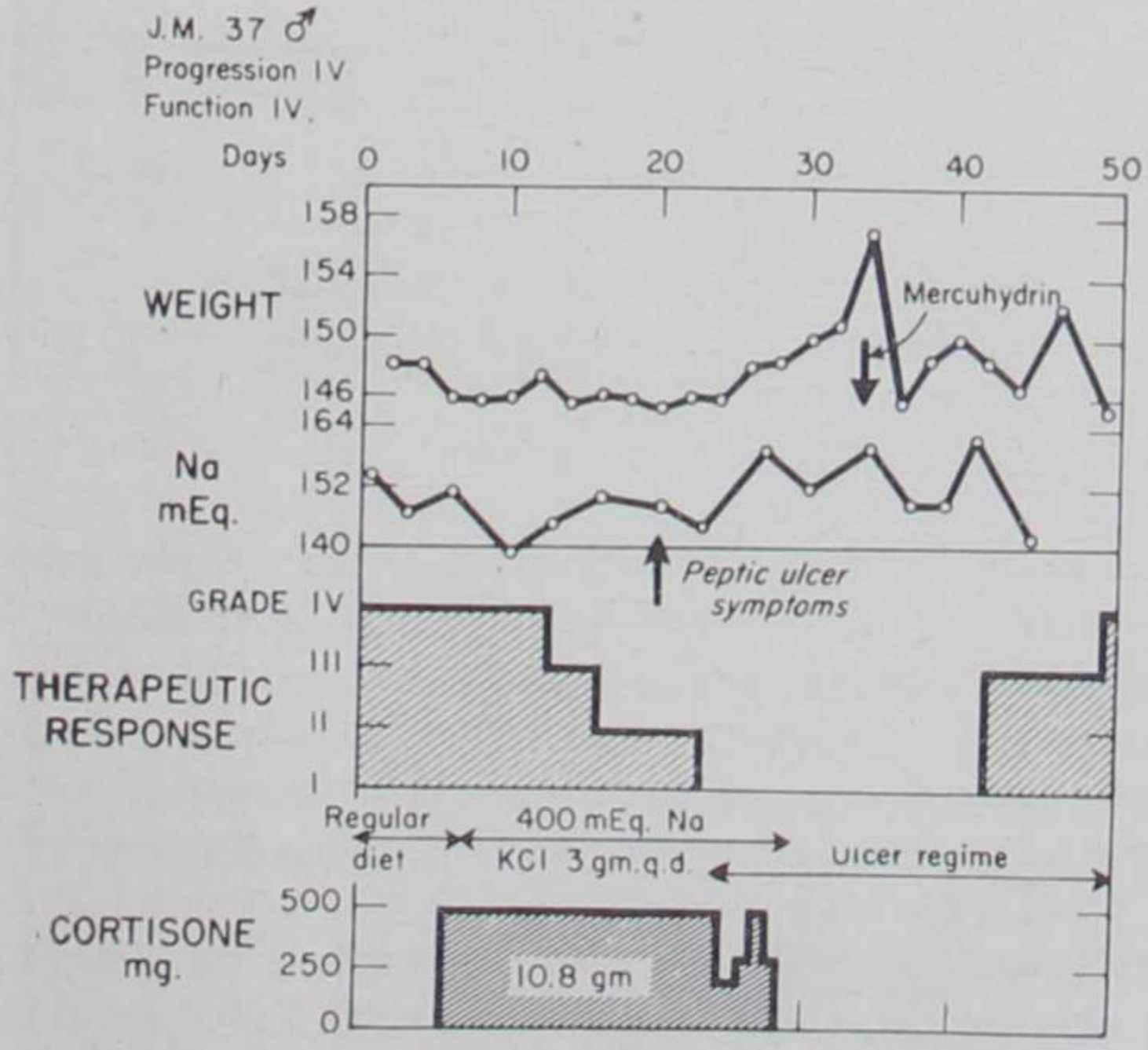


Fig. 60.—Clinical course with appearance of ulcer symptoms in second week of cortisone therapy. (Courtesy of Chase, J. D., and Lightbody, J. J.: J. Michigan M. Soc. 51:1167-1175, September, 1952.)

forced cessation of therapy on the 17th day in a woman, 56 (Fig. 59). Epigastric pain and x-ray evidence of an active duodenal ulcer were noted on the 14th day of cortisone therapy in a Negro, 37 (Fig. 60). Although cortisone withdrawal and a Sippy diet relieved the ulcer, dependent edema and sharp weight gain, requiring mercuhydrin,® resulted. A woman, 54, had glycosuria and a fasting blood sugar level of 128 mg./100 ml. during the second week of cortisone therapy,

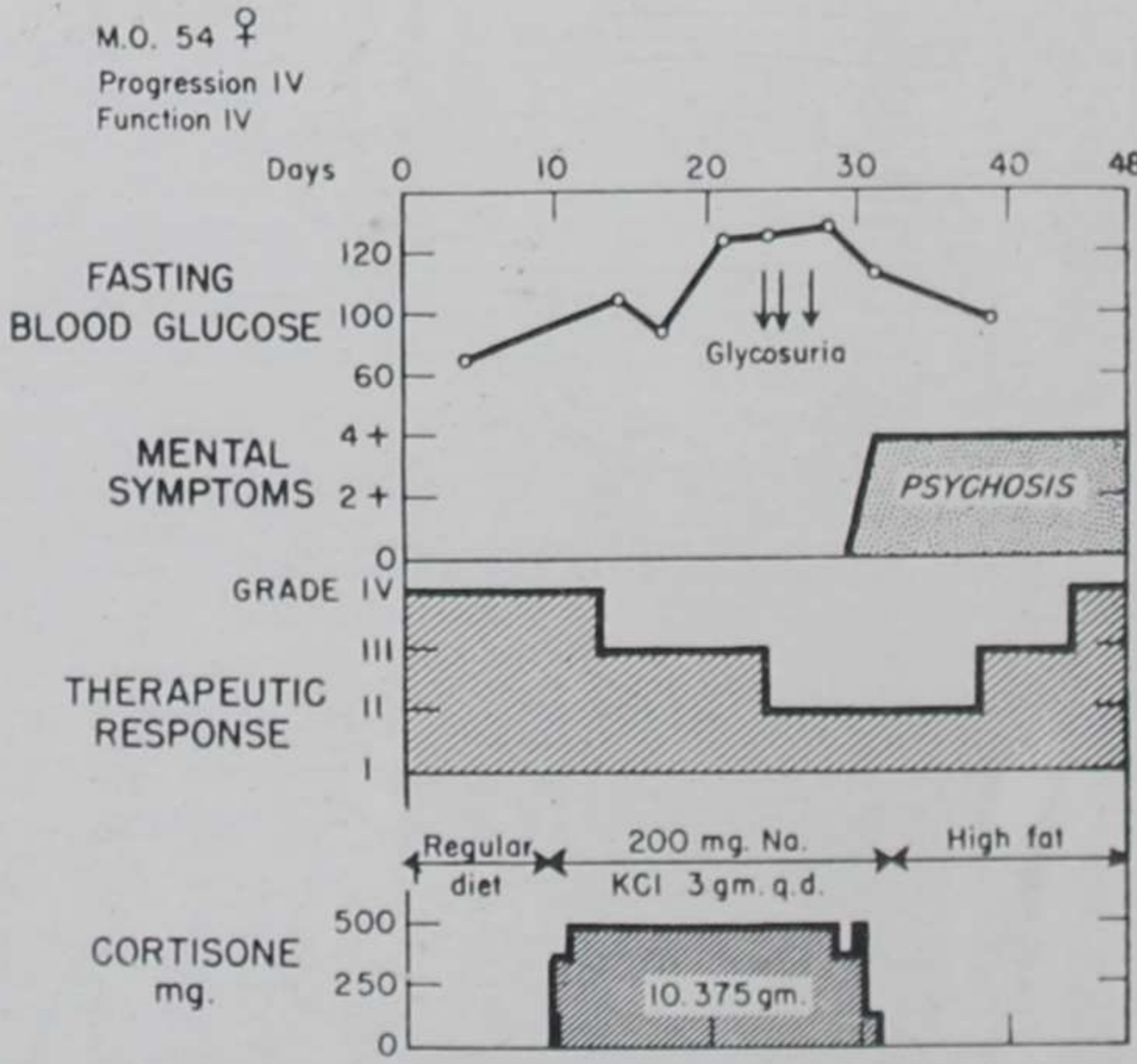


Fig. 61.—Glycosuria in third week of therapy followed shortly by appearance of psychosis. (Courtesy of Chase, J. D., and Lightbody, J. J.: J. Michigan M. Soc. 51:1167-1175, September, 1952.)

which had to be discontinued after three weeks because of hysterical behavior followed by psychosis with flight of ideas and hallucinations (Fig. 61). Severe depression was noted in another patient; hyperglycemia twice and facial fulness three times. A severe cutaneous infection required cessation of treatment in one patient and paroxysmal auricular tachycardia was noted in another.

Remission was maintained in one patient for 230 days and in another for 78. The other five patients failed to retain improvement beyond what might normally be expected. Synovial biopsy specimens taken before and during treatment showed reduced inflammatory reaction but no significant alteration in

the density of fibrous tissue. Testicular biopsy specimens before and during therapy in the four male patients showed no striking alterations. Urinary 17-ketosteroids and gonadotrophin excretion rose in all five patients tested.

The use of large doses of cortisone in rheumatoid arthritis is not advocated since it offers no advantage over routine low dose, long term therapy and imposes the added risk of cortisone toxicity.

Cortisone and Gold Therapy in Chronic Rheumatoid Arthritis. Harry E. Thompson and Harold J. Rowe[5] (Tucson) studied the combined therapy in 8 patients who responded only partially to gold therapy and for whom cortisone was added to gold and 13 others who took gold and cortisone concurrently. Of the 13, 7 had received gold before the investigation and therefore may not have been as responsive to gold. Cortisone was given intramuscularly in 100 mg. doses every 8 hours for 24 hours, then every 12 hours for 24 hours, then once daily for 21 days. It was then discontinued until relapse, when it was reinstituted at the previous level; after 14 days, 75-100 mg. was given parenterally every other day or 50-75 mg./day orally. It was again discontinued after varying intervals. A dose of 10 mg. gold was first given intramuscularly or intravenously; after that, 50 mg. was given at weekly intervals until total dosage reached 1 Gm. Gold was then continued at 10, 14, 21 and 30 day intervals.

Results indicate that when gold was given with moderate benefit to patients with active chronic rheumatoid arthritis, addition of cortisone did not help to arrest the disease. Despite excellent therapeutic response, remission was never complete; all patients relapsed to precortisone state soon after the hormone was discontinued.

Gold given concurrently with cortisone seemed to arrest rheumatoid arthritis about as often as gold alone but seemed superior to cortisone alone and to therapy without gold or cortisone. Concurrent administration produced excellent results, with immediate increase in functional capacity and, in some patients, complete remission of arthritis. The effects were lasting often enough when cortisone was discontinued to be of therapeutic significance.

Concurrent administration of gold and cortisone has sev-

(5) Ann. Int. Med. 36:992-1000, April, 1952.

eral therapeutic advantages. (1) Patients previously intolerant to gold can take it in combination with cortisone with less danger of reaction. (2) Cortisone permits immediate institution of rehabilitative measures long before gold levels would be high enough to be effective. (3) Cortisone may be discontinued in patients who respond to gold.

[In the early stages of rheumatoid arthritis, the combined use of gold sodium thiomalate and cortisone, together with physiotherapy and rehabilitation measures, is probably the most rational form of treatment. Cortisone seems to prevent some of the toxic reactions to gold, and gold apparently supplements the action of cortisone. Gold prevents relapse when the cortisone is eventually withdrawn.—Ed.]

Intra-articular Use of Hydrocortisone in Rheumatic Diseases. Paul J. Bilka[6] (Univ. of Minnesota) found that 37.5-50 mg. hydrocortisone acetate injected into the joints of 23 patients with rheumatoid arthritis produced moderate to striking local improvement in symptoms and objective findings for one to two weeks in 90%. Cortisone acetate injected in 100 mg. doses into the joints of seven others was about half as effective as hydrocortisone. Two patients had temporary local irritation. Local injections of hydrocortisone were not of much value in eight patients with osteoarthritis of the hip. In osteoarthritis of the knees, hydrocortisone acetate appears to have little value in the average case of chronic, low grade activity. However, in patients experiencing acute or subacute flares in symptoms as a result of new trauma, the local injection of hydrocortisone usually alleviates acute disability promptly.

Hydrocortisone acetate appeared helpful for local treatment of chronic gouty arthritis and of septic arthritis of the knee in two patients; in three others with acute periarthritis of the shoulder, it was not very helpful.

Intra-articular Hydrocortisone (Compound F) Acetate: Preliminary Report. C. R. Stevenson, J. Zuckner and R. H. Freyberg[7] (Cornell Univ.) injected either the regular aqueous suspension or the suspension of the crystalline steroid in water into 20 joints of 13 rheumatoid arthritis patients. Between 25 and 75 mg. was injected at intervals of 3-29 days to a total of 96 injections. The steroid was injected into the knees of all but one patient, in whom it was injected into the elbow. All tolerated local injections well and reported some prolonged

(6) Minnesota Med. 35:938-943, October, 1952.
(7) Ann. Rheumat. Dis. 11:112-118, June, 1952.

local benefit. Clinical results with hydrocortisone acetate in water and those with the standard suspension did not differ.

Subjective improvement estimated at 70% or more in 6 joints and 50% or more in 14 was reported. Objective improvement of 70% or more in 4 joints and 50% or more in 9 was clinically estimated. Some had no relief until after three or four injections, whereas others noted persistent partial relief after the first injection.

Whenever available for study, the synovial fluid after treatment showed a decrease in total number of cells and in the polymorphonuclear cell percentage. In four of nine patients the erythrocyte sedimentation rate decreased by more than 10 mm./hour.

Results indicate that hydrocortisone acetate injected intra-articularly acts primarily in the structures of the injected joint.

Treatment of Bursitis by Local Injection of Hydrocortisone Acetate. Owing to its antiphlogistic effect at the tissue level, this hormone has proved to be a specific agent for relief in bursitis. Egmont J. Orbach[8] (New Britain, Conn.) reports that when not more than 1 cc. of suspension containing 25 mg. of the undiluted hormone was accurately deposited into the inflamed bursa, three patients with acute bursitis had complete relief from pain within 24 hours and two more within 48 and 72 hours. Two patients with chronic subdeltoid bursitis obtained relief after 48 and 72 hours. Only one injection was required per patient in this group. In a patient with chronic popliteal bursitis it took five injections in 57 days for complete relief. Only two patients noted postinjection soreness, possibly due to use of procaine to anesthetize the needle pathway. The usual abrupt cessation of pain after hydrocortisone injection is advantageous. With local cortisone injection, which is temporary but annoying postinjection discomfort often follows.

[The preceding three articles demonstrate that when local administration is feasible, hydrocortisone is superior to locally and to systemically administered cortisone. The advantage of local or topical application lies in the fact that generalized metabolic effects, which are usually undesirable, are not produced.—Ed.]

Corticotrophin (ACTH) in Treatment of Acute Subacromial Bursitis appears to be more effective than radiation therapy. Although the latter is usually effective within 48 hours, at least 50% of patients experience intense aggravation

(8) J. Internat. Coll. Surgeons 18:159-163, August, 1952.

of shoulder pain and require opiates during this period. Moreover, a frozen or less mobile shoulder joint results unless physical therapy is soon inaugurated.

Charles LeRoy Steinberg and Andries I. Roodenburg[9] (Rochester, N. Y.) report that ACTH therapy produced complete relief from pain and return to normal function of the shoulder joint in five cases of acute bursitis. Complete relief from pain and almost complete return of normal function was obtained in one chronic case. Pretreatment x-rays of the shoulder in five patients showed calcification in the subacromial bursa. Follow-up x-rays showed disappearance of calcification within one month in one and no change in another. Various dosages were used in order to determine the optimal dose; it appeared that 50 USP units of ACTH given twice on the first day and once daily on two successive days is usually sufficient.

The ease with which ACTH may be administered and its clinical effect make this method of treatment worth while. Experience with hydrocortisone therapy has been insufficient to determine whether it is superior.

Osteitis Pubis Treated with Adrenocorticotrophic Hormone. Osteitis pubis is an infectious inflammation of the periosteum, bone, cartilage and ligamentous structures of the anterior half of the pelvic girdle, occurring usually after a suprapubic operation but sometimes after nonoperative disorders such as pyelonephritis. The clinical and x-ray findings rarely appear before 10 days postoperatively and usually require 2-6 weeks. The process generally begins at the symphysis and tends to involve the ischia. On x-ray, a moth-eaten bony destruction apparently beginning at the symphysis is characteristic, in association with evidence of periosteal reaction and widening of the cartilaginous space. Calcification across the symphysis may occur. Incapacitation and pain may last for weeks or months, but self-healing is the rule. Therapy has not been very successful. Symptomatic treatment gives some relief; results with antibiotics are equivocal.

A trial with ACTH was suggested to Victor F. Marshall, Willet F. Whitmore, Jr., A. T. Petro, J. W. Poppell, R. N. Grant and Rulon W. Rawson[1] (Memorial Cancer Center, New York City) by the clinical similarity of the clinical manifesta-

(9) J.A.M.A. 149:1458-1460, Aug. 16, 1952.
(1) J. Urol. 67:364-369, March, 1952.

tions in one case to those of an acutely rheumatic joint. Dramatic relief with early ambulation and resolution promptly followed corticotrophin administration in two cases of the acute disease after a total of 875 and 1,475 mg. had been given in 11 and 14 days, respectively. The clinical relief persisted after discontinuance of hormonal therapy. In one chronic and complicated case, limited but definite benefits were obtained.

Corticotrophin (ACTH) Therapy of Initial Attacks of Acute Rheumatic Fever in Children. Vincent C. Kelley[2] (Univ. of Utah) gave corticotrophin to 18 unselected children (11 boys), aged 3½-15, who had initial, acute attacks of rheumatic fever manifested by carditis, arthritis, fever, elevated sedimentation rates and, in most instances, one or more of the other major or minor manifestations. Treatment was started as soon as an unequivocal diagnosis was established. The patients were kept at bed rest and received no other medication except 500 mg. ascorbic acid daily. Fifteen children were given corticotrophin intramuscularly at six hour intervals, with an initial daily dose varying from 25 to 100 I.U. This was continued until the serum mucoprotein level substantially decreased and, in some cases, until the sedimentation rate had been less than 20 mm./hour (Wintrobe method) for three to five days. The daily dose was then decreased gradually, with successive decrements at intervals of two or more days if no clinical or chemical evidence of rheumatic activity occurred, until discontinuance of the drug. In some instances it was necessary to increase the dose after trial indicated that the initial dose was probably inadequate. In these cases the sedimentation rate failed to decrease within seven to nine days. Three patients received corticotrophin by slow intravenous infusion according to the same dosage schedule.

Prediction of the most economical dose, from the standpoint of the quantity of corticotrophin and duration of hospitalization required, is complex. Analysis of this group of patients indicates that calculation of the initial dose on body weight is more satisfactory than empiric dosage. The patients whose initial dose was greater than 1 I.U./lb./day required, on the average, a total of only 1,924 I.U. (33.16 I.U./lb.) corticotrophin and 38 3/10 treatment days, whereas those who

(2) A.M.A. Am. J. Dis. Child. 84:151-164, August, 1952.

received less than 1 I.U./lb. required a total dosage of 2,858 I.U. (38.6 I.U./lb.) and 60 treatment days. The initial daily dose of corticotrophin should therefore be between 1 and 2 I.U./lb./day intramuscularly.

After initiation of therapy, joint symptoms usually lessened within a few hours to one day and disappeared within two days. Temperature became normal within one day in eight patients and within five days in all patients. The electrocardiographic picture returned to normal within two weeks in 13 patients. In patients who received an adequate initial dose, average time for return of the sedimentation rate to normal was 13½ days. Moon-shaped facies, weight gain, abnormal appetite, striae, acne and mild glycosuria occurred but receded promptly with completion of therapy.

About half the patients showed laboratory evidence of rebound on discontinuance of therapy. None showed clinical evidence of rebound or have had recurrence of rheumatic fever. This emphasizes the desirability of continuing the initial dose until the serum mucoprotein level has decreased significantly and then tapering the dose gradually. Final acceptance of the conclusion that hormone therapy of rheumatic fever is merely suppressive should be held in abeyance.

Since the follow-up study has been brief (1-11 months), no definitive conclusions regarding residual cardiac damage can be made. However, although all the patients had cardiac murmurs during acute rheumatic fever, 13 have no residual murmur and 5 have a grade I mitral systolic murmur; 6 patients had significant diastolic murmurs which have disappeared. There is no other evidence of residual cardiac damage.

Disseminated Lupus Erythematosus

Corticotrophin and Cortisone Treatment for Systemic Lupus Erythematosus was administered to 30 patients by Edmund L. Dubois, Robert R. Commons, Paul Starr, Charles S. Stein, Jr., and Robert Morrison[3] (Los Angeles). Results were compared with those in 34 untreated patients, all of whom died of the disease. The aim of therapy was to produce hypercorticism as soon as possible, for this is usually accompanied by simultaneous remission of the disease. Large intravenous

(3) J.A.M.A. 149:995-1002, July 12, 1952.

doses of corticotrophin (40-60 mg. or more a day) proved most effective in this respect. The solution used for continuous intravenous administration was a dilution of the usual intramuscular corticotrophin preparation in 1,000 cc. of 2.5% or 5% aqueous solution of glucose with 10 mg. heparin sodium per liter to inhibit local thrombophlebitis. At 10 drops/minute, this amount usually lasts about 24 hours; a minimum of 16 hours/day is advisable. With the needle placed in a forearm vein, treatment may continue as long as nine days before it is necessary to change the site. Intramuscular clysis in the anterior thigh area with a 2.5% glucose solution may be used if there are no readily available veins.

Within 7-14 days after start of therapy a slight rise in blood pressure usually occurs, followed by acne, moon facies, hyperglycemia and glycosuria. In the presence of renal involvement, blood pressure may be initially elevated, and in such cases, cortisone is the drug of choice. When hyperadrenocorticism is reached, treatment is changed to intermittent muscular injection of about 20 mg. corticotrophin every six hours or to oral administration of cortisone, 25 mg. every six hours, to maintain the Cushing state. At this point the patient must be carefully watched for signs of relapse. If severe hypertension exists or develops with corticotrophin therapy and if the disease has not been adequately suppressed, cortisone should be used. In the presence of malignant hypertension, neither of these hormones should be used.

Adjuvant measures which may be necessary to combat the adverse effects of corticotrophin and cortisone include a 200 mg. sodium diet before and during early therapy, 8-12 Gm./day of potassium chloride or citrate orally and 500 mg. ascorbic acid daily. Large doses of testosterone were administered to combat the catabolic effects of corticotrophin and cortisone. As much as 500 mg. testosterone daily for as long as 35 days did not virilize seven women with active disease; however, after remission, these same patients could be masculinized with as large or smaller doses. During exacerbations about 10% of the administered testosterone was excreted as 17-ketosteroids, as compared with the normal excretion of 40%.

Differentiation of symptoms of the disease from complica-

tions of therapy is important. Convulsions from corticotrophin do not usually occur during early treatment. If, after a recent exacerbation, the patient is febrile and normotensive, has a positive tourniquet test result and no evidence of recent large weight gain, convulsions are probably due to the disease itself. The same applies to psychoses, provided hypopotassemia can be ruled out. Periorbital edema, common in exacerbations of the disease, should not be confused with that of an early Cushing syndrome, in which there is swelling in the malar and submandibular areas. Because of nephropathy due to the disease, hypochloremia and hyponatremia may occur, which may be corrected by diet supplementation. Hyperthyroidism occurred in two of eight patients receiving massive doses of hormones.

No patient died in whom a Cushing state was induced and maintained. Under treatment, fever usually abates in 24-48 hours, joint pains in several days and pleural effusions and cutaneous lesions in 1-2 weeks. Retinal changes, anemia and cachexia improve gradually over several weeks. Death may still occur before production of hypercorticism, despite weeks of massive intravenous corticotrophin therapy. L.E. cells disappeared completely within six weeks in seven patients who had remissions, five of whom had continuous treatment and two, only a brief course of therapy. Of the 14 patients in whom clearcut remissions were induced, renal abnormalities cleared completely in all of 5, anemia was greatly improved in 11 of 12 and leukopenia in 10 of 11, during the period of remission. In all patients the sedimentation rate remained elevated despite apparent remission.

An additional 15 patients were later treated according to the preceding regimen and a remission or Cushing's state was induced in 13. For the combined continuous treatment group of 21 patients, duration of the disease was a median of 30.5 months, an arithmetical mean of 36.1 and a geometric mean of 27.3. This represents an improvement over the control series. There were no ill effects from long term hormone therapy (up to 18 months), such as osteoporosis, psychosis or perforated ulcers; three patients, however, had spontaneous thrombophlebitis and five, advanced renal damage. The authors believe that the usual cause of treatment failure in this and other diseases which usually respond to these hormones is

inadequate dosage. The obvious clinical appearance of Cushing's state rather than stereotyped dosage schedules should be used as an end point to determine the effectiveness of therapy.

Corticotrophin and Cortisone in Acute Disseminated Lupus Erythematosus: Results of Long Term Use are reported by Louis J. Soffer and Richard Bader[4] (Mount Sinai Hosp., New York City). Eighteen patients were followed 3-20 months after therapy. The ratio of women to men was 2:1, a greater incidence in men than has previously been reported, probably owing to newer diagnostic criteria, including use of the L.E. cell phenomenon and less emphasis on the facial rash. Most patients were aged 10-40, but two patients between 50 and 59 stress the importance of making L.E. cell preparations in this age group, particularly in those suspected of having rheumatoid arthritis.

Clinical manifestations of the disease included fever and presence of L.E. cells in both peripheral blood and sternal marrow in all 18. Arthritis, not always present on admission, almost invariably occurred some time during the course of the disease. Facial eruption was present in 11 and lesions on the buccal or gingival membranes in 9. All patients had microscopic hematuria, 14 had hyaline and granular casts in the urine and 10 had a blood urea nitrogen level above 25 mg./100 cc. Anemia, leukopenia and thrombocytopenia were frequent.

All patients were hospitalized three to nine months. Before hormone therapy a preliminary trial with an antibiotic was made. Corticotrophin was started at 100 mg. daily given intramuscularly in divided doses, and cortisone, at 200-300 mg. orally or parenterally. Daily amounts were gradually reduced unless a relapse occurred. Most patients were ultimately maintained on 20-50 mg. corticotrophin or 50-100 mg. cortisone daily. During therapy all received a 200 mg. sodium diet and mercurial diuretics, when necessary, to combat edema resulting from treatment. Potassium chloride was given orally, 2-6 Gm. daily, to combat hypochloremic alkalosis and hypopotassemia. After discharge, parenteral treatment was self-administered, according to the hospital schedule. Most patients later received cortisone orally every six to eight hours.

(4) J.A.M.A. 149:1002-1008, July 12, 1952.

Most patients had marked improvement in well-being, with increased appetite and decreased irritability and depression within 24 hours after start of corticotrophin or cortisone orally and within three to four days after cortisone intramuscularly. Temperature returned to normal and serous membrane involvement responded rapidly. Joint, pleural, abdominal and pericardial pain disappeared in one to three days and pleural effusions in one to three weeks. Skin lesions, except for telangiectasia, usually responded within two to four weeks, and mucosal lesions also eventually healed. Raynaud's phenomenon in three patients disappeared but promptly recurred when dosage was reduced to inadequate levels. The organic mental syndrome cleared as the general febrile state improved. The EEG pattern, abnormal before therapy in 6 of 13 patients, reverted to normal in 3 during treatment. Retinal lesions in seven cleared slowly; in patients with severe relapse, preterminal or uremic retinal lesions reappeared. The sedimentation rate response was variable. Anemia improved slowly in five, changed little in eight and became more severe in three. Nine had an increase in white blood cell count, five had no change and four showed a further progressive fall. Serum albumin increased in 10, decreased in 4 and remained stable in 4. Serum globulin decreased in 11, increased in 4 and showed no change in 3. L.E. cells persisted despite a remission in the disease, although at times they disappeared temporarily. Renal damage tended to persist. In five patients, blood urea nitrogen level returned to normal after improvement in hydration. However, five had persistent azotemia despite vigorous therapy and three of these died. Autopsy of two revealed characteristic renal lesions. Of 13 patients without persistent azotemia but with microscopic hematuria, 3 died of causes unrelated to renal insufficiency.

Hypertension occurred during treatment in nine patients but responded to reduced dosage in all but four; of these, three died, two with azotemia. Pretibial edema in 10 patients responded to mercurial diuretics. Depression and euphoria associated with treatment tended to disappear with reduction in dosage. Convulsions occurred in four patients; two were preterminal, one had associated septicemia and one was in status epilepticus. About one third of patients had acne and hirsutism, which cleared when treatment was discontinued. Fulness of

the face in 15 tended to disappear when dosage was reduced or the drug discontinued. Congestive heart failure in 10 patients usually responded promptly to mercurial diuretics and digitalization. In one patient, diabetes mellitus developed during treatment; however, as corticotrophin dosage was reduced the insulin requirements became progressively less and eventually could be discontinued. Osteoporosis occurred during therapy in a woman, aged 58. Spinal x-rays also revealed compression of the first lumbar vertebra and narrowing of the twelfth thoracic vertebra. The impression was one of postmenopausal osteoporosis intensified by cortisone. After prolonged use of methyltestosterone, back pain decreased, but this was not associated with roentgen evidence of increased vertebral calcification.

Twelve patients were living, eight of whom required continuous treatment with 50-100 mg. of cortisone orally daily. Nine patients had gone without therapy for intervals of a week to as long as 11½ months. Despite the risks attendant on the use of these drugs, they constitute the most effective agents yet available for treatment of this disease. Although no actual cures result, some patients may be maintained in remission for an indefinitely prolonged period.

[The concept of disseminated lupus erythematosus has changed considerably, from both the diagnostic and the therapeutic standpoint, in recent years. The disease is by no means as rare as was formerly supposed, nor is it limited to women of child-bearing years. It may appear in the most bizarre forms, mimicking rheumatoid arthritis, renal disease, all varieties of circulatory disorders and various types of dermatoses. The course is not invariably unfavorable, as was previously thought. The disease may be extremely acute and short-lived or may persist in milder form over many years. The various types of endocrine therapy tried in the past, including bilateral oophorectomy and the administration of testosterone compounds, have not been entirely unsuccessful. Because of the variable course of the disease, however, the results of endocrine therapy were considered dubious.

In the severe form of the disease, when the course is short and the prognosis unfavorable, effects of cortisone or of corticotrophin have proved miraculous. As pointed out by Dubois *et al.*, good results are obtained only when sufficient hormone is administered to produce an advanced state of Cushing's syndrome medicamentosa. Unfortunately, this amount of hormone also produces highly undesirable features, particularly the manifestations ascribed to the catabolic actions of the hormones, e.g., osteoporosis. In my opinion, the administration of anabolic steroids such as methyltestosterone compounds, as advocated by these authors, is a distinct therapeutic step forward. Patients with disseminated lupus erythematosus can tolerate remarkable amounts of these hormones—an observation pointing to a presumed alteration of the metabolism of steroid hormones in this disease. The interested reader would do well to refer to the

originals of the two preceding articles. It is a satisfaction to note that the knack of writing good clinical papers has not been lost in these days of complicated laboratory studies.—Ed.]

Central Nervous System

Psychologic Response to ACTH, Cortisone, Hydrocortisone and Related Steroid Substances. Howard P. Rome and Francis J. Braceland[5] (Mayo Clinic) point out that although there has been a welter of speculation about the etiologic role of psychic factors in the structural changes characteristic of certain diseases, less is understood about the dynamic role of somatic factors in changing psychologic patterns. The true picture is obscured by efforts to isolate either the psychic or the somatic factors and then to objectify them as if they could function independently. It is here that studies of the total effects of ACTH and cortisone promise most for clinical psychiatry. It has been noted that nearly everyone who receives these hormones experiences some psychic change; two-thirds have some euphoria; mania, schizophrenia, catatonia, paranoia, depression and aggressive behavior have also been described. The psychic responses may be graded. Grade I is typified by, "I never felt better in my life!" These patients claim to be able to do better and more rapid creative thinking than before therapy. Grade II is an exaggeration of grade I, with effusive, expansive volubility, restlessness and insomnia, approaching hypomania. Grade III includes all psychologic stress patterns short of psychosis, which is reserved for grade IV. Fortunately, most psychotic reactions subside spontaneously within a few weeks of stopping treatment. In a heterogeneous group of more than 100 patients, grade I and II reactions were seen in 60%, grade III in 25-30% and grade IV in 10%. Presumably ego defenses are stressed by direct alterations in cellular function of the brain and also possibly by too sudden precipitation into feelings of good health. A study of 10 patients with Cushing's disease revealed that 3 were grossly psychotic and the rest depressed, irritable, anxious, agitated and difficult to control. A study of these hormones may lead to the long-awaited reunion of psychology and physiology.

[The cerebral metabolic basis for the central nervous system changes produced by these compounds is still not clear. The studies of Schieve *et al.* (J. Clin. Invest. 30:1527-1529, December, 1951) showed that in patients who developed psychoses during administration of these compounds, the

(5) Am. J. Psychiat. 108:641-651, March, 1952.

rates of oxygen uptake and glucose utilization by the brain were not abnormal." Studies of other metabolites were not reported. It is difficult to know whether the central nervous system aberrations should be ascribed to retention of salt and water, loss of potassium, alterations of carbohydrate metabolism or protein catabolic effects on the brain. It is interesting that cortisone and corticotrophin are convulsant agents, while desoxycorticosterone is an anticonvulsant. Hydrocortisone has less effect on the threshold to electroconvulsive shock—at least in rats—according to the studies of Woodbury.—Ed.]

Effect of Adrenocorticotrophic Hormone (ACTH) and Cortisone Administration in Patients with Myasthenia Gravis and Report of Onset of Myasthenia Gravis during Prolonged Cortisone Administration. According to David Grob and A. McGehee Harvey,[6] administration of these hormones produced a decrease in strength and in response to neostigmine in 8 of 12 patients. This effect was not accompanied by any alteration of the serum concentration of potassium, nor was it prevented or ameliorated by the administration of potassium chloride. Seven patients received 80-100 mg. ACTH intramuscularly for 4-6 days; one patient, 100 mg. daily for 3 days; one, 40 mg. daily for 4 days and one, an average of 112 mg. daily for 11 days. Two patients received an average of 150-200 mg. cortisone intramuscularly daily for 11 and 12 days. One of the patients receiving ACTH was later given an average of 200 mg. cortisone daily for eight days. After cessation of hormone administration there was a further decrease in strength and neostigmine response in five patients, lasting one to four weeks. No significant improvement in the myasthenia gravis occurred either during or after hormone therapy.

Myasthenia gravis was observed to begin during the seventh month of cortisone therapy in a 65 year old woman with rheumatoid arthritis and to become severe after cessation of the hormone. This was accompanied by a prolonged reduction in urinary 17-ketosteroid excretion. During the ensuing five months there was a gradual moderate improvement in the myasthenia coinciding with an increase in 17-ketosteroid excretion. Thus, it is possible that the onset and severity of the disease may have been related to the action of cortisone or to suppression of adrenal cortical activity.

Effects of Cortisone in Myotonia Atrophica, observed in six men, are reported by Ralph W. Barris and Harvey D. Strassman[7] (Univ. of California, Los Angeles). Cortisone

(6) Bull. Johns Hopkins Hosp. 91:124-136, August, 1952.
(7) Neurology 2:496-500, Nov.-Dec., 1952.

acetate (100-250 mg. daily) was administered orally or intramuscularly. Beginning on the seventh or eighth day after the start of therapy, a decrease in the time required for relaxation of affected muscles was noted. The test period averaged 21 days. Within 72 hours after use of the drug was discontinued, the myotonic reactions resumed the status observed before therapy.

Before, during and after cortisone therapy, frequent estimates were made of blood serum levels of sodium, potassium, cholesterol, cholesterol esters, creatine and glucose. Alterations in the levels of these substances were not significant. Creatinine tended to be lower after the first week of therapy. Urinary excretion of 17-ketosteroids, an index of the elaboration of androgenic hormone, ranged between 4.4 and 8.1 mg. Normal values vary from 7 to 17 mg. However low the normal excretion of 17-ketosteroids might be before cortisone administration, excretion decreased still further after administration of the hormone. After cessation of therapy, 17-ketosteroid excretion returned to precortisone levels.

In four of the six patients increased growth of hair was noted on the scalp, face and chest areas. Most of the patients reported an increased sense of well-being and felt less fatigued on walking and in other motor activities.

Hematologic Disorders

Effects of ACTH and of Cortisone on Platelets in Idiopathic Thrombopenic Purpura. Bernard M. Jacobson and William D. Sohier[8] (Massachusetts Gen'l Hosp.) report three cases which responded dramatically to ACTH and cortisone.

Case 1.—Woman, 59, was hospitalized March 1945 with thrombopenic purpura of several years' duration. Splenectomy was done, with pronounced improvement. Cholecystectomy in 1946 was uneventful. Purpura recurred in 1950 and became progressively more severe over six months. The only laboratory abnormality was a platelet count of 25,000/cu. mm. The marrow revealed abundant megakaryocytes without evidence of budding. Administration of ACTH, 100 mg. intramuscularly, daily for five days resulted in an increase in platelets to 580,000 (Fig. 62). On the ninth day a repeat marrow aspiration revealed abundant platelets at the margin of the megakaryocytes. She was discharged on 25 mg. ACTH every other day. Two days later, two hours after she took aspirin for an upper respiratory infection, purpura reappeared. She was readmitted with a temperature of 103 F.; the platelet count was only 21,000.

(8) New England J. Med. 246:247-249, Feb. 14, 1952.

ACTH dosage was increased to 100 mg. daily for nine days, followed by 50 mg. daily for four days. The platelet count reached 2,000,000 on the thirteenth day, when ACTH was stopped. The count slowly dropped to 200,000/cu. mm. over 49 days. A week later it fell to purpuric levels, where it has remained.

Case 2.—Man, 43, had intermittent purpura for five years, beginning in 1943. In 1948, when hospitalized for hemoptysis, the platelet count was 30,000/cu. mm. Splenectomy produced a remission and an increase in platelets to 100,000. In December 1949,

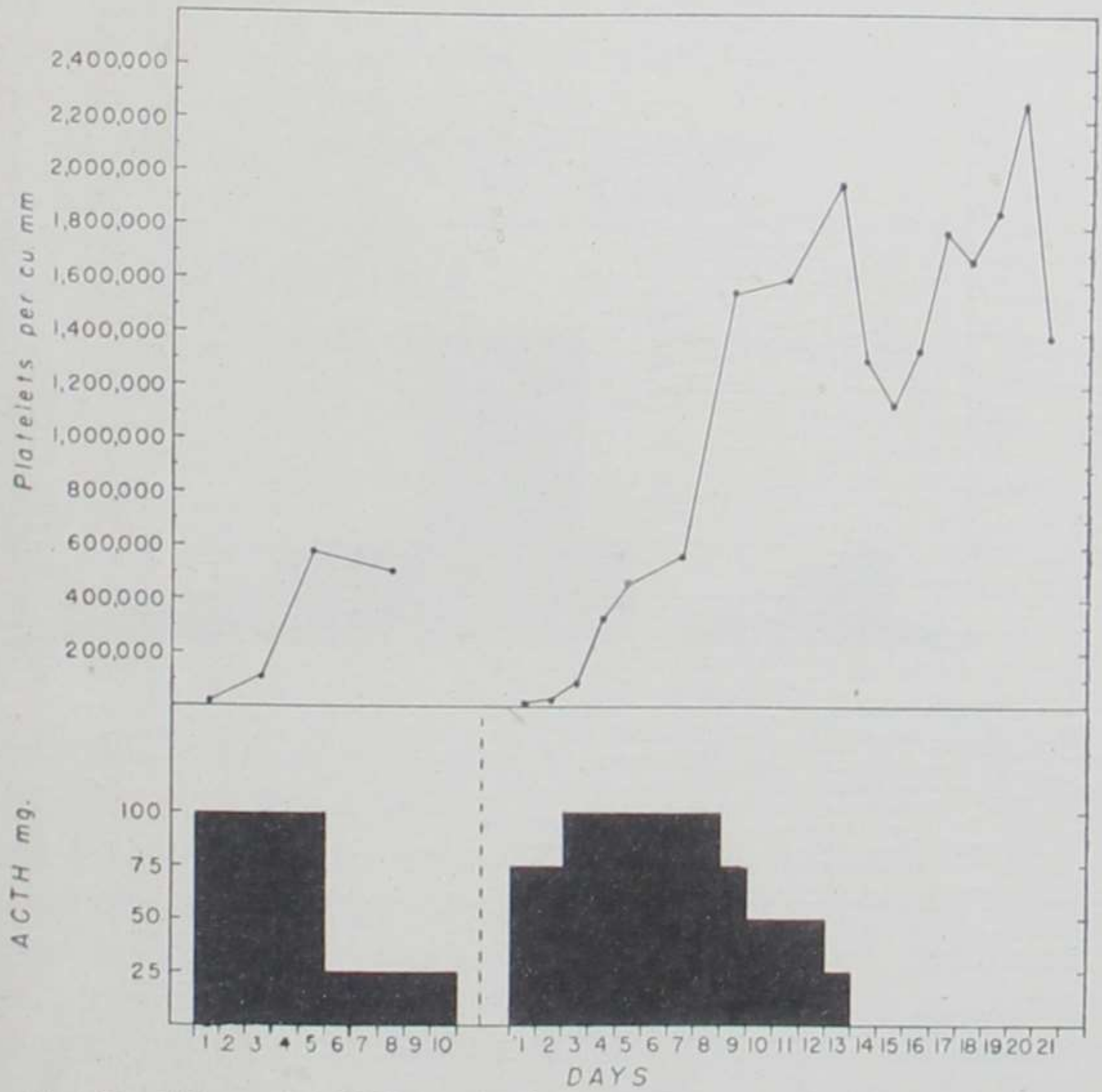


Fig. 62.—Effects of ACTH on platelet level. Interval of 10 days separates two periods. (Courtesy of Jacobson, B. M., and Sohier, W. D.: New England J. Med. 246:247-249, Feb. 14, 1952.)

purpura recurred with a platelet count of 64,000, which later fell to 20,000, at which time the left leg up to the midcalf was swollen and discolored. The patient was then given 25 mg. ACTH intramuscularly every six hours for two days, with rise in platelets, as shown in Figure 63. When ACTH was reduced to 25 mg. daily, improvement ceased. Cortisone therapy, 100 mg. orally every eight hours, was begun, with a rise in platelets to 1,000,000. However, within one week after the dosage was reduced to 50 mg. daily the count returned to purpuric levels.

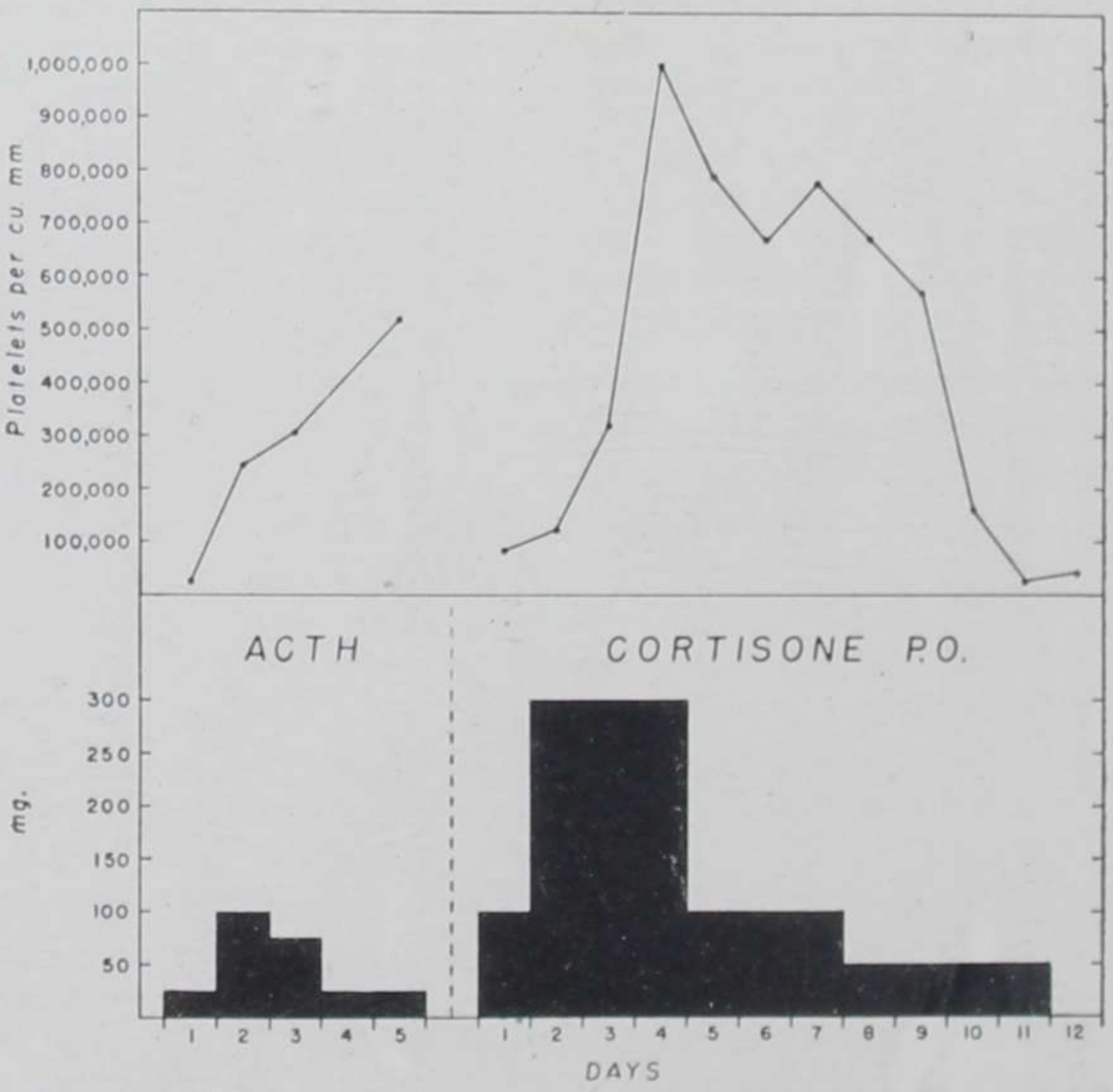


Fig. 63.—Effects of ACTH and cortisone on platelet level. Interval of four days separates two periods. (Courtesy of Jacobson, B. M., and Sohier, W. D.: New England J. Med. 246:247-249, Feb. 14, 1952.)

It is concluded that ACTH and cortisone are of special value in preparing the patient with thrombopenic purpura for splenectomy, so that the operation can be performed in the presence of a normal number of endogenous platelets. The hormones may also be useful in carrying the patient through a critical period if the spleen has already been removed.

[In general, these compounds are useful in the preparation of patients with thrombocytopenic purpura for splenectomy. After splenectomy, however, recrudescence of the disease still may be combated effectively with cortisone or corticotrophin. It will be recalled that Koller of Zurich proposed a rise in the platelet count as a sensitive index of the effectiveness of corticotrophin.—Ed.]

Use of ACTH and Cortisone in Idiopathic Thrombocytopenic Purpura and Idiopathic Acquired Hemolytic Anemia is reported by Muriel C. Meyers, Stanley Miller, James W. Linman and Frank H. Bethell[9] (Univ. of Michigan). The

(9) Ann. Int. Med. 37:352-361, August, 1952.

effect of ACTH and cortisone on lymphoid and reticuloendothelial activity, which are etiologically involved in both idiopathic thrombocytopenic purpura and idiopathic acquired hemolytic anemia, provided a rational basis for their therapeutic use.

In 12 of 17 thrombocytopenic purpura patients, clinical symptoms disappeared and platelet counts and bleeding times became normal with ACTH or cortisone therapy; remissions have lasted for 16-22 months in 5. One of the seven patients who relapsed after hormone withdrawal had previously failed

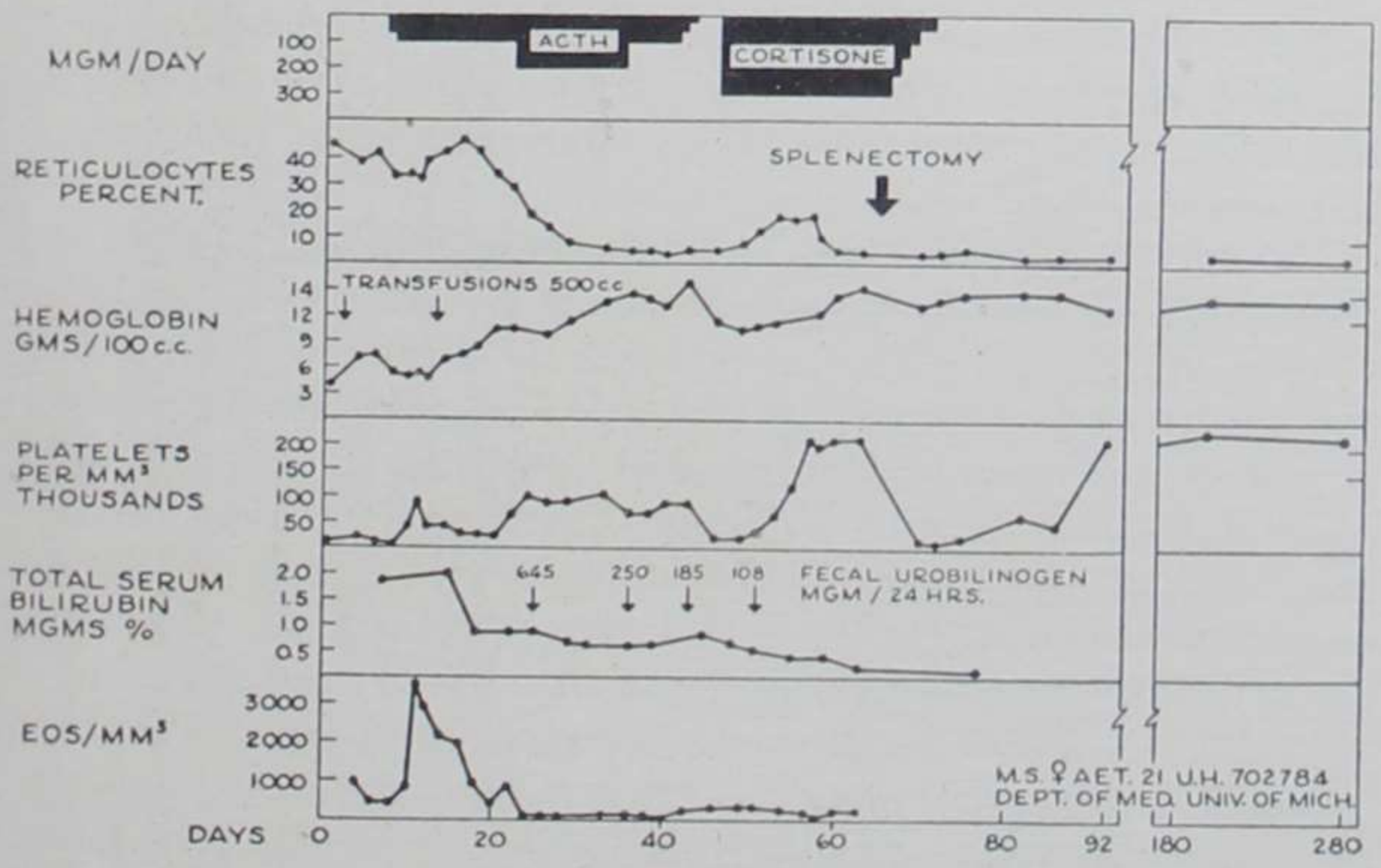


Fig. 64.—Acute acquired hemolytic anemia treated with ACTH, cortisone and splenectomy. (Courtesy of Meyers, M. C., *et al.*: Ann. Int. Med. 37:352-361, August, 1952.)

to respond to splenectomy; in the other six, a second or third remission was successfully induced and splenectomy was performed during hormone therapy. There have been no postoperative relapses. Therapeutic failures could not be correlated with low dosages or short courses of treatment; increasing ACTH above 100 mg. or cortisone above 300 mg. daily or prolonging treatment over 14 days did not enhance the therapeutic effect.

In six of seven patients, acquired hemolytic anemia was controlled with ACTH or cortisone. Remission has been sustained for 15 months without therapy in one patient; one patient had a partial relapse; in four, relapse required treat-

ment preparatory to splenectomy; one patient, who failed to obtain complete remission with either cortisone therapy or splenectomy alone, attained normal hematologic values after splenectomy when cortisone therapy was re-instituted. The response of the hematologic indexes to ACTH, cortisone and splenectomy in a woman, 21, with acute acquired hemolytic anemia is illustrated in Figure 64. If remissions were unsatisfactory in hemolytic anemia, longer treatment, not larger doses, was required. Intensive ACTH and cortisone therapy preoperatively does not interfere with wound healing.

Either ACTH or cortisone therapy in hypersplenic disorders may restore hemapoietic equilibrium through a combination of effects, among them modification of immune body reactions, diminished splenic hypersequestration and hyperphagocytosis and myeloid stimulation.

Hemostatic Defect in Thrombocytopenia as Studied by Use of ACTH and Cortisone. William W. Faloon, Richard W. Greene and Eugene L. Lozner[1] (State Univ. of New York, Syracuse) studied eight patients, five with idiopathic thrombocytopenic purpura and three with purpura and thrombocytopenia associated with leukemia. Capillary fragility test results always improved independent of any increase in platelet count, prothrombin utilization and clot retraction, which became normal in only two patients. An ACTH-induced remission did not differ from a spontaneous remission. Thus the purpura in thrombocytopenia seems to be based on two independent defects, one vascular, the other a reduced production or increased destruction of platelets. Since ACTH consistently improves the first and may improve the second, it is useful in: (1) tiding patients over an acute episode of thrombocytopenia; (2) preparing them for splenectomy or other surgery; (3) therapy of persistent or recurrent thrombocytopenia and purpura after splenectomy, and (4) symptomatic therapy for secondary purpura associated with other blood dyscrasias.

Hypercoagulability of Blood of Patients with Hepatic Cirrhosis Following Administration of ACTH. William J. Eisenmenger, Robert J. Slater and Alfred M. Bongiovanni[2] (Rockefeller Inst.) studied blood coagulation in 14 patients in whom hepatic cirrhosis was treated with ACTH. Bloody ascites and abdominal pain with tenderness suggesting portal vein throm-

(1) Am. J. Med. 13:12-20, July, 1952.
(2) Ibid., pp. 27-34.

bosis developed in three patients and was confirmed at autopsy in one. The plasma prothrombin time both before and after ACTH did not change in 12 patients, including those with portal thrombosis. Despite reduction in coagulation time, changes in plasma fibrinogen, antithrombin activity and platelet count were inconstant. Cosgriff has reported no increase in thromboplastic activity after ACTH therapy. There is, therefore, no explanation for the increased clotting tendency caused by ACTH.

Cortisone in Rh Incompatibilities. Since theoretically erythroblastosis fetalis should be susceptible to cortisone or ACTH therapy, Oscar B. Hunter, Jr., and John B. Ross[3] (Washington, D. C.) tried it in 12 patients sensitized to Rh antibodies. They found that adequate cortisone levels during the last

CORTISONE THERAPY OF ERYTHROBLASTOSIS

ALBUMIN AB. TITER	PREV. PREGNANCY	THERAPY	NEWBORN CONDITION	RBC
1:64	(2) Jaundiced	4 wk.	Satis., trans.*	3.84
1:32	(1) Normal	3 wk.	Satis., trans.	3.40
1:256	(1) Normal	3 wk.	Satis., trans.	2.37
1:8	(2) Died 3d day	3 wk.	Satis., trans.	3.87
1:512	(3) Died 12 hr.	2 mo.	Satis., trans.	4.60
1:512	(2) Stillbirth	2 wk.	SB @ 8 mo.	.....
1:512	(1) Normal	2 wk.	Jaundiced died	3.69
1:16	(2) Normal	1 wk.	Satis., trans.	4.57
1:8	(2) Normal	2 da.	Satis., trans.	4.30
1:16	(1) Died 2d day	1 mo.	Satis., Rh-neg.	5.5
1:4096	(3) Hydrops	1 mo.	Satis., trans.	5.02
1:32	(2) Died 3d day	1 mo.	Satis., trans.	3.3

*Transfused

trimester in sensitized Rh-negative women will prevent hemolysis in the fetus and allow delivery of a healthy child (table). All of the women were strongly sensitized and expectation of a healthy baby would have been poor. An adequate cortisone level in the Rh-negative mother will prevent postpartum sensitization to Rh, and cortisone in the newborn child suffering from erythroblastosis will modify the disease. Used in conjunction with exchange therapy, cortisone will salvage most erythroblastotic infants.

Unsensitized Rh-negative patients were given 100 mg. cortisone at time of labor and 100 mg. daily until delivery; daily for seven days thereafter 75 mg. was given. Sensitized Rh-negative mothers were considered for delivery at the end of the 38th week, and 100 mg. cortisone daily was begun in the 36th week. Smaller doses of cortisone were given earlier if

(3) South M. J. 45:732-738, August, 1952.

indicated by previous history and heights of antibody. At time of delivery, if the Coombs reaction is positive, exchange transfusion should be performed; hemolysis is not a reliable indication for transfusion since cortisone will prevent anemia. Cortisone is continued in the child as needed.

Nephrosis

Treatment of Nephrosis with Pituitary Adrenocorticotrophin. John A. Luetscher, Jr., Quentin B. Deming and Ben B. Johnson, with Julia Harvey, William Lew and Lee J. Poo[4] (Stanford Univ.), made a continuous series of measurements of fluid, electrolyte and protein shifts during ACTH treatment in 14 patients with nephrosis.

The initial effect was often an aggravation of edema and proteinuria. In six, diuresis appeared on the second to sixth day of ACTH followed by a rise in the sodium content of the serum, then of the urine; a second diuresis and loss of edema occurred when ACTH was stopped. In four, no diuresis occurred until ACTH was stopped after 14 days. In four, no change occurred. Of the 10 patients who lost their edema, 8 had a reduction in proteinuria; in 4, the excretion of protein in the urine fell to normal levels, and urinary sediment was completely normal in 3. The high serum cholesterol level was usually decreased, serum albumin level increased, creatinine tolerance improved and blood pressure usually improved after treatment. The variations in potassium were unpredictable but could be controlled by varying the intake. Clinical remission usually persisted for a few months, relapse appearing after a minor infection or without obvious cause. A second course of ACTH was sometimes as effective as the first. The studies did not demonstrate the regulating mechanism of the ACTH-induced diuresis.

Cortisone Treatment of Nephrosis. Gavin C. Arneil and H. Ellis C. Wilson[5] (Royal Hosp. for Sick Children, Glasgow) report results in six patients, aged 17 months to 7 years. They were confined to bed and given a diet containing less than 0.5 Gm. sodium/day for at least one week before and several weeks after the test period. Cortisone was given intramuscularly for five days in doses of 100-300 mg./day according to the expected weight of the patient, along with 2 Gm. potas-

(4) J. Clin. Invest. 30(pt. 2):1530-1541, December, 1951.
(5) Arch. Dis. Childhood 27:322-328, August, 1952.

sium chloride daily by mouth. Two children received second courses of hormone, thus increasing the tests to eight.

During five courses of cortisone there was some increase of edema, determined by changes in body weight; in no instance was the increase striking. In three of the four patients whose subsequent diuresis was most pronounced, weight during cortisone therapy either decreased or remained unchanged. Five patients had diuresis within 12 days after cessation of cortisone therapy. Edema returned after 67, 17 and 78 days in three and had not recurred after 9 months in two.

In all patients albuminuria increased during cortisone therapy and fell below the original level after the hormone was stopped. In two, albuminuria disappeared and had not reappeared after nine months.

During cortisone therapy the total protein level fell in three cases and was unchanged in one, but the decrease was never great. Four weeks after cessation of treatment an appreciable rise had occurred in all but one case. The fall in serum proteins is brought about almost entirely by a fall in albumin. The low level of plasma albumin in nephrosis may be in the nature of a protective mechanism intended to minimize loss of albumin in the urine and, incidentally, to lower osmotic pressure of the plasma. In all patients who were later to have diuresis, a definite fall in serum globulins occurred some weeks after cortisone therapy; when diuresis did not occur the globulins were little altered.

During administration of cortisone the plasma cholesterol level fell in four cases and remained unchanged in one. Two weeks later the levels showed a tendency to rise slightly. In patients in whom relapse occurred and in those who did not show diuresis, the plasma cholesterol level rose to the original high levels within one month after treatment and remained elevated. The two patients with clinical cure had normal levels three months after treatment.

Adrenocorticotrophic Hormone (ACTH) Therapy of Nephrotic Syndrome in Children. Jack Metcoff, Charles P. Rance, Weston M. Kelsey, Nobuyuki Nakasone and Charles A. Janeway[6] (Harvard Med. School) report results of 56 courses of therapy given to 45 children. Intramuscular administration of ACTH, 150-200 mg./sq. m./24 hours for at least 8 and usually

(6) Pediatrics 10:543-566. November, 1952.

10 days, resulted in complete diuresis in 81% of full courses and in 75% of patients. Diuresis usually began between the 8th and 12th days. About 50% of patients (16) undergoing diuresis maintained clinical remission three months or more, 12 for over six months and 6 for over one year. Most relapses were observed within four months of diuresis. Diuresis and remission were associated with improved renal function, particularly glomerular filtration rate and filtration fraction. Some diminution of proteinuria and increased serum protein levels were noted after diuresis, and serum cholesterol levels fell toward normal. Consistent minimal changes in serum electrolyte patterns were noted. An increase of 2-4 mM./L. in sodium, slight alkalosis and a decrease in serum potassium were usual responses.

Four patients died of complications associated with therapy, two from overwhelming Escherichia coli infection and two from severe hypertension and electrolyte disturbance. Principal complications were infection, severe hypertension and hypotonicity of the extracellular fluid. Prompt recognition and treatment of complications with immediate withdrawal of ACTH require constant vigilance and careful observation. ACTH therapy is not a safe outpatient procedure.

Two considerations prompted the trial of ACTH in the nephrotic syndrome. The observation that remissions often follow acute infections, particularly rubeola, suggested that the response to stress might be the common denominator and might be artificially reproduced by ACTH. The hypothesis that the basic renal lesion is an injury caused by the local combination of antigen and antibody in the kidney suggested the trial of an agent known to affect allergic reactions. That ACTH therapy proved to have a rather dramatic effect on the disease cannot be considered as proof of either of these theories, although it is consistent with them. Adequate dosage, normal diet without salt restriction but without added or excessive salt, and possibly a limited period of reduced renal function appear to favor diuresis. Neither age of patient nor duration of disease seemed to influence the outcome in children.

Although ACTH therapy may not cure, it does seem to alter the course favorably in a significant number of patients

and therefore appears to be the treatment of choice for the active phase of the nephrotic syndrome in children.

[At the rate data on the action of these compounds in nephrosis are accumulating, it may only require another year or two until the mechanism of the therapeutic effect will be elucidated. Diuresis often follows the sudden withdrawal of corticotrophin in patients with nephrosis. The further studies of Luetscher, Deming, and Johnson suggest that a salt-retaining steroid may act as a possible aggravator of fluid accumulation in nephrotic patients. The compound held responsible appears to be similar to that described by Grundy, Simpson, Tait and Woodford (p. 154).—Ed.]

Pulmonary Disorders

Effects of Adrenocorticotrophic Hormone (ACTH) and Cortisone on Sarcoidosis. Lawrence E. Shulman, Edyth H. Schoenrich and A. McGehee Harvey[7] gave one or more courses of adrenocorticotrophic hormone or cortisone to 15 patients, 8 of them women, with a broad variety of the manifestations of active sarcoidosis. Average age was 33; 10 were Negroes. The hormones were given in various doses and by various routes. With adrenocortical activity heightened, nearly all had a striking regression of signs and symptoms of active disease. Those in whom prolonged sarcoid activity had produced extensive fibrotic change, showed little improvement. The pattern of events after cessation of treatment has varied considerably. Some patients have had prolonged remission, others, a prompt relapse; in the rest, continued suppression of some manifestations and reactivation of others have been noted. A few patients have, after a prompt relapse, once again entered a period of remission.

Weight gain during and after treatment was noted in 8 of 11 patients with a history of appreciable weight loss before treatment. Fever and tachycardia were reduced during treatment in all patients. Dramatic inactivation of the lesions of acute sarcoid uveitis was observed in eight patients. Vision, however, returned only in patients with recent onset of severe uveitis. The tendency toward relapse was great. Topical application of cortisone ophthalmic ointment suppressed the signs of active anterior uveitis in two patients. Such ocular manifestations as retinitis and conjunctival nodules were also suppressed. Respiratory symptoms disappeared entirely during treatment; after treatment, most patients remained symptom-free. Pulmonary signs cleared during treatment and re-

(7) Bull. Johns Hopkins Hosp. 91:371-415, November, 1952.

mained clear thereafter, except for transitory recurrences right after treatment in half the patients. There were striking x-ray signs of improvement; although the lesions did not clear entirely, they changed so much in four patients that they were not recognizable as sarcoid. Changes in vital capacity paralleled symptomatic improvement.

Various skin and subcutaneous manifestations cleared entirely in 9 of 10 patients; in 5, the lesions gradually reappeared after one to nine months, whereas in the other 4, lesions did not reappear. Peripheral lymph nodes were no longer enlarged in 11 of 13 patients during hormonal treatment and remained impalpable in 6 after treatment. Enlarged mediastinal lymph nodes regressed during treatment in 10 of 12 patients, but regression was never complete and, after treatment, 8 had relapses, usually to pretreatment status.

In most patients, hepatic and splenic enlargement regressed fully. Two patients had striking reductions in elevated bromsulfalein retention and two in grossly elevated alkaline phosphatase activity. Evidence of liver disease returned in most patients, but never to pretreatment status.

In all four patients with "uveoparotid fever," the enlarged, nodular parotid glands regressed to normal size. After therapy, two had partial but transitory recurrence; the other two had no recurrence. Serum calcium concentrations decreased rapidly to normal range in three patients with hypercalcemia; all of them also had moderately severe renal disease. Renal function improved in one patient studied for two years, during which four courses of ACTH or cortisone were given. Muscle strength increased both during and after ACTH therapy in a patient with severe muscular wasting caused by extensive seeding of the muscles with sarcoid tubercles. No significant change was noted during treatment of three patients who had had x-ray evidence of bone rarefaction before treatment.

During hormone therapy, most patients had striking reductions in the erythrocyte sedimentation rate, serum globulin concentration, cephalin-cholesterol flocculation and thymol turbidity. Anemia disappeared in two patients.

None of the patients gave clinical evidence of tuberculosis during or after treatment; nor did tuberculin sensitivity increase in the five patients in whom it was measured before and after treatment.

The data are insufficient to allow comparison of the relative effects of ACTH and cortisone.

Effects of Cortisone in Sarcoidosis: Study of 13 Patients who had received cortisone 4-15 weeks was made by Louis E. Siltzbach[8] (Mount Sinai Hosp. and Montefiore Hosp., New York City). The daily dose was 100-150 mg. given orally or intramuscularly. Ten of the patients were followed for 1-11 months after cessation of therapy. Nine were female and 5 Negro; 10 were under age 40. All but 1 had active sarcoidosis, and multiple organ systems were involved in 12. Active and progressive lesions were carefully noted and their course was used as the basis for assessing the value of cortisone therapy. Because of the possibility of coincidental spontaneous remissions, a reversal of trend had to be prompt to be considered significant.

All 13 patients showed improvement though no cure was claimed. The response was irregular, often transitory; some lesions regressed while others remained refractory in the same patient. Of seven patients with severe disability, five obtained significant relief from major symptoms during therapy; in the other two, regressive phenomena were limited to lesions of lesser import. In no patient was progression of lesions detected during treatment. However, 4-15 weeks is a short span in so chronic a disease. In general, fresh lesions seemed to be more amenable to therapy than older ones, although lesions known to have existed as long as two years also proved responsive. Of the 10 patients followed, 7 relapsed; 3 of these had a return of the disease in as severe a form as before therapy. Of the three who did not relapse, two had regression persisting from one to over four months at all sites; the third had received benefit only at minor sites of involvement.

In all cases peripheral lymph nodes showed some degree of shrinkage. Nodes in different chains regressed at the same rate. Although some enlarged again after therapy, they usually did not reach their previous size. Mediastinal nodes of recent involvement were benefited. Fresh pulmonary lesions seemed responsive, but relapses were frequent. Ocular lesions responded dramatically when the uveitis had not progressed to irreversible scarring. Of the two patients with subcutaneous lesions (Darier-Roussy sarcoidosis), one had clearing of the

(8) Am. J. Med. 12:139-160, February, 1952,

lesions while under therapy but a complete relapse after cessation, and the other had only slow incomplete regression. A favorable response was observed in one patient with a localized skin lesion and in one with a large parotid swelling. There was a temporary alleviation of symptoms in one patient with spinal cord involvement. Bronchostenosis due to sarcoidosis was cleared under cortisone and antibiotic therapy.

Of six patients with serum globulin levels above 3.0 Gm./100 cc., four showed a fall in concentration during therapy; in two the concentration dropped to 3.0 Gm./100 cc. or less. Four of these six patients had an inverted albumin-globulin ratio; in three, however, the albumin again exceeded the globulin at the end of therapy. Three patients showed the cutaneous papules of a positive Nickerson-Kveim reaction when cortisone therapy was undertaken. In all three the papules faded and flattened within three to seven days, leaving slightly indurated pigmented areas. Sections of lymph nodes removed from different sites during therapy showed uniformity of regression in individual patients. Some had marked hyalinization in post-treatment biopsies, whereas others treated for the same period had only slight regression histologically. In this series the favorable effect of the drug on the peripheral lymph node lesions appeared to be more consistent and relapse occurred less often than at other sites of involvement. However, involvement of peripheral nodes is rarely a source of major disability to the patient. Eventually, spontaneous resolution without significant residua occurs. Ocular and pulmonary lesions, on the other hand, heal with scarring which may produce severe, irreversible damage to the organ. Ocular lesions caused loss of vision in four patients. Lung lesions led to pulmonary insufficiency in two. Some cases with advanced involvement of eyes and lungs show how little can be gained from cortisone therapy when extensive scarring has already occurred. For the present it would seem wise to use cortisone particularly when the site and extent of involvement portend dire consequences to the patient.

[Although present evidence suggests that cortisone and corticotrophin can produce remissions in sarcoidosis, their use is unusually dangerous in patients with this disease. These agents produce not only the usual undesired metabolic effects but, in patients with sarcoid, apparently cause a greater incidence of the spread of tuberculosis than in patients with other disorders. It will be recalled that some investigators have considered sarcoidosis to be a noncaseating form of tuberculosis. Present

evidence counsels strongly against the use of cortisone or corticotrophin in patients with active or quiescent pulmonary tuberculosis.—Ed.]

Maintenance Cortisone in Severe Bronchial Asthma was studied by W. S. Burrage, J. W. Irwin and J. S. Gibson[9] (Massachusetts Gen'l Hosp.). Six patients with chronic bronchial asthma which had not responded to nonsteroid therapy were placed on a moderately low sodium diet and given an approximate average of 75 mg. cortisone daily divided in three doses. All obtained complete relief from asthma with some evidence of increased pulmonary reserve and were maintained for months without significant untoward effects. Appetite improved, and all gained weight without gross edema. Minimal facial rounding developed in all; slight facial hirsutism occurred in one woman; menses became regular in one; libido increased in one man, and slight to moderate euphoria developed in four patients. Striae, muscular weakness, basic personality changes, alterations in blood pressure or significant changes in glucose tolerance and serum electrolytes did not occur. The number of circulating eosinophils increased after cortisone therapy in two patients, decreased in two, remained unchanged in one and was variably elevated or depressed in one patient. Observation of the vessels of the bulbar conjunctiva revealed clumping of the cellular elements of the blood with localized edema during therapy. Intramuscularly administered cortisone appears to be more effective, milligram for milligram, than orally administered.

[I have been shocked recently to learn that several patients with a first attack of mild bronchial asthma were being treated with cortisone rather than with ephedrine or epinephrine, each of which is not only less toxic but is highly effective for this complaint. It cannot be reiterated too frequently that cortisone and corticotrophin are exceedingly potent agents; their proper use is limited to conditions in which the therapeutic benefits will outweigh the pharmacologic hazards. These agents are invaluable in treating intractable asthma—that which does not respond to milder measures—but they should not replace simpler measures when these are effective.—Ed.]

Sudden Death during Cortisone Therapy of Bronchial Asthma is reported in two patients by Klaus A. J. Järvinen[1] (Univ. of Helsinki).

Case 1.—Woman, 53, after prolonged bronchial asthma and bronchitis, was treated with ephedrine, epinephrine, penicillin, theophylline ethylenediamine and potassium iodide with some relief of symptoms. An ECG showed an enlarged right ventricle. During

(9) J. Allergy 23:310-321, July, 1952.
(1) Ann. med. int. Fenniae 41:165-176, 1952.

a severe asthma attack, she was given a total of 400 mg. cortisone parenterally in four days; symptoms subsided during treatment. Suddenly she felt ill, became extremely pale, had stertorous and labored breathing and died. Autopsy revealed cor pulmonale, bronchitis and acutely congested gastrointestinal tract.

Case 2.—Man, 39, with history of severe bronchitis and bronchial asthma, was treated with penicillin, ephedrine, epinephrine, theophylline ethylenediamine, potassium iodide and an antihistamine compound during an asthma attack. There was no relief of symptoms. He was given 550 mg. cortisone parenterally during six days with pronounced relief. Two days after cortisone therapy was stopped, the symptoms returned and he was given 75 mg. cortisone during eight hours. Asthma and respiratory difficulty became severe and he died. Autopsy revealed severe bronchitis with an area of bronchiectasis and a cor pulmonale.

Neither patient showed evidence of excessive cortisone or potassium iodide dosage. Although no signs of known complications of cortisone were found in either patient, the possibility cannot be excluded that the drug played a part in the fatal outcome. Perhaps the symptom-alleviating and euphorizing effect of cortisone made the patient's condition seem less grave than it really was. There is a remote possibility of anaphylactic shock. Common to both patients was the acute vascular insufficiency evidenced by capillary congestion of the viscera at autopsy.

Great caution is indicated when cortisone is given to an asthmatic patient with severe pulmonary emphysema and a cor pulmonale.

Miscellaneous Disorders

Effect of Cortisone on Nontropical Sprue (Idiopathic Steatorrhea). Despite high protein, high calorie, low fat diet, liver extract, calcium and vitamin supplements, folic acid, serum albumin and intestinal detergents, the treatment of nontropical sprue has remained unsatisfactory. Cortisone therapy was suggested by the similarity between sprue and adrenal insufficiency. Both are characterized by fatigue, weakness, hypotension, pigmentation, a flat glucose tolerance curve, decreased 17-ketosteroid and corticosteroid excretion, steatorrhea and impaired phosphorylation necessary to fat absorption.

Ashton B. Taylor, Eric E. Wollaeger, Mandred W. Comfort (Mayo Clinic) and Marschelle H. Power[2] (Mayo Found.)

(2) Gastroenterology 20:203-228, February, 1952.

report the effects of cortisone in six patients, two of whom were studied on the metabolic ward. Cortisone was equally effective orally or intramuscularly in doses of 25-100 mg. a day. In every instance improvement in sense of well-being, appetite and strength was striking. Abdominal cramping and distention vanished. Stools decreased in number and volume. The nocturia characteristic of sprue was diminished. Fecal fat and nitrogen contents decreased by 50% or more and became normal in one patient. The prolonged prothrombin time became normal in every patient. Vitamin A loss in the stool fell from 33% to 14% of the ingested dose. Serum albumin level rose from 2.1 Gm. to 4.6 Gm. in one patient. The expected positive sodium and chloride balance and negative potassium balance were noted. Calcium and phosphate balances were variable. Unchanged carbohydrate tolerance indicated no improvement in carbohydrate absorption. Hypertension appeared in one patient and edema was usual when dosage was 100 mg. a day. Cortisone is now the most effective means of treating nontropical sprue. Its importance in long term management remains to be evaluated.

[It is a long time since Professor Verzar and Miss MacDougall (now Frau Professor Verzar) originally proposed that adrenal steroids influence intestinal phosphorylation and absorption. This theory has been almost forgotten, although the very persons who deprecated it most have gradually come to an almost identical concept. Recent studies of the effects of cortisone on intestinal absorption in the various types of steatorrhea have bolstered the theory proposed by Verzar and MacDougall. The animal and clinical studies of T. L. Althausen are likewise in harmony with the Verzar-MacDougall theory. I do not know whether the clinical application of this work will continue much longer now that studies by Anderson in Fraser's laboratory at Birmingham, England, have incriminated gluten as the apparent cause of steatorrhea. Possibly elimination diets, rather than hormones, will be used to control the disorder. Such management would be all to the good, since osteomalacia often develops in patients with steatorrhea and I doubt that cortisone would have a beneficial effect in osteomalacia. It could only be expected to induce the added complication of osteoporosis.—Ed.]

Corticotrophin, Cortisone and Hydrocortisone in Treatment of Ocular Disease are discussed by E. H. Steffensen[3] (Henry Ford Hosp.). The benefits of fever therapy apparently are derived from acceleration of mechanisms evoked in acute stress states. Reaction to such stress depends on the endogenous release of corticotrophin, which in turn stimulates the adrenal cortex to liberate 11-oxycorticosteroids. Intravenously

(3) J.A.M.A. 150:1660-1664, Dec. 27, 1952.

injected killed typhoid organisms have produced a temporary state of hyperfunction of the adrenal cortex in patients with inflammatory ocular disease.

When corticotrophin was first available for clinical use in 1949, evidence had accumulated which suggested that it might be of value in certain eye diseases. Subsequent studies showed both corticotrophin and cortisone to have a favorable action. Ocular lesions in which these drugs have or may have an effect when administered by currently accepted therapeutic programs are shown in Tables 1 and 2. Corticotrophin and

TABLE 1.—Ocular Lesions That Respond Favorably to Currently Accepted Modes of Corticotrophin and Cortisone Therapy

	Systemic, Corticotrophin or Cortisone		Topical, Cortisone
Allergic conjunctivitis	—		+
Allergic blepharoconjunctivitis	—		+
Vernal conjunctivitis	—		+*
Episcleritis	—		+
Keratoconjunctivitis			
Phlyctenular	—		+
Marginal ulcer	—		+
Keratitis			
Tuberculous	—		+
Sclerosing	—		+
Acne rosacea	—		+
Profunda (nonspecific)	—		+
Superficial (nonspecific)	—		+
Syphilitic interstitial	—		+
Uveitis			
Acute anterior, nongranulomatous	+	and/or	+
Acute posterior, nongranulomatous	+		—
Acute diffuse, nongranulomatous	+		—
Acute focal choroiditis	+		—
Acute optic neuritis	+		—
Acute retrobulbar neuritis	+		—
Central angiospastic retinitis	+		—
Sympathetic ophthalmia	+		—
Burns, chemical or thermal	—		+
Glaucoma surgery, postoperative therapy	—		+*

*Ointment form.

cortisone appear to give comparable results in short term treatment. When there is associated hypertension, renal disease or cardiac decompensation, cortisone may be better tolerated, though the limitations that attend the use of corticotrophin ultimately arise.

Lesions which respond to topically administered medication should not be treated parenterally. Certain acute lesions,

notably iritis that is refractory to topical medication, respond so rapidly to a few doses of either cortisone or corticotrophin that hospitalization is not necessary. In general, however, institutional care is desirable, at least in the early stages of treatment. Dosage must be adjusted to the patient and maximal suppression of disease obtained with the least possible amount of hormone. White blood cell counts and direct eosinophil counts are helpful in evaluating the level of circulation corticosteroid. Rapid withdrawal of either hormone produces a temporary period of severe hypofunction of the adrenal cortex, during which there could be a recurrence of the ocular lesion. Gradual cessation of therapy may avoid this.

TABLE 2.—Ocular Lesions That Respond Variably to Currently Accepted Modes of Corticotrophin or Cortisone Therapy

	Systemic, Corticotrophin or Cortisone		Topical, Cortisone
Herpes zoster ophthalmicus	+		+
Uveitis			
Chronic anterior, nongranulomatous	+	and	+
Chronic anterior, granulomatous	+	and	+
Chronic posterior, nongranulomatous	+	and	+
Chronic posterior, granulomatous	+	and	+
Sarcoid	+	and	+
Erythema multiforme	+	or	+
Retinitis pigmentosa	+ (temporary improvement only)		—
Exudative retinitis (Coats's disease)	+		—

Topical administration is of value primarily in diseases of the anterior segment. No harmful effects have been noted even when therapy has been prolonged for months. Cortisone in moderate doses suppresses fibroplastic proliferation, without a pronounced effect on regeneration of corneal epithelium; however, heavier doses definitely retard epithelization. Minute amounts of topically administered cortisone reach the posterior segment of the eye but are not sufficient to resolve posterior segment eye disease without prior parenteral hormone therapy.

From results in 68 patients treated with topically administered hydrocortisone, it appeared that effectiveness of this newer preparation is equal, if not superior, to that of topically administered cortisone.

[Two points in this valuable paper warrant repeated emphasis: (1) with either cortisone or hydrocortisone, topical administration, when effective, is superior to systemic administration, because the undesirable

metabolic effects are avoided; (2) present evidence strongly suggests that for topical or local administration, hydrocortisone is more effective than cortisone. Of course, there is no reason to give corticotrophin (ACTH) topically, since this agent works only by stimulating the adrenal glands.—Ed.]

Cortisone, ACTH and Antibiotics in Fulminant Hepatitis. Hector Ducci and Ricardo Katz[4] (Univ. of Chile) gave cortisone and/or ACTH with aureomycin and/or terramycin to three patients with acute fulminating hepatitis complicated by coma and three with subacute and chronic hepatitis. Two of those with fulminating hepatitis survived.

Youth, 20, was hospitalized in coma after abdominal pain for a week and vomiting a few times. When first seen by a physician four days later he had slight jaundice and fever of 109 F. He later became disoriented. At the hospital deep jaundice and active reflexes were noted. Liver and spleen were palpable. Acute hepatitis was confirmd by laboratory studies. He was given 1.5 Gm. terramycin and glucose intravenously. After brief mental improvement, he lapsed into deep coma. He was then given 500 mg. cortisone intramuscularly and eight hours later was conscious, when a second dose of 500 mg. was injected. During 17 days, a total of 3,525 mg. was given both orally and intravenously. Improvement was rapid after the first dose, and laboratory studies showed improved liver function. Treatment was discontinued for a few days because of lack of medication, and a rapid relapse occurred. After therapy was reinstituted, the course rapidly progressed toward recovery.

Liver biopsy, seven days after cortisone treatment ended, confirmed acute hepatitis. A second biopsy four months later revealed normal liver.

The patient with fulminating hepatitis who died was extremely ill when treatment was instituted. The three patients with chronic hepatitis, treated according to the same plan, all died. Complicating severe biliary disease was found at autopsy in one.

The authors observe that their large experience with acute hepatitis had indicated that coma was formerly invariably followed by death.

Use of Adrenal Cortical Hormone in Alcoholism: Report of 100 Consecutive Cases. R. G. McAllister[5] (Richmond, Va.) was led to consider this treatment by a member of Alcoholics Anonymous who "had been fighting an urge to get soused for three days. . . ." On his way to a liquor store the man had stopped at McAllister's office: " . . . I thought I'd give you a chance to keep me from drinking," and confronted him

(4) Gastroenterology 21:357-374, July, 1952.
(5) Virginia M. Monthly 79:70-73, February, 1952.

with a cure-all lauded in a lay magazine. The article referred to the use of adrenal cortical extract to treat and prevent alcoholism. The patient was given 0.5 cc. lipoadrenal extract intramuscularly and 1,000 mg. ascorbic acid by vein. The patient reported three days later that the overpowering urge had disappeared and had not returned.

Subsequently in 100 consecutive instances of alcoholism, 53 patients were treated with 1 or 2 cc. adrenal cortical extract and 500 or 1,000 mg. ascorbic acid given together intravenously; medication was repeated every 6-24 hours as indicated. After control of acute symptoms, the patient was maintained on 0.5 cc. lipoadrenal extract intramuscularly every one or two days; this dose was also helpful in abolishing the "urge" to drink. Patients included those with "urge" only to those with acute alcoholism and hallucinosis or attempted suicide. Results were classified as: (1) excellent—no further alcohol, rapid improvement and complete recovery from the acute attack; (2) fair—some improvement, and (3) poor—failure to alleviate alcoholism, continued imbibing. Results were excellent in 71, fair in 10 and poor in 15; 4 were lost to follow-up; only 1 injection was given 56 times, 2 injections 28 times and 3-12 injections 16 times. Initially none of the patients was treated in the hospital but some finally had to be hospitalized. Adrenal cortical extract or vitamin C alone was not as effective as the two combined. They appeared to stop the need and craving for alcohol and to prevent a binge if taken before indulgence; they had no effect in preventing further alcoholic bouts.

[I don't know whether adrenal cortical extract, cortisone or corticotrophin is truly useful in the treatment of alcoholism. I do know that it is a pleasure to read such a delightfully written account as this.—Ed.]

SEXUAL PRECOCITY

The material in this section includes reports which could as well be distributed among the sections on the adrenal cortex (sexual precocity or pseudosexual precocity due to adrenal cortical hyperplasia or adrenal cortical tumor) and the sections on the female and on the male reproductive systems. A separate section seemed indicated, in order to incorporate reports on sexual precocity due to intracranial lesions and of the constitutional or familial type. The familial or constitutional form, which is not associated with any apparent endocrine lesion, is the type most frequently seen, particularly in girls. Sexual precocity also occurs in girls with Albright's syndrome and is thought to result from impinge-

ment of the thickened bone at the base of the skull on the hypothalamus. It is most important, of course, to differentiate precocity of familial or constitutional origin from that associated with adrenal or gonadal lesions, as well as from the types caused by intracranial tumor or encephalitis. In general, in these patients a careful search into the familial pattern of puberty and detection of any preceding encephalitis or other central nervous system disorder, together with physical examination to determine whether the precocity is in the direction of the patient's own sex or the opposite sex, will enable the physician to come very close to an exact diagnosis. Laboratory tests also may be most valuable in this group of conditions.

It is to be noted that sexual precocity does not result from lesions of the pituitary gland. Lesions of the pineal gland, brain, adrenals, ovaries or testes account for all known types, except the familial or constitutional variety. Nevertheless, examination of the urine of sexually precocious boys or girls for the presence of pituitary gonadotrophin may be a valuable procedure, since its presence indicates that the cause of the precocity lies in a constitutional or central nervous system disorder. It also fairly well excludes adrenal, testicular or ovarian sources.

The type of heterosexual precocity associated with congenital adrenal cortical hyperplasia is discussed at greater length in the section on the Adrenal Cortex.—Ed.

Follow-up Report of a 5 Year Old Sexually Precocious Boy. Sexual precocity in boys may be (1) familial (without any demonstrable lesion); (2) postencephalitic, or (3) endocrine, due to hyperplasia or tumor of the adrenal cortex or to tumor of a testicle or of the pineal gland. H. Lisser and Lionel Player[6] (Univ. of California) report the 20 year follow-up of a case of sexual precocity due to adrenal carcinoma, the second such instance to be reported of survival after removal of an adrenal tumor.

Boy, 4 years and 11 months when first seen in 1931, had a mustache, deep voice, muscular development and appearance of an 8 year old, skeletal age of a 12 year old, sexual hair of a boy 15 and genitalia of an adult (Fig. 65, *A*). He was mentally normal and well behaved despite almost nightly emissions and prostatic secretion containing considerable amounts of lecithin and numerous spermatozoids. A retrograde pyelogram revealed a mass above the left kidney. A well encapsulated carcinoma weighing 278 Gm. was removed. Adrenal insufficiency was not noted postoperatively. Subsequently, genital appearance and hirsutism did not change, but erections and emissions became infrequent and his demeanor more childish, happier and quieter. Skeletal growth continued to be abnormal, amounting to 11½ in. between 5 and 8 years, 5½ in. between 8 and 13½ and only 1 in. afterward (*B-D*).

(6) Postgrad. Med. 11:267-271, April, 1952.

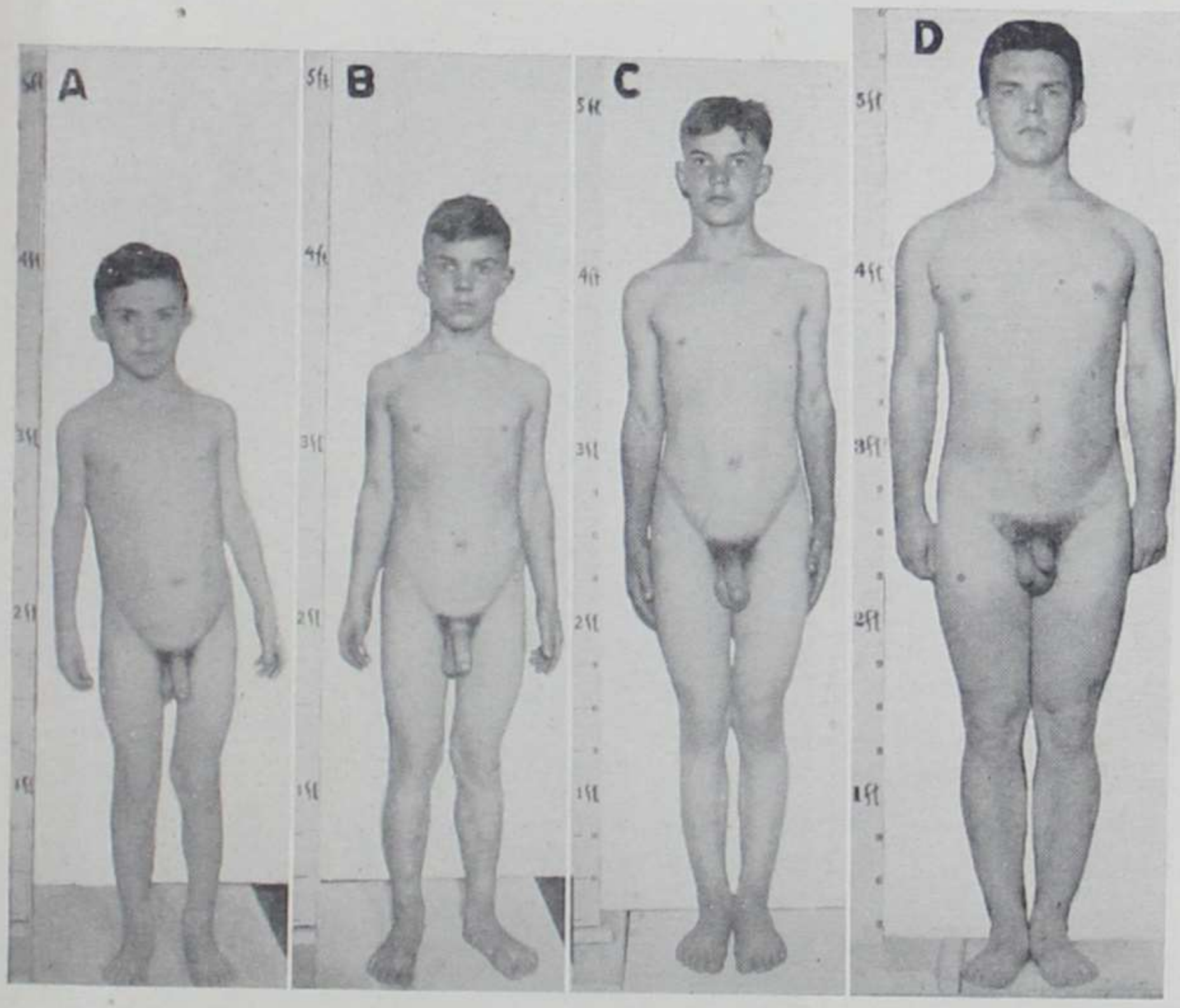


Fig. 65.—*A*, at age 5 years 1 month, before operation; note tallness for age, mustache, pubic hair and adult-size genitalia. *B*, at age 6 years 4 months, 14 months after removal of adrenal tumor; grown 5 in. *C*, at age 8 years 11 months; grown 8 in. in 2½ years. Note muscular build and massive thighs. *D*, at age 21 years 4 months; grown 4¾ in. since *C*, but only 1 in. since age 13½. Note husky physique. (Courtesy of Lisser, H., and Player, L.: Postgrad. Med. 11:267-271, April, 1952.)

At age 21½, he is a healthy man with 24 hour 17-ketosteroid excretion of 15.5 mg.

[It is interesting that this is one of the first two cases reported in which sexual precocity in a boy was cured by removal of an adrenal tumor. Since the second instance was described in 1942 by W. A. Reilly (Clinics 1:669-676, 1942), a great number of similar cases have been reported.—Ed.]

Interstitial Cell Tumor of Testis: Study of 5 Year Old Boy with Pseudoprecocious Puberty. Charles D. Cook, Robert E. Gross, Benjamin H. Landing and Aniela S. Zygmuntowicz[7] (Boston) report a case which is similar to the eight others in the literature in that onset was between ages 2 and 6 and adult male sex characteristics were present without functional maturity (formature of mature sperm).

(7) J. Clin. Endocrinol. 12:725-734, June, 1952.

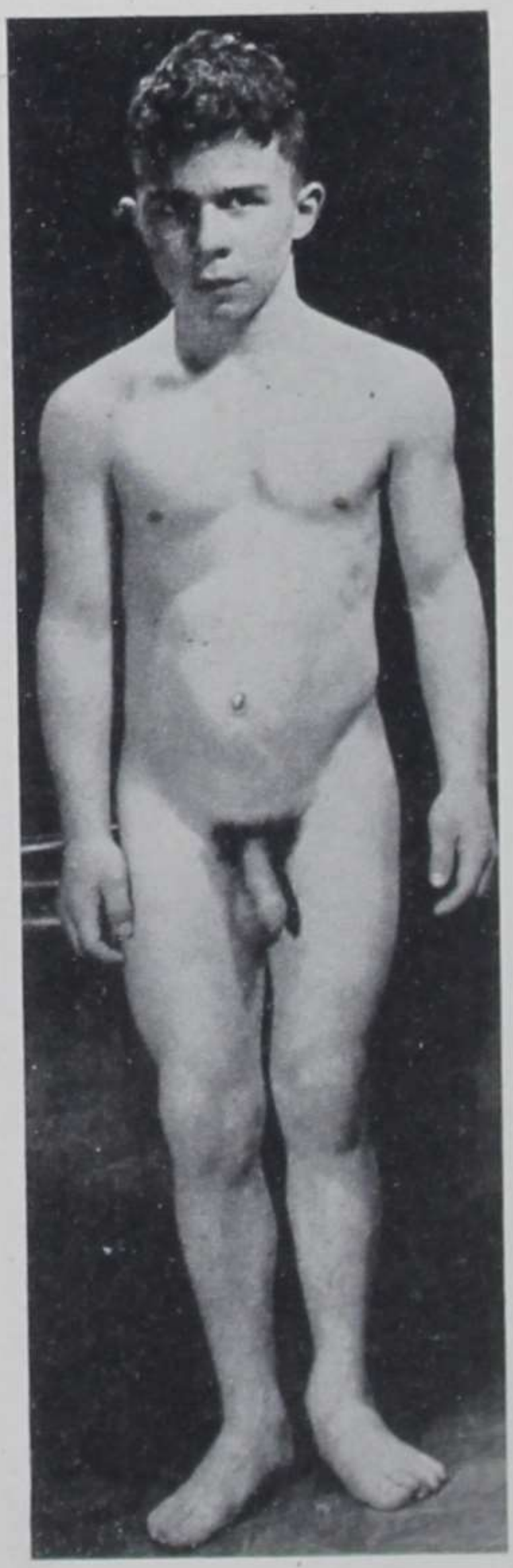


Fig. 66.—Patient before operation. (Courtesy of Cook, C. D., *et al.*: J. Clin. Endocrinol. 12:725-734, June, 1952.)

Boy, 5, was hospitalized because of progressive masculinization over eight months, manifest by deepening voice, rapid growth of stature and penis, and appearance of pubic, axillary and lip hair. Acne developed, and the boy became hyperactive and aggressive. A mass was noted in the right scrotum. There were no known erections, emissions, urinary symptoms or pain in the tumor. The boy's weight and height were consistent with those of a boy, 9, and the genitalia resembled those of an adult (Fig. 66). Bone age on x-ray was 13½ years. Urinary 17-ketosteroid excretion was 16.8 mg./24

hours, the upper limit of normal being 1 mg. at this age. Urinary 11-17-oxycorticosteroid excretion was normal. The eosinophil count was low (0.27/cu. mm.). After the scrotal mass was removed, 17-ketosteroid excretion fell to 1.13 immediately and to 0.273 mg. one month later. The eosinophil count rose to 88 after operation and to 99 a month later. Although his appearance did not change during the following year, the boy became less aggressive and the acne improved slightly. A mild hypertension (138/90) vanished. Histologic study of the tumor showed a benign adenoma with Leydig cells. Chromatographic study of the urinary 17-ketosteroids revealed features which distinguish this syndrome from adrenocortical virilism.

Precocious Sexual Development Due to Interstitial Cell Tumor of Testis is reported by G. H. Newns[8] (Hosp. for Sick Children, London). This tumor is rarely the cause of sexual precocity, which is more commonly due to adrenal cortical hyperplasia or tumor. In all three conditions, excessive androgen excretion causes sexual precocity and extreme muscular development of the infant Hercules type. Sexual development is incomplete, as the testes remain infantile without spermatogenesis. Palpation of a testicular swelling enables differentiation of the interstitial cell tumor from adrenal disease.

Boy, 2 years 4 months, was hospitalized six months after his mother noted penile enlargement, pubic hair, voice changes and rapid physical growth. He had pronounced generalized muscular development, rather aggressive facial appearance, with coarse buccal skin, thick lips and a penis 4 in. long. Right testicular swelling, hard and mobile, about the size of a hen's egg was palpated. Urinary 17-ketosteroid output was 13.5 mg. in 24 hours, but fell to normal one week after the tumor was excised. After 18 months he was well; the penis had become slightly smaller, pubic hair had disappeared and he had grown several inches. Muscular development and deep voice remained unchanged.

Precocious Growth of Sexual Hair without Other Secondary Sexual Development: "Premature Pubarche," a Constitutional Variation of Adolescence. Samuel H. Silverman, Claude Migeon, Eugenia Rosemberg and Lawson Wilkins[9] (Johns Hopkins Hosp.) report data on 28 girls who had sexual hair before age 8 and 1 boy who first had pubic hair at about age 8. There were no other signs of adolescence. Coarse, crinkly hair appeared first on the labia majora of the girls, later on the pubis and finally in the axillae. None showed evidence of true virilization. Most were taller than average, and osseous development was one to four years ahead of chronological age. Urinary 17-ketosteroid excretion

(8) Brit. J. Surg. 39:379-381, January, 1952.
(9) Pediatrics 10:426-432, October, 1952.

of 20 girls averaged 2.15 mg./day (0.8-4 mg.). Except for one girl, aged 10, none of the girls showed any estrogenic manifestations of adolescent female development when first examined (9½ years or younger). Nipples were infantile. No mammary tissue was palpable; labia minora were thin and undeveloped; the vulval mucosa was pinkish red and glistening, without secretions. Vaginal smears showed absence of estrogenic changes. The output of urinary estrogens was not abnormal in respect to age. In 13 girls, followed until age 9-15, the age when breast development and menarche occurred did not differ significantly from normal. In the one boy, there was no change in the genitalia until after age 12. At age 15, he had matured along normal lines.

Hyperadrenocorticism due to tumor or hyperplasia is the principal disorder to consider in differential diagnosis. Evidence of excessive androgen secretion such as enlargement of the clitoris or acne usually appear at the same time or shortly after growth of pubic hair. Virilization is progressive with rapid acceleration of growth and osseous development, increased musculature, increasing hirsutism of masculine type and deepening voice. A definite increase in 17-ketosteroid excretion or presence of large amount of dehydroisoandrosterone are highly suggestive of an adrenal disorder.

If there are no androgenic manifestations except sexual hair and slightly increased somatic growth and osseous development, and if urinary 17-ketosteroids are not materially increased beyond normal limit for age, observation is sufficient. If 17-ketosteroid excretion does not increase considerably and there is only slow increase in hair without other evidence of virilization, it is safe to assume a harmless variation in the pattern of adolescence. This may be due to (1) increased sensitivity of sexual hair follicles to normal levels of androgen present during the preadolescent period or (2) premature increase in secretion of adrenal androgen before the pituitary gonadotrophic mechanism becomes activated. Early growth of pubic hair probably occurs more often than is realized.

[Wilkins and his group have called attention to the fact that the individual puberal manifestations may occur independently and at widely varying ages. We are confronted by the words "pubarche," indicating that the sexual hair has appeared, "thelarche," indicating that the breasts have developed, and "adrenarche," indicating the age at which the adrenal began to stimulate growth of sexual hair. In this particular report, pubarche is used as an accurate description of the result of the adrenarche.—Ed.]

Hereditary Sexual Precocity: Report of Family with 27 Affected Members. A. Wilmot Jacobsen and Madge T. Macklin[1] (Univ. of Buffalo) report on a family with 27 members affected by this rare condition, hitherto recorded in only five instances. This kindred (Fig. 67) demonstrated that the trait was not lethal, marriages were not consanguineous and males were affected exclusively. The trait is dominant since it passed through four generations of males in one instance, and it is not fully penetrant since two unaffected males transmitted it.

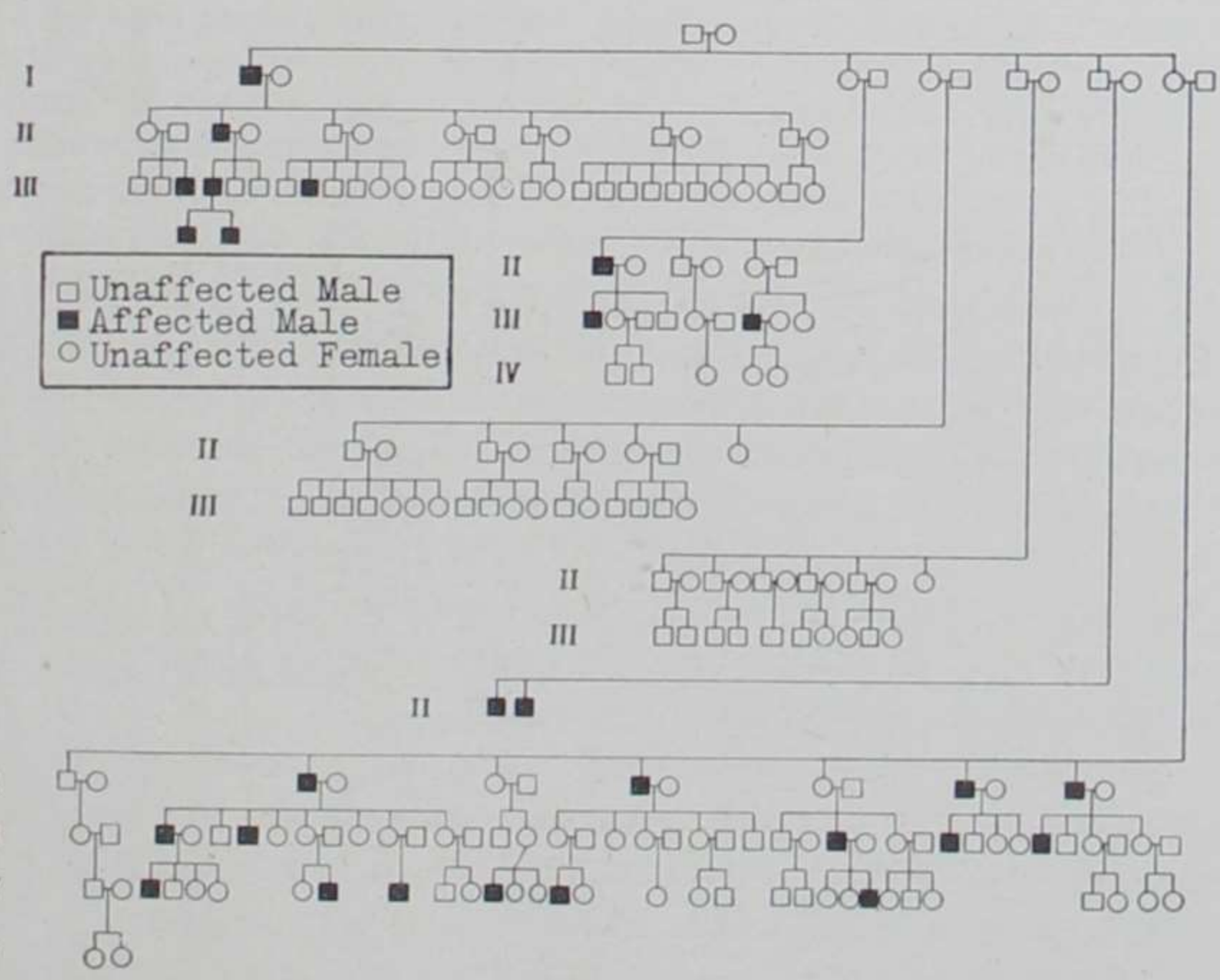


Fig. 67.—Pedigree. (Courtesy of Jacobsen, A. W., and Macklin, M. T.: Pediatrics 9:682-695, June, 1952.)

Thus, the trait is dependent on a sex-linked autosomal gene with 93% penetrance. It is passed on to half the females, who then transmit it to their sons or daughters as carriers. In one instance it went through at least three generations of unaffected females before reappearance.

Individuals with the trait are healthy. They have an unusually early, but otherwise normal, puberty. Urinary 17-ketosteroid and gonadotrophin levels were low. This trait is to be differentiated from a score of heterogeneous pathologic neural and endocrine disorders which may cause sexual precocity and pseudoprecocity.

(1) Pediatrics 9:682-695, June, 1952.

[Just to keep the record straight, this appears to be the same family originally reported by Rush *et al.* (Endocrinology 21:404, 1937).—Ed.]

Constitutional True Sexual Precocity occurring in at least seven males of a single family is described by Stuart H. Walker[2] (William Beaumont Army Hosp., Fort Bliss, Tex.).

First seen was a boy, 4, who had been normal until age 20 months, when growth suddenly increased. He had pubic hair, large penis and testes of adult size. Muscles were firm and strong and bone age was approximately 10 years. Despite rapid somatic and genital growth there were no advanced sexual interests. No neurologic abnormalities, abdominal masses or evidence of adrenal cortical hyperactivity was found. X-ray, EEG and pneumoencephalography revealed no skull or brain abnormalities. Total 17-ketosteroid excretion was 7.77 mg./24 hours, of 11-oxycorticosteroids, none, and of gonadotrophins, less than 50 m.u. Prostatic secretion appeared essentially normal for an adult with 3-5 sperm cells/high power field.

The father and five other male members of the family all had a history of sexual precocity before age 5. In all, skeletal and muscular growth, enlargement of penis, pubic hair, deepening of the voice appeared rapidly. In contrast to pseudosexual precocity, spermatogenesis begins with enlargement of the testes. None gave evidence of adrenal or pineal disease, chorioepithelioma or similar embryonal neoplasm, Albright's syndrome or interstitial cell tumor of the testis. True sexual precocity is believed to be of a constitutional nature and can be established on hereditary grounds.

Spermatogenesis with only slightly increased urinary gonadotrophin excretion — inconsistent with secreting embryonal cell tumor — and the absence of the central nervous system lesion are indicative of true sexual precocity.

Although all seven family members probably had procreative ability before age 4, psychologic development was not unusually rapid; each person affected progressed through an apparently normal childhood. None showed any unusual early interest in sexual matters. Their only abnormality was a slight reduction of stature due to early maturation of the bones. All became perfectly normal adults.

Precocious Puberty in Two Mongoloids is reported by Mathilde De Biehler[3] from Poland, where mongolism is rare.

Case 1.—Girl, born of parents of superior intelligence who were 38 and 39 at her birth, had typical mongoloid features. The palpebral fissures were narrow and oblique, the eyes small and the space between them wide; there were definite epicanthus and occasional nys-

(2) J. Pediat. 41:251-257, September, 1952.
(3) Arch. franç. pediat. 9:270-273, 1952.

tagmus. The hands were flat with no palmar crease; the phalanges were atrophied and the little finger curved. She weighed 3.0 kg. at birth, 7.0 kg. at 1 year. The first tooth appeared at 1½ and the fontanel were still open at 4 years. She stood at 2 and walked at 4; she spoke simple words at 1½ and sentences at 2½-3. She had congenital mitral insufficiency.

She was given thyroid therapy and seen periodically. By 6, intelligence had developed remarkably. She could read and was starting to write, understood Polish as well as French and played the piano. At 7½, secondary sex characteristics, including pubic and axillary hair, anogenital pigmentation and increase in size of the breast, were noted. Fifteen months later she began to have regular, painless, scant menses. Although typically mongoloid in appearance, she was of normal size and interested in everything. When 12, she contracted tuberculosis from her father, and died of cardiac decompensation.

Case 2.—Girl, the third child of father, 38, and mother, 30, showed typical mongolism. Two older brothers were well. Dentition started at 18 months and was regular thereafter. Intellect improved somewhat on thyroid therapy. She was seen every four or five months. When 7, axillopubic hair was noted, and four months later her breasts had developed. Regular menstruation, abundant and painful at first, started about half a year later. Precocious puberty did not affect mental development; she remained a typical mongoloid. She died at 10 of typhoid fever.

Pubertas Precox with Hypothalamic Tumor and Recklinghausen's Disease is reported by Achille Piotti[4] (Univ. of Zurich). In pseudoprecocious puberty, the genital organs are functionless; in true precocious puberty, they are functional. Pseudoprecocious puberty is associated with granulosa and theca cell tumors of the ovary, Leydig cell tumors of the testis and tumor or hyperplasia of the adrenal cortex. True precocious puberty (pubertas praecox cerebralis) is due to the early release of gonadotrophic substances from the pituitary gland and has been associated with (1) tumors of the wall or floor of the third ventricle (with or without internal hydrocephalus); (2) tuberous sclerosis with a tumor in the region of the corpora mammillaria; (3) diffuse encephalitis or infectious processes in the wall of the third ventricle, and (4) polyostotic fibrous dysplasia. Whether internal hydrocephalus alone can produce precocious puberty is questionable. There is no explanation for the constitutional precocious puberty of girls.

Boy, 13, complained of headache and decreased vision. He had been abnormally heavy since age 7 months. Pubic hair had ap-

(4) Acta endocrinol. 10:66-68, 1952.

peared at 7 years and by 9, the secondary sexual characteristics were completely developed. At 13, he weighed 176 lb. (normal 77 lb.), had normal fat distribution, well circumscribed pigmented skin nevi and two small nodes composed of neurofibromatous tissue. He had optic atrophy and bitemporal hemianopsia. Skull x-ray revealed a normal sella and calcification in the region of the floor of the third ventricle. Ventriculograms revealed pronounced internal hydrocephalus and displacement of the ventricular system. Duration and lack of recent progression of the visual disturbance indicated a benign tumor, presumably a neurofibroma of Recklinghausen's disease, in the wall of the third ventricle and impinging on the optic chiasm.

FEMALE REPRODUCTIVE SYSTEM

The widespread use of estrogens has led to a great increase in the number of commercially available preparations. Since these preparations vary in duration of action and may be given by different routes, a few basic considerations should be kept in mind. Like all potent agents, estrogens are capable of producing great harm as well as much good. Estrogens have many actions: they not only stimulate the production of secondary sexual characteristics in the female but suppress certain pituitary functions, cause retention of salt and water and stimulate the formation of bone matrix (useful in the treatment of postmenopausal osteoporosis and osteitis deformans). Nature avoids cumulative effects from endogenous estrogen by intermittent interruption of its secretion. The effects of uninterrupted secretion of endogenous estrogen are seen in the clinical syndrome of metropathia hemorrhagica, in which elaboration of a small amount of estrogen over a long period produces endometrial hyperplasia and eventually menorrhagia or polymenorrhea. Prolonged estrogenic stimulation likewise produces undesirable changes in tissue in both the female and the male breast. A valuable technic in administering estrogens is, therefore, to emulate nature and give the agents cyclically, thereby obviating cumulative effects on the breast and endometrium. A practical plan is to give the compound for 20-40 days and omit it for 5-10 days, then repeat the cycle as needed.

In addition, serious edema, even anasarca, may result from the salt-retaining property of these compounds, particularly when they are given in large doses. When this dire complication occurs, it is extremely important that the physician be able to withdraw the hormone. Prompt termination of hormonal activity can only be obtained when short-acting agents have been administered by mouth. Hair-trigger control cannot be obtained with long-acting agents given as pellets, depot implants or compounds that are stored in the body fat.

The last year added few reports of clinical experience with combinations of estrogens and androgens. It will be recalled that careful studies showed these combinations to be superior to estrogens, given in small doses, in the management of menopausal symptoms. A few reservations, however, are in order. In the series originally reported by Greenblatt, Barfield and their associates, and in that of Glass and Shapiro, the estrogen was diethylstilbestrol given in a dose of 0.25 mg. per day. Consequently, it is not surprising that the results with combined hormones, 0.25 mg. stilbestrol and 5 mg. methyltestosterone a day, proved more successful than those obtained with the inadequate

amount of estrogen. In most cases the combination is probably not more effective than estrogen alone, *in adequate dosage*. Specific indications for the combination do exist. For example, in a patient with menopause characterized by severe depression, the addition of small, nonvirilizing doses of methyltestosterone may produce remarkable specific alleviation of the mental symptoms. In general, I believe these combinations should be looked on as adjuncts, not as replacements of standard therapeutic methods. In the treatment of postmenopausal osteoporosis, in particular, I have been disappointed in combinations from the standpoint both of efficacy of the smaller doses of each type of sex hormone and of the incidence of acne, hirsutism, hoarseness, vaginal discharge and bleeding. The combination, like estrogens alone, should always be administered cyclically. Otherwise there may be unpredictable and occasionally severe vaginal bleeding. The occurrence of such bleeding despite the simultaneous administration of androgens indicates that androgens do not always neutralize the effects of estrogens.

The occurrence of menstrual disorders in disturbed thyroid function is discussed in the section on the Thyroid Gland. The female reproductive system is also touched on in the sections on the Pituitary Gland, the Adrenal Cortex, and Sexual Precocity. Management of the pregnant diabetic is covered in the section on Diabetes Mellitus. The use of cortisone and corticotrophin in the treatment of Rh incompatibilities during pregnancy is discussed in the section on Cortisone, Hydrocortisone and Corticotrophin.—Ed.

General Considerations

Some Hormone Studies in Normal and Toxemic Pregnancy. Patients with eclampsia or pre-eclampsia have been shown to have an increased urinary antidiuretic activity and an increased sensitivity to exogenous posterior pituitary hormone. It has also been shown that nonpregnant patients in positive water balance have a relatively low corticosteroid excretion with a high level of antidiuretic activity in the serum; conversely, in the presence of a negative water balance, relatively low levels of antidiuretic activity and high levels of corticosteroids occur. C. W. Lloyd, E. C. Hughes, J. Lobotsky, J. Rienzo and G. M. Avery[5] (State Univ. of New York, Syracuse) made simultaneous studies of antidiuretic and adrenal cortical substances on 7 normal pregnant women and 11 patients with pre-eclampsia. Because pregnanediol and chorionic gonadotrophin excretions are altered during toxemia, these were also measured.

Results showed that there is no significant increase in serum antidiuretic activity during normal or toxemic pregnancy (Fig. 68). The total corticosteroid level increases throughout pregnancy, reaching a peak before delivery. In toxemia, the corticosteroid level is considerably increased

(5) J. Clin. Invest. 31:1056-1063, December, 1952.

above levels found in normal pregnancies of the same stage. The poorly water-soluble component of corticosteroid is also increased, and in one eclamptic patient chromatography demonstrated a material with the characteristics of 3-oxygen-containing steroids such as desoxycorticosterone. If a material similar to these salt-retaining hormones were present, it could explain the salt and water retention in eclampsia. Possibly the 5-oxygen-containing steroids such as cortisone are increased as

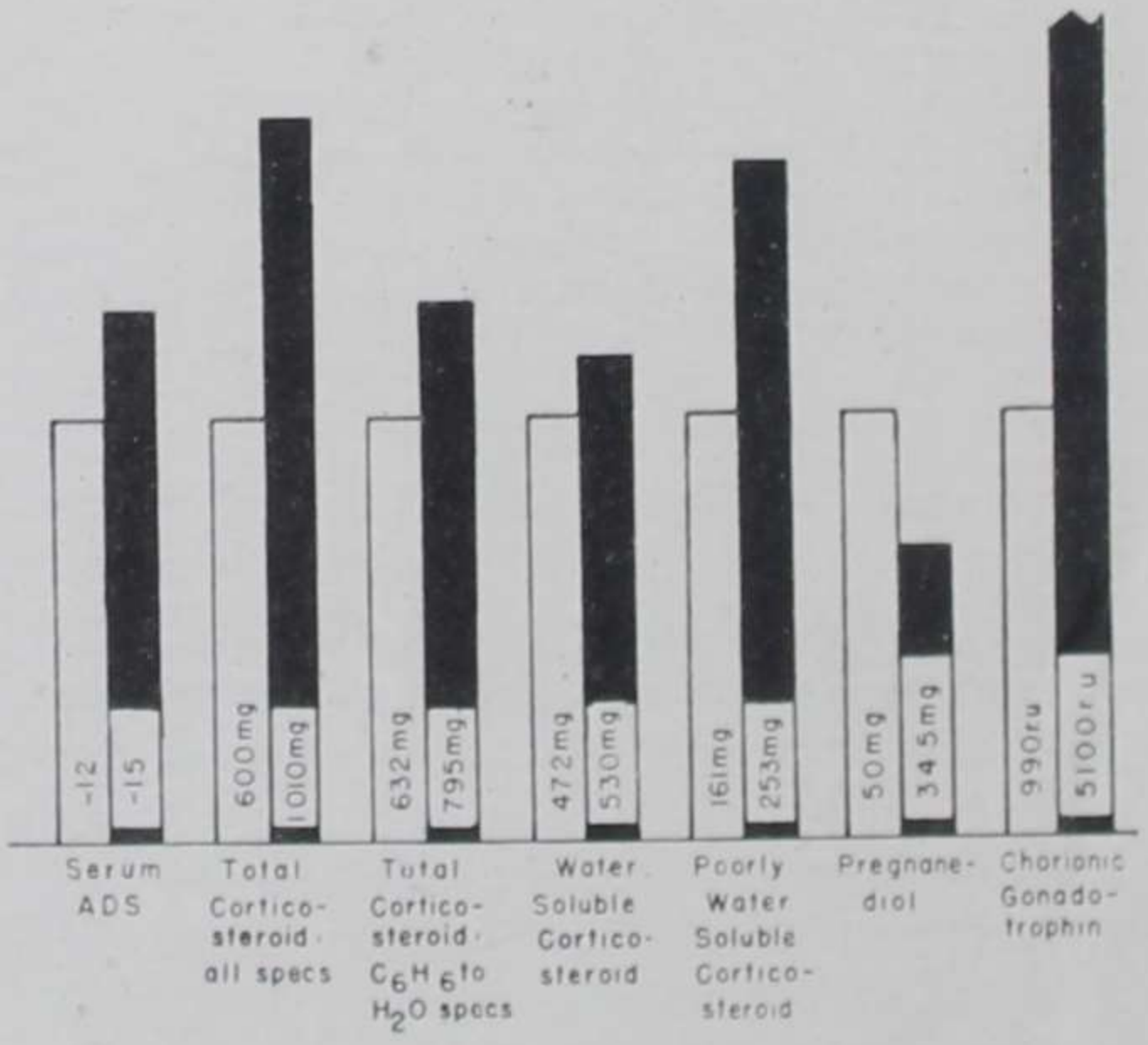


Fig. 68.—Serum antidiuretic activity (ADS) and urinary corticosteroid, pregnanediol and chorionic gonadotrophin levels in women with normal (white column) and toxemic (black column) pregnancy, in 27th week to delivery. (Courtesy of Lloyd, C. W., *et al.*: J. Clin. Invest. 31:1056-1063, December, 1952.)

a compensatory mechanism, since in many respects they can antagonize the effects of the salt-retaining steroids. The vascular changes of the placenta could account for the altered excretion of chorionic gonadotrophin and pregnanediol seen in eclampsia (Fig. 68).

[A few years ago, Dr. Aird and I had occasion to administer as much as 30-60 mg. desoxycorticosterone a day by the highly effective buccal route to two patients throughout pregnancy (J.A.M.A. 145:715-719, Mar. 10, 1951). This therapy was started as an experimental form of managing intractable epilepsy before the patients were pregnant. Attempts to terminate the administration of the steroid during pregnancy were un-

successful because the status epilepticus supervened on each occasion. Considering the large doses of this potent salt-retaining steroid, it is interesting that neither of the patients had toxemia.—Ed.]

Saliva Test for Prenatal Sex Determination. Using the Richardson pregnancy test, which depends on presence of free estrone rather than conjugated or modified estrone or similar 17-ketosteroids in maternal blood or urine, Gustav Wm. Rapp and Garwood C. Richardson[5a] (Loyola Univ., Chicago) applied the test to saliva from pregnant women. It was noted that even though the test result was positive in the urine, it was negative in the saliva of 148 women who later delivered female infants (7 had false positives) and positive in saliva of 218 women with male infants (3 had false negatives). The substance responsible for the test is unknown but is presumably an androgenic substance selectively screened out by the female salivary glands, since administration of testosterone or androsterone likewise produces a positive reaction. Male saliva is also a positive reactor. Although preliminary, the data strongly suggest a method for determination of the sex of the unborn child.

Correlation of Cytology of Urinary Sediment with Endometrial Histology. E. Stewart Taylor and Paul F. McCallin[6] (Univ. of Colorado) studied specimens from 27 women with normal menstrual cycles, 8 postmenopausal women, 7 patients with anovulatory bleeding, 4 with endometrial hyperplasia, 5 with adenocarcinoma of the fundus, 1 with ectopic pregnancy and 1 with a masculinizing adrenal tumor.

Of the 27 endometrial specimens from women with normal menses, 8 were classified as proliferative, 3 as midinterval and 16 as secretory. Urinary smears correlated with the endometrial picture in all cases. The proliferative smear showed scattered and small clusters of epithelial cells with pyknotic nuclei and cytoplasmic granules and vacuoles. In the midinterval smear, clusters of cells, nuclear pyknosis and cytoplasmic granules were more prominent, and intermediate epithelial cells with vesicular nuclei and moderately homogeneous cytoplasm were more numerous. The secretory smear showed large numbers of cell clusters with great cellularity. The intermediate cells were more numerous and showed clustering and wrinkling with mixed vesicular and pyknotic nuclei. Urinary smears from the women with anovulatory bleeding and with endo-

(5a) Science 115:265, Mar. 7, 1952.
(6) Am. J. Obst. & Gynec. 63:1009-1018, May, 1952.

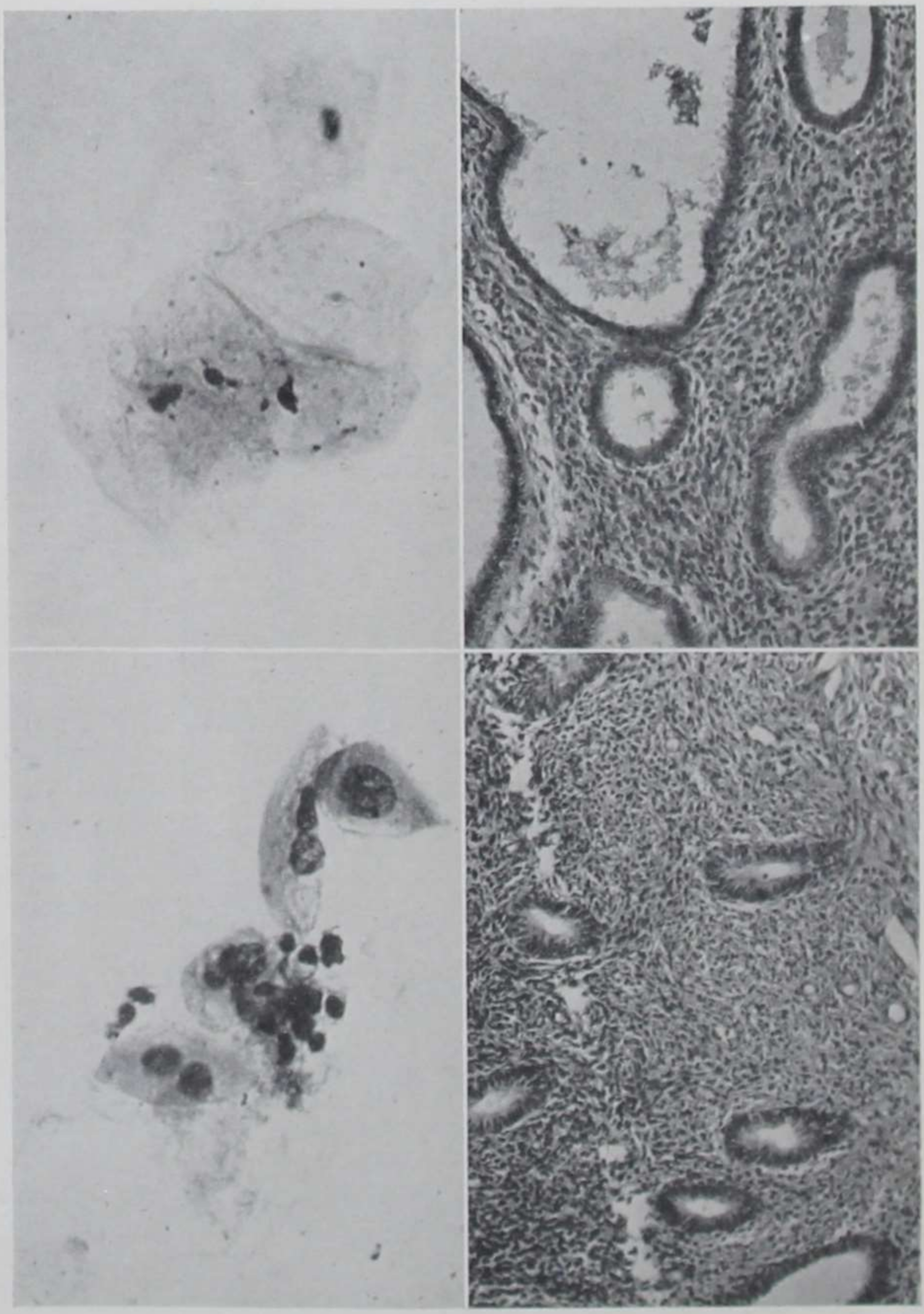


Fig. 69 (top).—Hyperplastic endometrium and urinary smear showing superficial cells with nuclear pyknosis and cytoplasmic granules.

Fig. 70 (bottom).—Atrophic endometrium and urinary smear showing minimal hormonal stimulus, from postmenopausal woman. Note large nuclei as compared with total cell size.

(Courtesy of Taylor, E. S., and McCallin, P. F.: Am. J. Obst. & Gynec. 63:1009-1018, May, 1952.)

metrial hyperplasia resembled smears taken from normal women at about the midportion of the proliferative phase, except that in the smears taken from women with endometrial hyperplasia estrogen effects were more prominent. The cells were more acidophilic with numerous cytoplasmic granules and pyknotic nuclei, and there was a predominance of superficial cells with a paucity of intermediate forms (Fig. 69).

Only a few cells, variable in size and with large nuclei in proportion to the amount of cytoplasm, were seen in the urinary smears of the postmenopausal women. Nuclei were a mixture of granular and vesicular types; the cytoplasm was homogeneous, and no large squamous like cells characteristic of estrogen effect were seen (Fig. 70).

Of the women with adrenocarcinoma of the uterus, four were postmenopausal and the urinary smears showed no estrogen effect. In one patient, whose last normal menses had occurred one year previously with subsequent irregular bleeding, the urinary smear showed mild estrogen effect manifested by scattered superficial cells with cytoplasmic granules and pyknotic nuclei.

The urinary smear of the patient with ectopic pregnancy (tubal abortion) revealed a few scattered superficial cells showing mild estrogen effect. The smear did not resemble that of pregnancy, perhaps because of death of the conceptus.

Urinary smears of a woman, 37, with an adrenal tumor, amenorrhea for five years and characteristic signs of a masculinizing tumor, showed scattered, rather large, squamous cells with homogeneous basophilic cytoplasm and large granular nuclei resembling cells from normal male urine. No estrogen effect was evident.

The urinary smear is not sufficiently specific to determine day-to-day changes, but any one smear is specific enough to be classified as proliferative, midinterval or secretory. The only advantage of a urinary sediment study of this type is that infection and blood are not present as they are in the vaginal smears used for studying various types of hormone responses and absences.

Oral Manifestations during the Female Climacteric (Postmenopausal Syndrome). Maury Massler[7] (Univ. of Illinois

(7) Oral Surg. 4:1234-1243, October, 1951.

College of Dent.) collected data on 86 women with oral symptoms who, on the basis of general symptomatology, were in some stage of the climacteric. They were referred to the dental clinic because of oral complaints or because discomfort precluded the wearing of a dental prosthesis (52).

Of 80 with burning mouth, 63 had glossodynia, 50 burning or itching gingiva, and 31 burning buccal mucosa. In 62, abnormal taste sensations (usually salty, peppery and sour) resulted in irregular eating habits or poorly balanced diets. Oral cancerophobia was conspicuous in 77. Demonstrable oral lesions included atrophic glossitis and chronic, slowly healing canker sores, especially before and after menstruation, in most cases and, in a few, chronic desquamative gingivitis.

It is suggested that most postmenopausal women suffer from a vitamin B complex deficiency which accounts for the oral lesions. In this series, approximately one-third responded quickly and dramatically to intensive vitamin B complex therapy and two-thirds slowly or not at all; one-third responded to estrogen therapy, and another third only when vitamin and hormone therapy were combined.

True Hermaphroditism. A true hermaphrodite in the classic sense should be able to fertilize a female, be fertilized by a male and fertilize itself, but no such instance has been reported. In the current medical sense true hermaphrodites have gonads of both sexes and can be classified as: (1) bilateral, with ovary and testis on both sides; (2) unilateral, with ovotestis on one side and ovary or testis on the other side, or (3) alternating, with testes on one side and ovary on the other.

John I. Brewer, Harold O. Jones and Harry Culver[8] (St. Luke's Hosp., Chicago) present an example of the unilateral type.

Girl, 18, was hospitalized because of a genital deformity. Hospital and county court birth records showed the patient registered as a male. The mother did not accept this opinion and reared the child as a girl. Although a tomboy in childhood, the patient believed herself entirely feminine in high school, went to dances and partook of boys' kisses and caresses with pleasure. Because she had never menstruated and feared that her genital deformity would prevent marriage, medical assistance was sought. Examination revealed a well developed female with feminine hair distribution and well formed

(8) J.A.M.A. 148:431-435, Feb. 9, 1952.

breasts. She had a phallus 4 cm. long and 2.4 cm. in diameter. There was a urethral orifice but no vaginal opening in the median raphe and no labia minora.

Laparotomy was performed to determine the true sex before reconstructing the external sex structures. A small noncanalized uterus without a cervix was identified, and both ovaries were visualized to

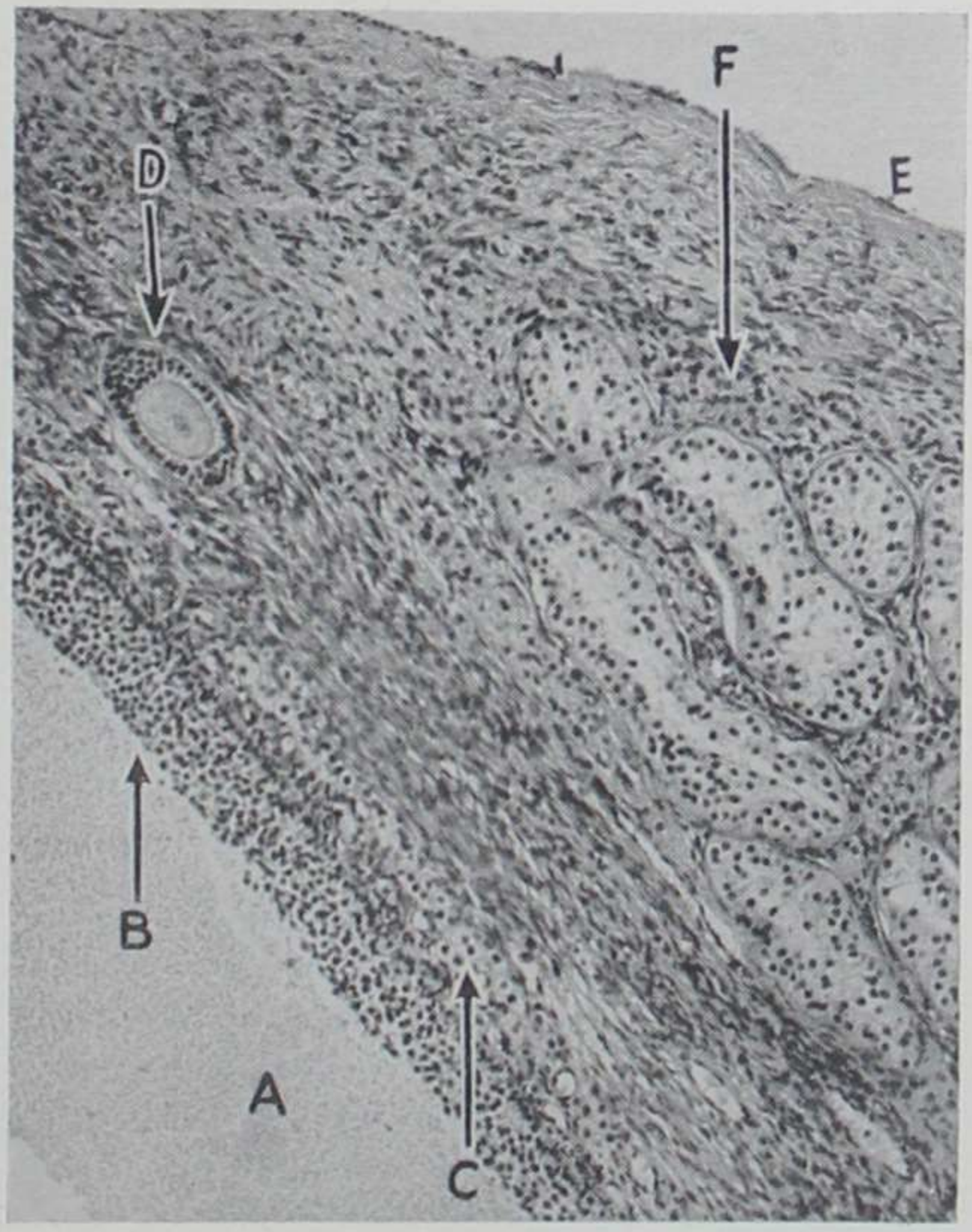


Fig. 71.—Tissue resected from right intra-abdominal gonad. Maturing graafian follicle has normal central cavity (*A*), normal granulosa cell border (*B*) and normal peripheral theca cell layer (*C*). Adjacent to it is normal graafian follicle (*D*) in early stages of growth, with intact ovum. Germinal epithelium (*E*) on surface of ovary is intact in most portions of sections. In ovarian cortex there are testicular tubules surrounded by interstitial cells (*F*). (Courtesy of Brewer, J. I., *et al.*: J.A.M.A. 148:431-435, Feb. 9, 1952.)

be grossly normal, although biopsy of the right gonad later revealed testicular elements as well as normal ovarian stroma, ova and follicles (Fig. 71). There was no spermatogenesis in the tubular structures. One year after surgical reconstruction of the vagina the patient was married and described normal sexual experience.

The authors consider genetic and psychologic sex both important in determining the most desirable sex to which the

patient should be converted. The genetic sex, or the predominant gonad sex, is usually the most important if it can be determined in infancy, before psychologic sex is developed. The psychologic sex is the most important if it is already developed and firmly fixed. Adult hermaphrodites should have psychiatric evaluation. In the surgical conversion to one or the other sex, castration is never indicated even though the gonads are of the opposite sex. Judicious management can make useful and socially acceptable persons of hermaphrodites.

Relation of Obesity to Menstrual Disturbances was evaluated by Joseph Rogers and George W. Mitchell, Jr.[9] (Tufts College) because of the repeated clinical impression that the two symptoms are related. Incidence of obesity was calculated in 100 females aged 16-40 who had functional menstrual disturbances including amenorrhea, abnormal uterine bleeding, premature menopause, infertility and habitual abortion. When weight was 20% or more above the ideal, obesity was diagnosed. Of the 100 patients, 43 were classified as obese as against 13% in a control group of 201 females with normal menses and 9.6% in 730 normal women. Of the 100 patients, 60 had amenorrhea and 29 (48%) of them were obese. Of 19 patients with functional uterine bleeding, 11 (58%) were obese. Obesity and menstrual irregularity coincided more strikingly in subjects aged 16-29 than in those aged 30-40. Whether one is secondary to the other or whether both have a common etiology is unknown.

[Frequently amenorrhea is relieved by simple weight-reducing measures.—Ed.]

Use of Monobenzyl Ether of Stilbestrol in Treatment of Functional Amenorrhea (Chronic Secondary Amenorrhea): Preliminary Report. Studies in rabbits and rats have indicated that this compound has a pituitary-stimulating action but almost no estrogenic activity. This led N. T. Werthessen and S. L. Gargill[1] (Boston) to treat 18 women with secondary amenorrhea who had not menstruated, except for withdrawal bleeding, for at least a year before monobenzyl ether therapy. The patients represented sterility problems; intermittent therapy with estrogens, with estrogens and progesterone combined

(9) New England J. Med. 247:53-55, July 10, 1952.
(1) J. Clin. Endocrinol. 12:169-177, February, 1952.

or with chorionic gonadotrophin had resulted only in anovulatory withdrawal bleeding. Desiccated thyroid, vitamin E and weight reduction programs had also been valueless.

The monobenzyl ether of stilbestrol was given intramuscularly in 1.0 mg. doses three times a week for three weeks and, after a week's interval, a second or third course was given if response indicated it. Occasionally the dose was raised to 2 mg. No toxic reactions were observed. Ten postmenopausal women with previous good response to estrogens were studied as a control group four to six weeks after stilbestrol was stopped. The controls showed no change in vaginal epithelium, continued to have high gonadotrophin excretion and had no post-treatment menses.

In the experimental group nine women who had only one course of treatment failed to menstruate. Nine others menstruated after a second or third course; five resumed cyclic bleeding and three, whose histories are given, became pregnant.

Case 1.—Woman, 23, had had menarche when 12 and irregular menses until age 21½. After being married for 1½ years, she became totally amenorrheic. Appendectomy 10 weeks before the study revealed normal ovaries and an infantile uterus. Physical examination, laboratory test and endocrine evaluation gave normal results except for atrophic vaginal epithelium and atrophic endometrium. Treatment was started and three days after the fourth injection, the breasts became painfully engorged; two days later menses ensued and lasted five days. Basal body temperature and vaginal smears did not indicate ovulation. A second series of injections was given for three weeks. Three days after the last injection the cycle of swollen breasts and anovulatory bleeding was repeated. A third series of injections, however, was followed by five days of ovulatory flow. She became pregnant in the next cycle. Spontaneous cyclic menses resumed after successful labor.

Case 2.—Woman, 25, had irregular menses from age 12 to 17, when amenorrhea developed without other symptoms. Physical examination and laboratory test results were normal. Vaginal epithelium was atrophic and endometrium varied from atrophic to proliferative. The usual gamut of therapy, including two courses of irradiation of the ovaries, had no results. She had three series of 1.0 mg. injections and two series with 2 mg. monobenzyl ether of stilbestrol. These were all accompanied by breast swelling and anovulatory flow. Seven weeks after the last injection regular cyclic ovulatory menses began; three months later she became pregnant.

Case 3.—Woman, 32, had regular menses from age 13 to 22

when, four months after marriage, amenorrhea without other symptoms began. Usual forms of therapy, including x-ray, did not help. Biopsy showed atrophic endometrium. Physical examination and laboratory test results were normal. She was given three series of injections with 1 mg. and three series with 2 mg. monobenzyl ether of stilbestrol. Each was followed by anovulatory flow except for the last, which appeared ovulatory. Despite spontaneous ovulatory flow for the next two months, she insisted on a course of irradiation of the ovaries (3 doses of 25 r each). The next month menses did not appear; she was pregnant.

[I must admit that I was extremely skeptical about the action of this compound before I had the opportunity of studying, with Dr. E. W. Overstreet, a patient with typical female eunuchoidism due to lack of pituitary gonadotrophins. Other pituitary functions were normal. Cyclic administration of estrogen and progesterone produced withdrawal bleeding but nothing else. She was then treated with the monobenzyl ether of stilbestrol. To our surprise, pituitary gonadotrophins were then found in her urine (positive at 40 m.u. and borderline positive at 80 m.u.).—Ed.]

Treatment of Endometriosis and Other Gynecologic Conditions with Large Doses of Estrogens. Lewis M. Hurxthal and Anne T. Smith[2] (Lahey Clinic) report results in 25 patients, 9 with histologically verified lesions, treated with large doses of estrogens, 5-50 mg. daily. Pain disappeared in 4 and decreased in 12. Satisfactory results were obtained in eight

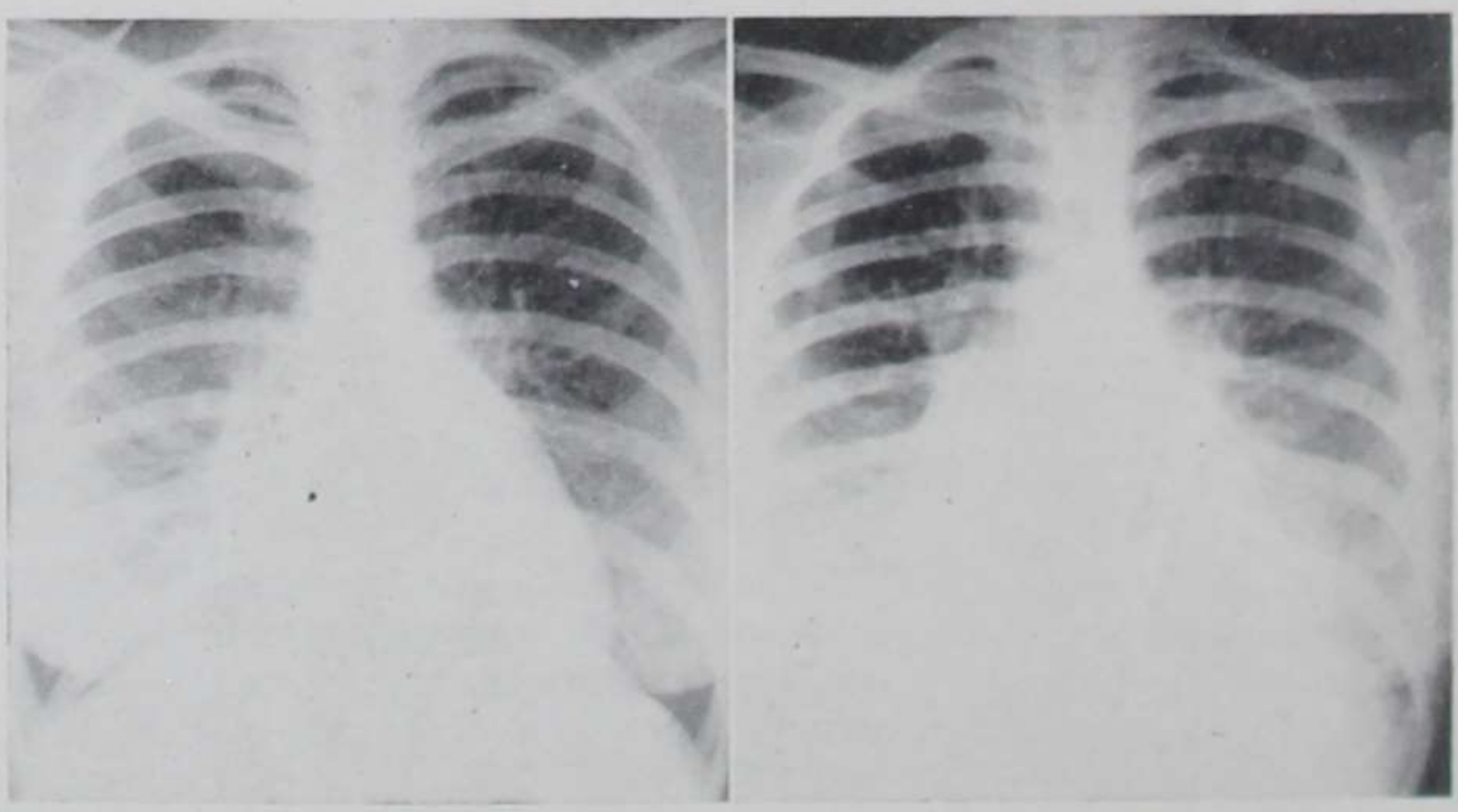


Fig. 72 (left).—Mitral stenosis before stilbestrol therapy (loaned by Dr. Max Ritvo).

Fig. 73 (right).—Pulmonary congestion (associated with dyspnea and orthopnea) which developed when patient was given stilbestrol.

(Courtesy of Hurxthal, L. M., and Smith, A. T.: New England J. Med. 247:339-343, Sept. 4, 1952.)

(2) New England J. Med. 247:339-343, Sept. 4, 1952.

patients, with menorrhagia with or without fibroids and in two with chronic cystic mastitis, with a decrease in the size of the fibroids and nodules. About half the women became nauseated, especially during the first two weeks of therapy. Simultaneous use of testosterone did not counteract this unpleasant effect. Treatment had to be stopped in seven patients because pain was not affected or because of unpleasant effects, including dependent edema, edema of the labia, swelling, pigmentation and soreness of the breasts, psychosis and pulmonary edema. This last occurred in a woman, 29, with rheumatic heart disease and mitral stenosis. Figures 72 and 73 show chest x-rays made before and after three months of stilbestrol therapy (25 mg. daily), when dyspnea and orthopnea appeared. All signs and symptoms of heart failure disappeared a few days after cessation of therapy. In the patient with psychic complications, severe headaches, irritability, alcoholism and homicidal tendencies developed after 25 mg. daily for one month. Carcinoma of the breast occurred in two patients but it is not believed that breast cancer is caused by stilbestrol, although if a carcinoma of subclinical size is present the growth may be accelerated in some cases. Estrogens probably should not be used for an extended time in any patient with a definite family history of cancer.

Hormonal Control of Functional Uterine Bleeding is discussed by Robert B. Greenblatt and Wm. E. Barfield[3] (Med. College of Georgia). A combination of gonadal steroids containing 1.66 mg. estradiol benzoate or its equivalent, 25 mg. testosterone propionate and 25 mg. progesterone daily for five days will control nearly 95% of all functional bleeding due to various causes and is superior to either steroid alone. Bleeding is usually arrested within 6-48 hours and withdrawal bleeding will ensue two to seven days after cessation of therapy. In severe bleeding, a double dose of the combined steroids initially may be advantageous. Withdrawal bleeding may subsequently be produced at monthly intervals until cyclic ovulatory menses, determined by basal temperature records, have begun. When bleeding is acute and the patient exsanguinated, it is advisable to use estrogen intravenously every four to six hours until bleeding is arrested and then administer estrogens orally

(3) Am. J. Obst. & Gynec. 63:153-157, January, 1952.

in decreasing doses for 25 days, delaying withdrawal bleeding until the patient has recovered. Care must be exercised in the selection of patients since moderately good, but temporary, results may also be obtained in ectopic pregnancy and bleeding due to endometrial carcinoma.

[As pointed out by the authors, it is extremely important not to overlook the other possible causes for uterine bleeding before assuming that it is functional and therefore may be treated with hormones. A favorable response to therapy cannot be taken as a diagnostic criterion since hormones may occasionally relieve bleeding caused by carcinoma of the endometrium or other serious conditions.—Ed.]

Endocrine Treatment of Dysmenorrhea. P. M. F. Bishop and Eduardo Orti[4] by questionnaire ascertained that 16.5% of 472 nurses at two hospitals complained at some time of incapacitating dysmenorrhea, i.e., pain so severe as to necessitate lying down or abandoning work. Menstrual irregularity at some time was recorded by 16.8%. Dysmenorrhea was experienced by 25.6% of those with regular cycles. The suggestion that "menstrual instability" is associated with a tendency to dysmenorrhea is strengthened by the observation that there was a greater scatter in age of menarche in patients complaining of dysmenorrhea.

Treatment of dysmenorrhea varies widely between two extremes. Hamblen, for instance, maintains that the acceptance of menstrual discomfort should be urged and that no hope for euphoric genital bleeding should be extended. He also feels that few, if any, healthy sexually adequate and psychosomatically sufficient women have dysmenorrhea. Other physicians strongly favor active and even drastic steps, such as presacral neurectomy. The proper treatment probably lies between these two extremes. Endocrine therapy is forced to play a prominent role in the management of incapacitating dysmenorrhea.

Among 330 dysmenorrhea patients, the authors charted 945 menstrual cycles, 631 during estrogen therapy in 73 patients. In view of Sturgis and Albright's contention that true spasmodic dysmenorrhea occurs only in ovulatory cycles, 148 cycles were studied, using basal temperature records to determine whether ovulation had taken place. The cycle was nonovulatory and painless, or ovulatory and painful in 87%.

Because of the element of suggestion, the first two or three cycles tend to be painless whatever the treatment. To assess

(4) Proc. Roy. Soc. Med. 45:803-805, November, 1952.

the true effect of estrogen therapy it is necessary to study the response of the patient over a long period. For this reason, 27 patients were studied an average of 20 cycles, of which an average of 13 cycles were treated with 2 mg. stilbestrol (or its equivalent) daily for 14 days commencing within 5 days of the first day of the previous period. This was almost always followed by a painless "period" (estrogen withdrawal bleeding). This treatment is palliative, not curative, for even after two years, when it was discontinued, painful ovulatory cycles recurred in each of the patients.

[Suppression of ovulation by administration of estrogens is ordinarily effective for only three or four months. Usually then, despite continued estrogen therapy, ovulation breaks through and the patient again has a painful menstrual period. Subsequently, ovulation may be successfully suppressed for another three or four months.—Ed.]

The Stein-Leventhal Syndrome

Bilateral Polycystic Ovaries Associated with Sterility, Amenorrhea and Hirsutism. According to Mason C. Andrews[5] (Norfolk), the clinical features of the Stein-Leventhal syndrome are sterility, menstrual irregularity (amenorrhea principally), hirsutism (in 50% of cases) and ovulation failure. Pathologically, there are bilaterally enlarged ovaries (two to five times normal size), with pale, smooth, thick coverings and containing multiple cysts. The stroma of the ovaries is dense and compressed, and there is hyperplasia of the theca interna with frequent luteinization.

Woman, 23, complained of sterility for 4½ years, increasingly long periods of amenorrhea and increasingly heavy hair on the lip, chin, arms and legs. Her periods had begun normally at age 12 and had been regular until marriage at 18, when they became farther and farther apart and scantier. At age 21, an endometrial biopsy on the 27th day of the cycle revealed nonsecretory endometrium and she was treated with hormones. At age 22, after a heavy vaginal bleeding, curettage revealed atrophic endometrium.

The patient was of a masculine habitus. The uterus was normal in size; the right ovary was twice and the left ovary 1½ times normal size. Endometrial biopsy after three months of amenorrhea showed proliferative endometrium. Glucose tolerance was normal. 17-Ketosteroid excretion was 21 mg./24 hr. A spine x-ray showed moderate decalcification. When laparotomy was done, both ovaries were found to be twice normal size, smooth, pale and polycystic. A wedge of each was resected. After surgery she menstruated regularly every 32 days. She conceived during the third cycle, but

(5) Virginia M. Month. 79:544-548, October, 1952.

aborted at 24 weeks. She again became pregnant. Six months after the operation, 17-ketosteroid excretion was 8.8 mg./24 hr. The hirsutism was improving.

It is probable that the malfunctioning ovaries in this condition produce a variety of steroid hormones, which sometimes produce hirsutism. The rarity of the condition makes exact diagnosis essential to prevent unnecessary unprofitable and harmful operations. The presence of follicle cysts per se has little or no clinical significance. More harm is probably being done by cutting into ovaries containing these cysts than will be outweighed by the good accomplished.

[The original article is worth the time of any physician who is interested in good medical writing. Andrews points out that this syndrome, mentioned only in the most recent texts, may be so common that large series of cases have been accumulated by individual observers. I do not think that the minimal criteria for the diagnosis of this syndrome are yet established. Few physicians are willing to submit their patients to laparotomy unless bilaterally enlarged ovaries are palpable. Whether this conservative attitude is justified will depend, of course, on the patient's reaction to infertility and amenorrhea. Hirsutism has rarely been cured by the procedure used in the treatment of this condition. There is a strong possibility that the changes in the ovary are secondary to a masculinizing influence originating elsewhere, perhaps in the adrenals. —Ed.]

Hirsutism in Stein-Leventhal Syndrome. Stein described the syndrome of bilateral cystic ovaries giving rise to amenorrhea, sterility and abdominal pains. In 7 of 10 patients with this syndrome, Leventhal found hirsutism. H. Rottinghuis[6] (Amsterdam) observed three cases, with hirsutism in only one.

Unmarried woman, 25, with hirsutism and oligomenorrhea, for two years had had vague pains in the lower abdomen. The menarche occurred at age 13, and the menstrual cycle varied from 2 to 12 months with definite hypomenorrhea. At 14, hair appeared on the chin, upper lip and legs. At age 22 she had been given estrogens; at that time she had to shave daily. Studies two years later were not remarkable except for a BMR of +20%; 24 hour excretion of 17-ketosteroids was 24.2 mg. and of estrogens, 100 I.U.

Vaginal examination revealed an enlarged right ovary. She was given 0.05 mg. ethinyl estradiol for several months. During this course, temperature curve and endometrial fragments during "menstruation" showed an anovulatory cycle and a proliferative endometrium with hyperplastic glands. Seven months later the left ovary was also enlarged. At that time, x-ray studies of the kidneys and sella turcica and neurologic and ophthalmologic examinations showed nothing abnormal. Urine contained 28.9 mg. 17-ketosteroids, 150 I.U. estrogens and less than 40 units of gonadotrophins per 24

(6) Gynaecologia 134:108-116, August, 1952.

hours. Laparoscopy showed ovaries with follicle cysts; at laparotomy, firm ovaries, the size of a chicken egg, were noted and palpation of adrenals revealed no tumor. Wedge resection of the ovaries was performed. The specimen showed numerous follicle cysts with intense luteinization of the theca interna.

The postoperative course was uneventful; 2½ months later, hirsutism had greatly diminished and abdominal pain had disappeared. Normal menses started soon thereafter, and the temperature curve was characteristic of ovulatory cycles. Fourteen months after operation the patient no longer shaved, hirsutism of legs had decreased but pubic hair still showed male distribution. Excretion of 17-ketosteroids was 18.6 mg./24 hours.

Masculinization Associated with Luteinized Microcysts of Ovary. Myra K. Beattie, W. W. Kay, Arnold Elton and Albany G. Hucker[7] report an instance of masculinization associated with cystic changes of the ovaries.

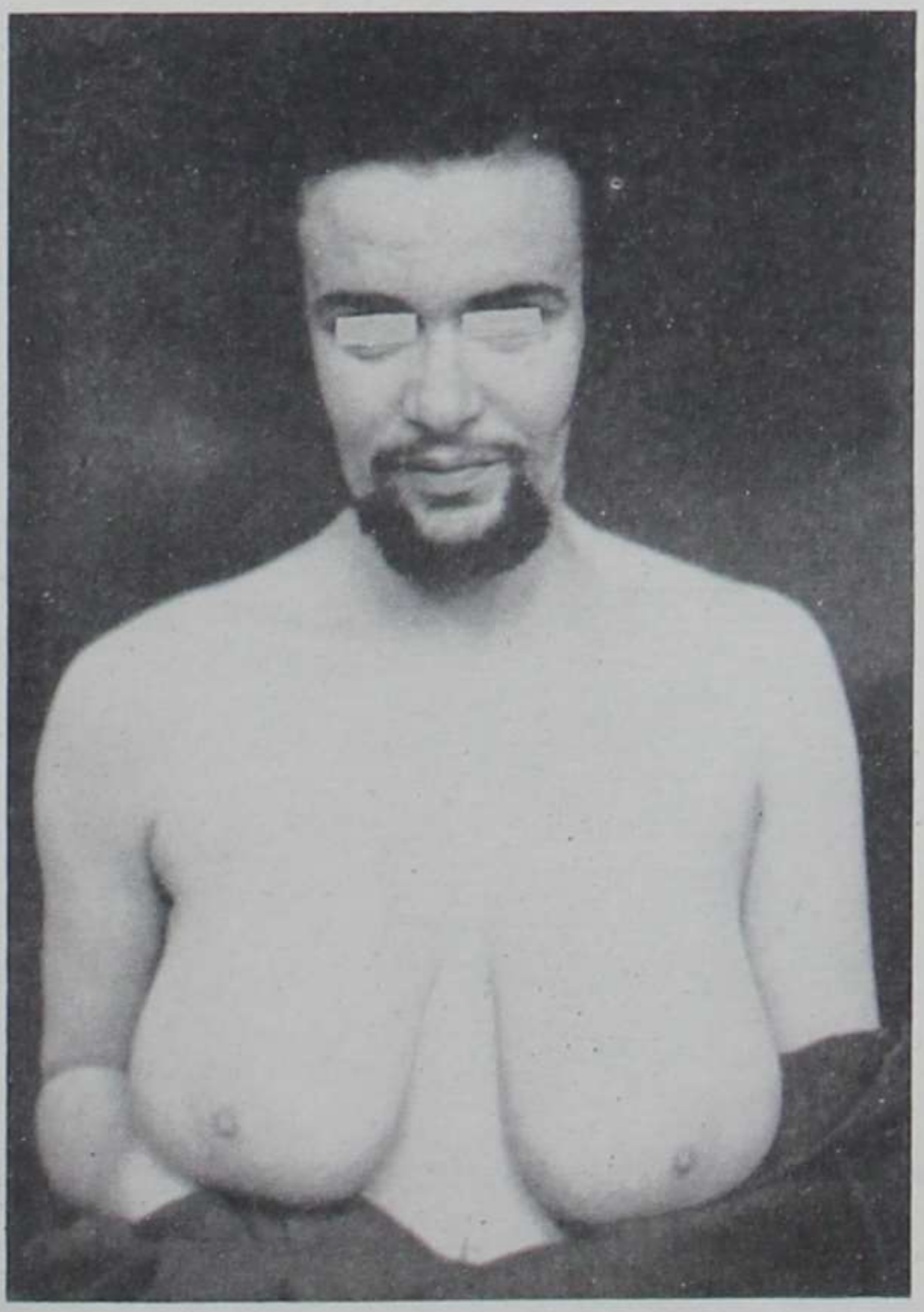


Fig. 74.—Patient before oophorectomy. (Courtesy of M. K. Beattie.)

(7) J. Obst. & Gynaec. Brit. Emp. 59:465-470, August, 1952.

Schizophrenic girl, 21, had had a beard since age 18. The menstrual history was unknown before hospitalization, but in the six years thereafter she had 14 normal periods at irregular intervals. She had a 2 in. beard on the chin and cheek (Fig. 74), male distribution of pubic hair and moderate growth of hair on the arms, legs

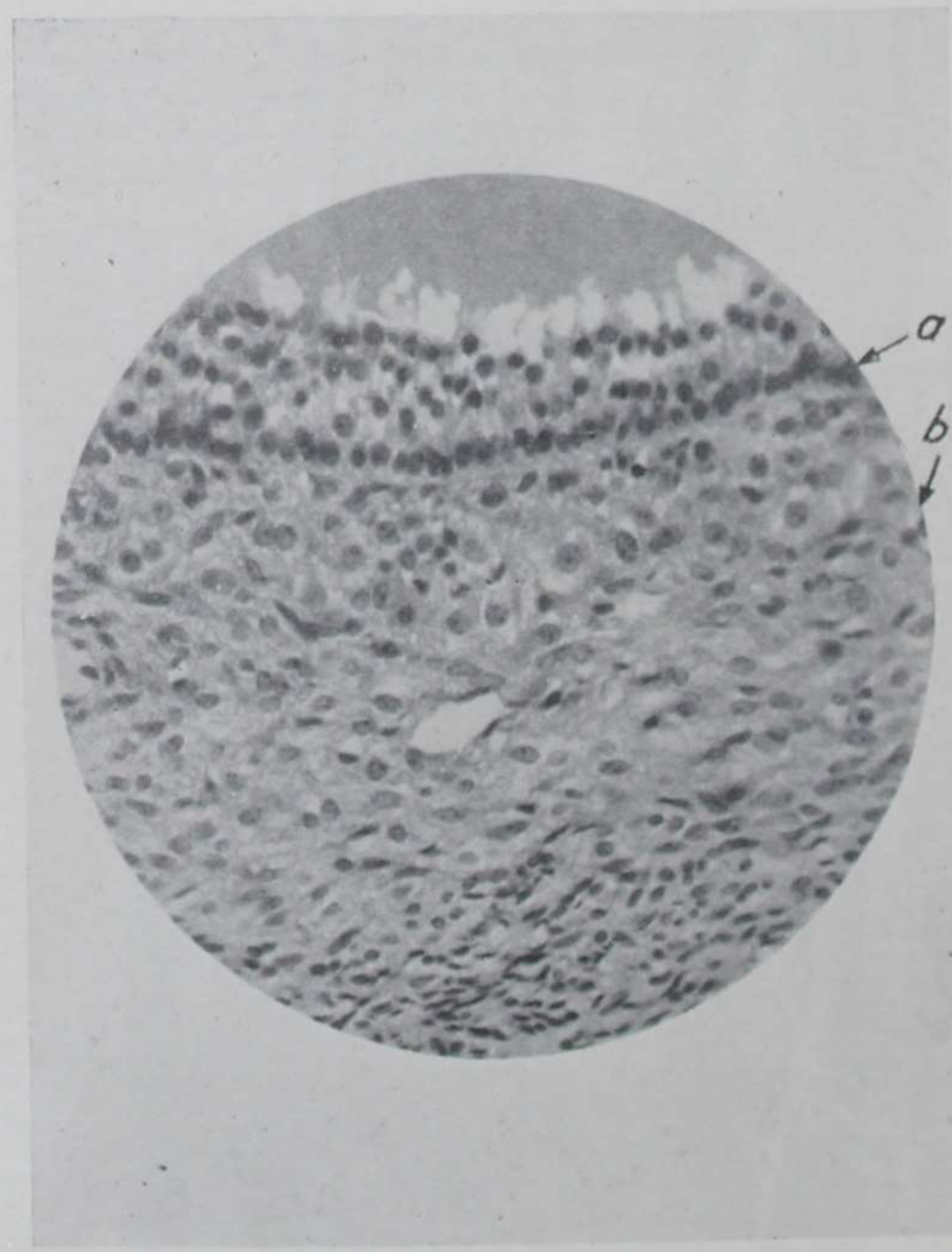


Fig. 75.—Section of ovary showing granulosa cells (*a*) and luteinized theca cells (*b*); × 320. (Courtesy of Beattie, M. K., *et al.*: J. Obst. & Gynaec. Brit. Emp. 59:465-470, August, 1952.)

and shoulders. The clitoris was not hypertrophied. Owing to mutism, it was not possible to assess voice changes. General shape was that of a well built female with predominantly feminine body movements, although homosexual tendencies were noted in the hospital. Blood pressure and skull were normal as were serum electrolytes (except potassium level of 26 mg.), proteins and cholesterol. The 24

hour 17-ketosteroid excretion was 5.3 and 6.4 mg. and the corticosteroid excretion 0.63 and 0.66 mg. The result of a Friedman test was negative. A laparotomy to rule out adrenal virilism revealed normal adrenals; the ovaries were, however, cystic and abnormality in a biopsy specimen led to removal of both ovaries. Luteinized polycystic changes with bilateral dermoids were found (Fig. 75). Postoperatively the beard did not grow as rapidly, but persisted after two years. Mental state did not change. Potassium levels fell to normal.

[This is an unusually severe degree of hirsutism for this condition. —Ed.]

Endocrine Tumors of the Ovaries

Masculinovoblastoma or Masculinizing Adrenal Rest Tumor of Ovary. Jonathan E. Rhoads, Harold A. Zintel and Robert C. Horn, Jr.[8] (Univ. of Pennsylvania) report a case.

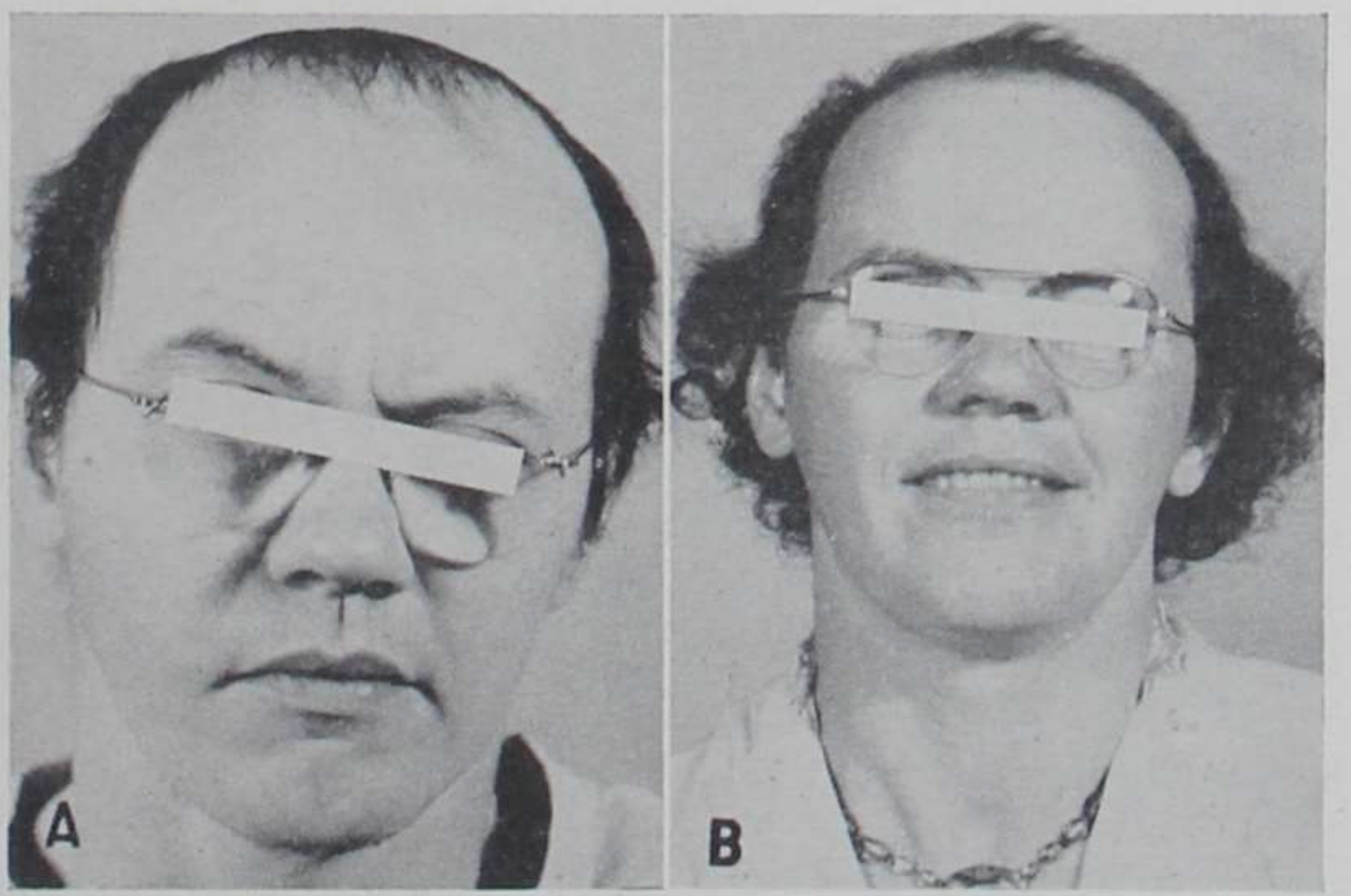


Fig. 76.—*A*, immediately before and, *B*, 5½ years after operation. (Courtesy of Rhoads, J. E., *et al.*: J.A.M.A. 148:551-552, Feb. 16, 1952.)

Woman, 37, was well until eight years previously when, soon after the birth of a baby, she noticed gradual lessening of menstrual flow to complete cessation after four years, gradual atrophy of breasts, alopecia, facial and bodily hirsutism, deepening of voice and, three months previously, dizziness. Weight had remained constant and sexual reactions had not changed. On examination, she appeared masculine with muscular extremities, coarse, ruddy skin, hirsutism of chest, face, abdomen and extremities and masculine distribution of pubic hair. The scalp hair was sparse, thin and dry,

(8) J.A.M A. 148:551-552, Feb. 16, 1952.

with little hair from occiput to forehead (Fig. 76, *A*). The blood pressure was normal; no abdominal masses were palpable and external genitalia and pelvis were normal.

An enlarged left ovarian mass was removed and found on microscopic examination to be an adrenal rest tumor. Menses began in 30 days and within 3 months were normal. Her voice became higher in pitch, scalp hair began to increase and body hair to decrease; facial hair diminished after 1 year and was almost completely gone after 3 years; breasts became larger, and she had been well for 5½ years (*B*).

[It would be interesting to know the 17-ketosteroid and 11-oxysteroid excretion in this remarkable case. Note, however, that the laboratory tests were not essential to diagnosis. Actually, the data on 17-ketosteroid excretion in masculinizing tumors of the ovary are quite limited and generalizations are probably not in order. Most of the elevated 17-ketosteroid levels so far reported have been associated with "adrenal rest tumors" of the ovary, whereas normal or low levels have been associated with arrhenoblastomas. More information on this point is sorely needed but will probably have to be derived from a collection of individual case reports, since the condition is so rare.—Ed.]

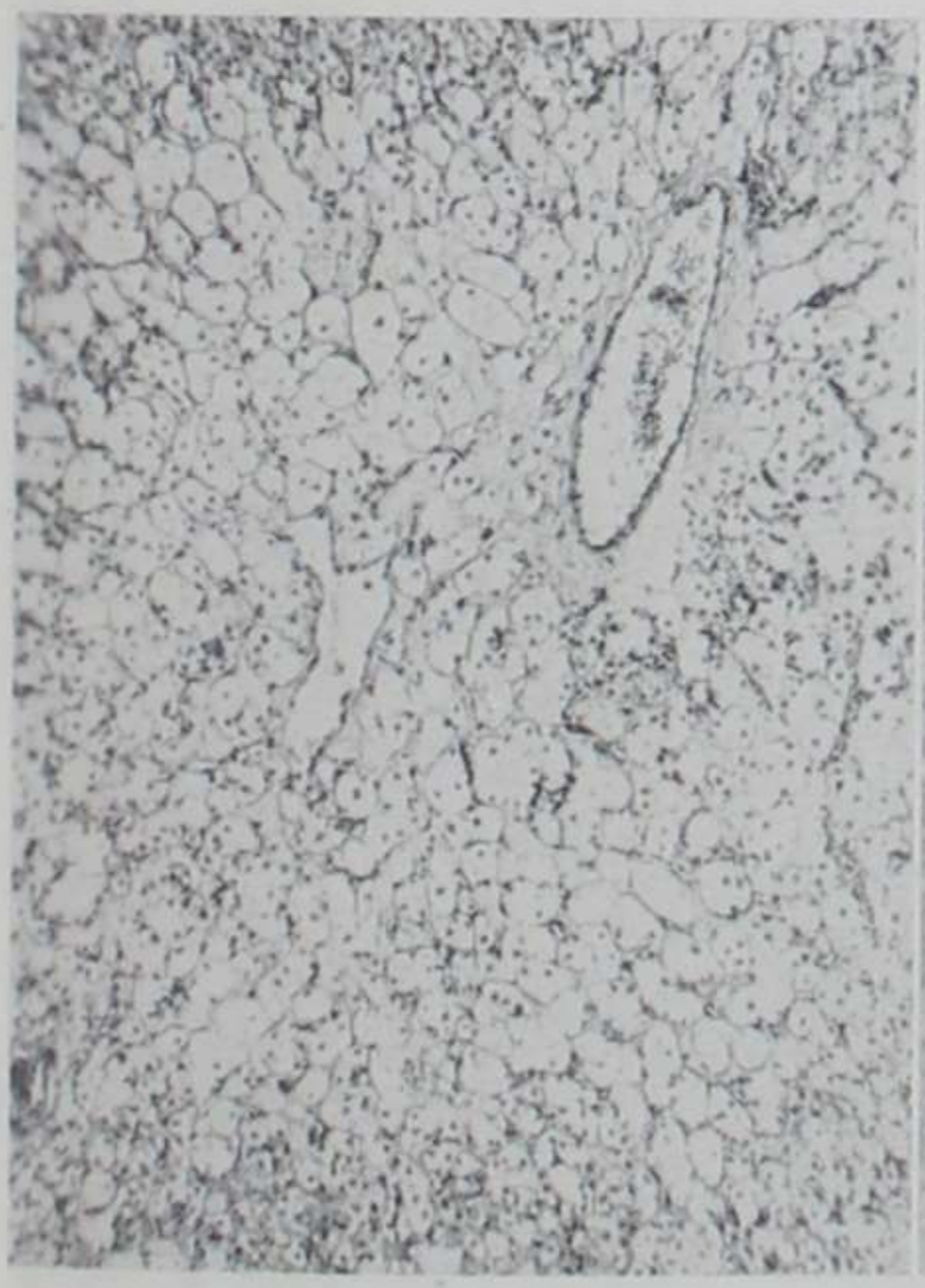
Masculinizing Tumors of Ovary. Nasid Erez and Ertugrul Yenen[9] (Univ. of Istanbul) report two cases.

Case 1.—Woman, 40, had amenorrhea, hirsutism, thickening of the skin, loss of scalp hair, deepening of the voice and hyperglycemia for eight years. The vulva was normal and the uterus slightly enlarged. The left adnexa were normal, but a movable, nodular mass the size of a fist was palpable on the right. Preliminary curettage suggested atrophic endometrium. Laparotomy revealed a soft, nodular encapsulated tumor, the size of an orange, replacing the right ovary. Histologically, delicate, fibrillary, well vascularized stroma surrounded the parenchyma, which in certain areas was rich in columns of cells similar to those of the zona fasciculata of the adrenal. In other areas there were polygonal cells four or five times larger, with clear protoplasm and small, round, eccentric nuclei (Fig. 77). Scarlet red stain showed lipoid material completely filling the cells. The general appearance was similar to that of a hypernephroma, and the diagnosis was adrenocortical tumor of the ovary with lipoid cells. The postoperative course was excellent. Masculinizing signs regressed, blood sugar became normal, menses were regular and premenstrual scrapings showed secretory endometrium.

Case 2.—Woman, 30, had normal menses up to age 17, then delay and finally arrest of menstruation. She felt that for 10 months the abdomen had been growing larger, and she had had intermittent pain. Except for dry skin, hirsutism and flaccid breasts, physical examination showed nothing unusual. The genitalia were normal, but a mass the size of an infant's head was palpable on the right. At laparotomy, the uterus and left ovary were normal; on the right a cystic, freely movable, encapsulated tumor replaced the ovary.

(9) Gynaecologia 133:345-360, June, 1952.

Histologically, columns of two or more rows of small, deeply staining cells were noted amid dense stroma. In some areas these cells, more intimately mingled with stroma, resembled connective tissue; in others, they were disorganized and formed a fibrillary architecture (Fig. 78). In the solid part of the tumor healthy ovarian tissue with follicles was noted. Because of the location of the tumor near the hilus and its histologic appearance, arrhenoblastoma was suspected. Curettage done 10 days after operation showed proliferative endometrium; repeated curettage during several regular



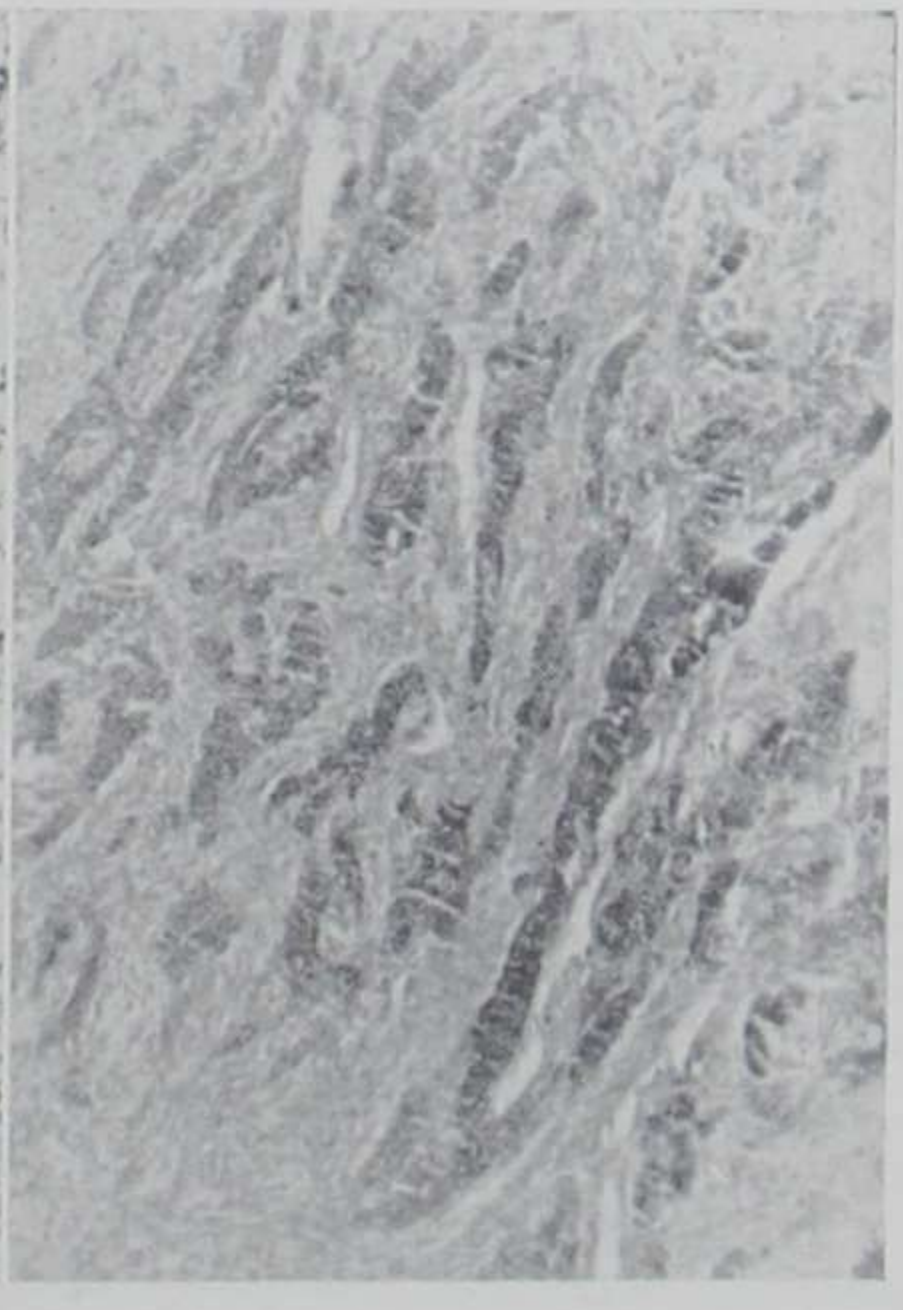


Fig. 77 (left).—Section of masculinizing ovarian tumor in Case 1.
Fig. 78 (right).—Section of tumor in Case 2.
(Courtesy of Erez, N., and Yenen, E.: Gynaecologia 133:345-360, June, 1952.)

cycles that followed showed proliferative and secretory endometrium at appropriate times.

Virilizing ovarian tumors should not be lumped together. Various theories have been proposed for their origin. The histogenesis of arrhenoblastomas is best accounted for by R. Meyer's hypothesis, i.e., that these tumors arise from the potentially masculine elements included in the rete ovarii. The masculinizing tumor with lipoid cells is best explained by the proximity, in early embryonic life, of the adrenal cortex and the ovarian medullary nucleus; this permits migration of adrenal particles into the ovary, where they may give rise to these tumors.

Endometrial Carcinoma Associated with Feminizing Tumors of the Ovary: Report of Two Cases. The importance of the combination of these tumors is not their rarity nor the mortality but the possible light they may shed on the etiology of endometrial cancer. R. M. Corbet, A. A. Miller and W. H. Tod[1] discuss endometrial carcinoma combined with thecoma in one patient and with granulosa cell tumor in another. One

Fig. 79.—Sagittal section of uterus showing hyperplastic endometrium and polyp with adenocarcinoma. Hematoxylin-eosin; enlarged from × 1⅔. (Courtesy of Corbet, R. M., *et al.*: J. Obst. & Gynaec. Brit. Emp. 59:368-371, June, 1952.)

patient, 56, para III, complained of two years of irregular bleeding after two years of normal menopause. The other, never pregnant, was 70 and complained of intermittent vaginal discharge and bleeding which had been almost continuous for three months. Each had total hysterectomy and bilateral salpingo-oophorectomy; Figure 79 shows the uterine polyp with adenocarcinoma in the second patient.

Of 70 reported instances of the combined tumors, none were in young women. Feminizing ovarian tumors during re-

(1) J. Obst. & Gynaec. Brit. Emp. 59:368-371, June, 1952.

productive life do not apparently increase the risk of uterine cancer. Only when the ovarian tumor appears after the menopause does uterine cancer appear; the risk is assessed at 12-27%. The thecoma rather than the granulosa cell tumor is the probable estrogen producer, and it has been suggested that the granulosa cell tumor is estrogenic only to the extent that it contains thecal elements. Thus the rarer but biologically more active tumor is more often associated with endometrial cancer than its less active but more common counterpart. This strongly suggests that the long unopposed action of estrin on the endometrium predisposes to uterine cancer.

[It is still controversial whether the relatively large incidence of endometrial carcinoma in patients with feminizing tumors of the ovary is evidence of a carcinogenic effect of estrogens. Available statistical data have been variously interpreted by different authors. It does seem, however, that prolonged and uninterrupted administration of estrogens is undesirable.—Ed.]

Granulosa and Theca Cell Ovarian Tumors: Prognosis. A. W. Diddle[2] (Knoxville, Tenn.) studied 35 patients with feminizing ovarian tumors and analyzed 1,189 cases from the literature. These tumors arise from granulosa cells, their remnants or their mesenchymal precursors and develop into theca or granulosa cell types, in a ratio of 1:4. Thecomas predominated in older women and were not found among girls under 10 who, in contrast, had 6% of the granulosa cell tumors. The chief symptom was bleeding and occurred nearly five times as often as amenorrhea, which might be expected with tumors that produce an excess of estrogens. Other symptoms or signs included tumor, pain, precocious puberty, pregnancy with amenorrhea, sterility, hirsutism, mastalgia and shock in decreasing frequency. Pregnancy and tumor coexisted in 16, nearly a third of whom went to term with a 50% postpartum mortality from intraperitoneal tumor hemorrhage; the other half had no complications; two-thirds either aborted or died of metastases.

Most tumors were unilateral. Of those with bilateral tumor, 90% died or had recurrences. Nearly 40% had associated uterine fibromyoma or hypertrophy and 73 women had adenocarcinoma of the endometrium, 9 carcinoma of the breast and 17 other ovarian neoplasms. It is estimated that the incidence of endometrial cancer is increased 100-fold when

(2) Cancer 5:215-228, March, 1952.

feminizing tumors coexist. Metastases spread by direct or regional lymphatic extension; 83 had ascites. Reaction to the Aschheim-Zondek test was always negative. High estrogen levels in the blood and urine largely disappeared within 36 hours of surgical removal of the tumor.

Feminizing ovarian tumors are malignant more often than was formerly believed. Patients should not be permitted to undergo labor with such a tumor because of danger of torsion or rupture of the neoplasm during labor. Since the outcome is difficult to predict, total hysterectomy with bilateral salpingo-oophorectomy is the treatment of choice in older patients. If the neoplasm is well encapsulated, less formidable procedures may be recommended for younger patients. Since feminizing ovarian tumors are usually radiosensitive, palliative irradiation is advised for metastases.

The tumor recurred in 96 instances (92 granulosa cell tumors and 4 thecomas). Since over a third of the recurrences were noted after 5 years and a fifth after 10 years, a five year survival does not indicate cure.

[This is a valuable review which points out, among other greatly needed pieces of precise information, that malignancy is more common in this condition than has been stated by some authorities.—Ed.]

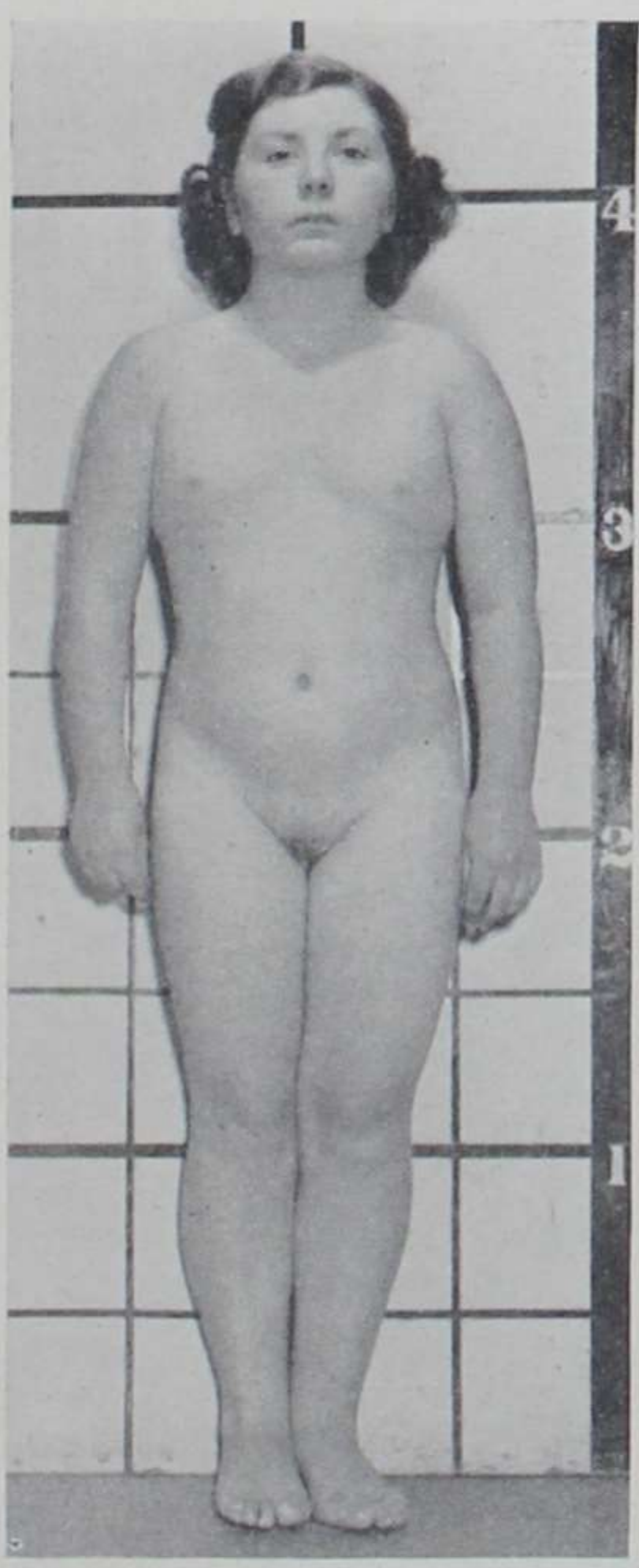
Ovarian Agenesis

Congenital Ovarian Aplasia: With Minimal Evidence of Ullrich-Turner Syndrome. Alex Russell and G. I. M. Swyer[3] report a case.

Girl, 14, was hospitalized because growth had been arrested from age 9-10. Two paternal aunts were even smaller than she; one aunt was 51½ in. tall and had webbing of the neck. She herself was stocky and 52½ in. tall (Fig. 80). Limb-body proportions and bone age were normal. There was no immaturity of the face, nasal bridge or jaw. Minimal webbing of the neck was noted on flexion (Fig. 81). The carrying angle was increased at the elbows, and there was no true breast development. The genitalia were infantile, perineal hair was scanty and she had no axillary hair. Blood pressure was 150/105 in the arm, 175/115 in the leg. An abnormally high urinary gonadotrophic output was linked to an abnormally low estrogen level. Urinary 17-ketosteroid excretion was 6.7 mg. and 11-oxysteroids, 0.43 mg./24 hours. Laparotomy revealed that the ovaries were represented only by rounded fibrous cords. There was no his-

(3) Proc. Roy. Soc. Med. 45:596-598, September, 1952.

tologic trace of follicles in any stage. Cyclic administration of 2 mg. stilbestrol daily, for three weeks, then suspending for one week, supplemented by 10 mg. methyl androstenediol in an effort to promote growth without accelerating epiphyseal fusion resulted in 1¼ in. increment in height in three months, visible breast development, increasing pubic hair and withdrawal bleeding. Areolar pigmenta-



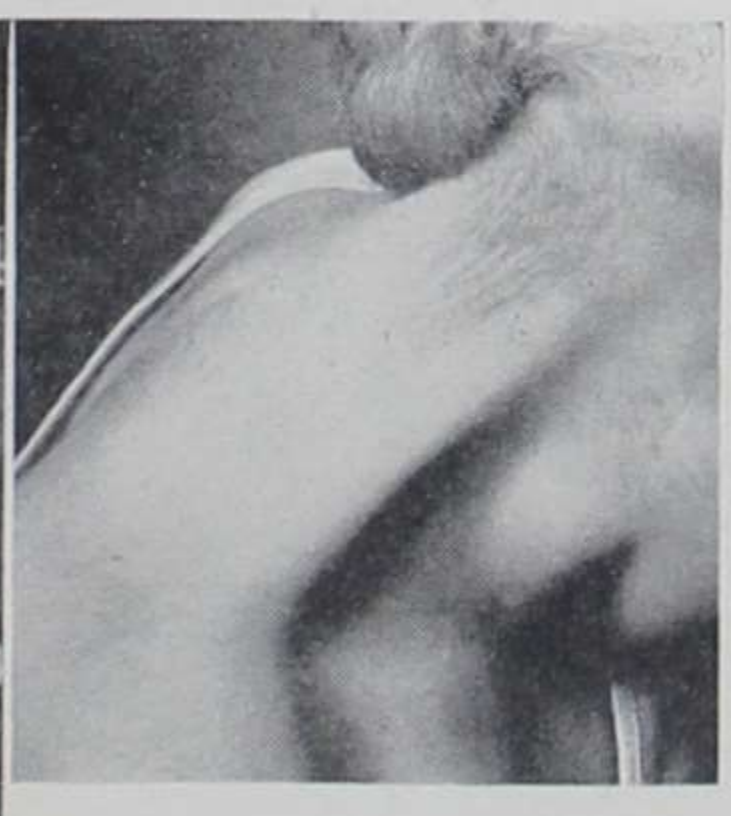


Fig. 80 (left).—Congenital ovarian aplasia with features of the Ullrich-Turner syndrome showing stunted growth.

Fig. 81 (above).—Lateral view of right side of neck; webbing displayed by flexion.

(Courtesy of Russell, A., and Swyer, G. I. M.: Proc. Roy. Soc. Med. 45:596-598, September, 1952.)

tion and sun tanning are evident for the first time. Her complete freedom from other multiple congenital anomalies, cardiovascular, musculoskeletal or ocular, is noteworthy.

[This report suggests that this disease may be familial. Incidentally, the authors quantitated the degree of cubitus valgus in their patients, using as reference data the statistics of Atkinson and Elftman (Anat. Rec. 91:7, 1945).—Ed.]

Turner's Syndrome and Its Relation to Bonnevie-Ullrich Status. F. de Veyt and V. Moia[4] (Univ. of Louvain) report on Turner's syndrome in two young women, aged 18 and 25, of small stature and complaining of amenorrhea. Congenital absence of the ovaries was established in each. At birth, one patient had had edema of the hands and feet which had lasted for several months. Besides small stature and genital infantilism, Turner's syndrome is often characterized by other congenital malformations, of which webbed neck, cubitus valgus and aortic coarctation are most typical.

Studies of the various malformations, particularly the congenital edema, localized at the nape of the neck and in hands and feet, which persists for several months after birth, supported by genetic investigations, have led to a credible hypothesis of pathogenesis of the malformations. Ullrich described a group of congenital anomalies (Bonnevie-Ullrich status) in newborns and very young children which forces the basis of Turner's syndrome in the adolescent. Bonnevie's experimental studies clarified the pathogenesis of the two syndromes. Using the Bagg-Little mouse (myencephalic bleb), a mutation with malformations of the head and the extremities produced by irradiation, she proved that the anomalies arise from exudation of cerebrospinal fluid under the skin of the nape. In the normal mouse embryo, the fluid issues through a temporary orifice at the level of the fourth ventricle, anterior foramen or foramen of Weed, collects under the epidermis and is resorbed. In the embryo of the Bagg-Little mouse, cerebrospinal fluid accumulates excessively in the region of the nape and forms a vesicle or bleb. The bleb migrates under the skin toward the lateral walls of the head, the face, trunk and extremities. Stagnating fluid compresses and disorganizes the young tissues, causing permanent deformities. Application of this theory of exudation and migration of cerebrospinal fluid in man would plausibly explain the genesis of the multiple malformations encountered in Turner's and the Bonnevie-Ullrich syndromes.

In the two cases reported, treatment with large doses of synthetic estrogens (ethinyl estradiol) resulted in development of secondary sexual characteristics and establishment of an artificial cycle, to the great psychic benefit of the patients.

(4) Ann. endocrinol. 12:1111-1118, 1951.

Estrogens

Responses of Vaginal Epithelium of Postmenopausal Women to Single Doses of Estrogens. Ann M. Shearman, Mildred Vogel and Thomas H. McGavack[5] (New York Med. College) serially examined the vaginal smears of 150 women, aged 41-85, to establish correlation between size of estrogen dose, age of subject, intensity of effect, duration of action and lag-time (the time elapsing between administration of a potent preparation and the first appreciable change in the vaginal smear). Vaginal smears were obtained before injection and at 12-24 hour intervals after administration of a single dose of an estrogen. Observation periods ranged from 96 hours to 4 weeks. The estrogens used were: estradiol in sesame oil, 1-3 mg.; estradiol in propylene glycol, 1-2 mg.; estradiol in aqueous suspension, 0.5-1 mg.; estradiol dipropionate in sesame oil, 1-5 mg.; estradiol benzoate in peanut oil, 1 mg.; estradiol benzoate in propylene glycol, 1-2 mg.; estradiol benzoate (1 mg.) and estradiol (1 mg.) in sesame oil; estradiol benzoate (1 mg.) and estradiol (0.5 mg.) in propylene glycol; estradiol benzoate (2 mg.) and estradiol (1 mg.) in propylene glycol; estrone in aqueous suspension, 1-4 mg., and estradiol cyclopentyl-propionate in sesame oil, 1-5 mg.

In 100 subjects lag-time ranged from 24 to 180 hours. Neither the patient's age nor the amount of hormone administered was apparently a factor. Duration of follicular reaction varied from 24 to 480 hours. In general, higher doses produced alterations of longer duration. Age was apparently not a factor in duration of response.

There was an inverse relation between the patient's age and the height of the follicular reaction. The amount of hormone injected did not alter the inverse relation between age and intensity of effect.

Relative Duration of Action of Natural and Synthetic Estrogens Administered Parenterally in Women with Estrogen Deficiency was measured by J. Ferin[6] (Univ. of Louvain). Esters of estrogens were given in 5 mg. doses every three days for four doses; emulsions and suspensions of natural estrogens were given in two doses of 10 mg. each within nine days. The interval between cessation of treatment and beginning of

(5) J. Gerontol. 7:549-554, October, 1952.
(6) J. Clin. Endocrinol. 12:28-35, January, 1952.

withdrawal bleeding was used as a gross indication of duration of action.

The estrogens tested are listed in order of increasing duration of action (range given in days): (*a*) estradiol 3-benzoate, estradiol 3-furoate, diethylstilbestrol dipropionate and diacetate, in oil solution (7-10); (*b*) estradiol dipropionate in oil solution (12-16); (*c*) estradiol 17-caprylate and estradiol 3-benzoate 17-n-butyrate, in oil solution (14-23); (*d*) diethylstilbestrol n-dibutyrate in oil solution, diethylstilbestrol difuroate in small crystal oil suspension (17-26); (*e*) estradiol 3-benzoate in aqueous emulsion (28-34), and (*f*) estradiol 3-benzoate in microcrystalline aqueous suspension and diethylstilbestrol difuroate in large crystal oil suspension (30-79).

Storage of Estrogen in Human Fat after Estrogen Administration was studied by Robert B. Greenblatt and Nelson H. Brown[7] (Med. College of Georgia). Preliminary experiments in rats revealed that hexestrol was not stored in body fat but that tri-p-anisyl-chloroethylene (tace®) was. Before surgery, 11 normal women scheduled for laparotomy received tace,® estrone, estradiol or stilbestrol. Subcutaneous fat was obtained at operation, extracted with benzene and alcohol and assayed by the mouse uterine weight method for estrogenic activity. Such activity was found only in fat from tace®-treated patients. Because of nutritional implications, fat from a chicken caponized with stilbestrol was examined but showed no estrogenic activity.

[Roosters are caponized by the implantation of a small pellet of stilbestrol in the neck; the neck should be severed below this point when the bird is killed. As shown in this article, in these circumstances the consumer is in no danger of accidentally ingesting estrogen. Some difficulty has been experienced, however, by animal growers, particularly those who raise minks, who have used the head and neck for food for their animals.—Ed.]

Estrogenic Effect of Tri-P-Anisylchloroethylene (Tace®) in the Human Postmenopausal Female. From studies on 19 women, aged 50-85, Irving Rothchild and Harry Keys[8] (Ohio State Univ.) found that the minimal effective oral dose of tace® required for virtually complete cornification of the postmenopausal vagina is 24-48 mg. administered in four daily doses of 6-12 mg. Similar doses administered on alternate

(7) Am. J. Obst. & Gynec. 63:1361-1363, June, 1952.
(8) Proc. Soc. Exper. Biol. & Med. 81:539-540, November, 1952.

days did not induce much cornification of the vaginal mucosa but led to some growth of the intermediate cell layers. Duration of effect of these minimal doses was not remarkably different from that of other estrogens given orally (ethinyl estradiol, dienestrol), but it is possible that the prolonged effect reported for tace® appears only with doses greater than the minimal ones.

The maximal effect of this drug lasted about one week from the time of the last dose. It appeared two to six days after the last dose was given.

Clinical Assay of New Synthetic Estrogen: Vallestril. M. I. Sturnick and S. L. Gargill[9] (Harvard Med. School) administered a new synthetic estrogen (Fig. 82) to 28 women with severe menopausal symptoms, 1 young woman with acne vulgaris, 3 women with postmenopausal osteoporosis and 1 elderly man with prostatic cancer and osseous metastases.

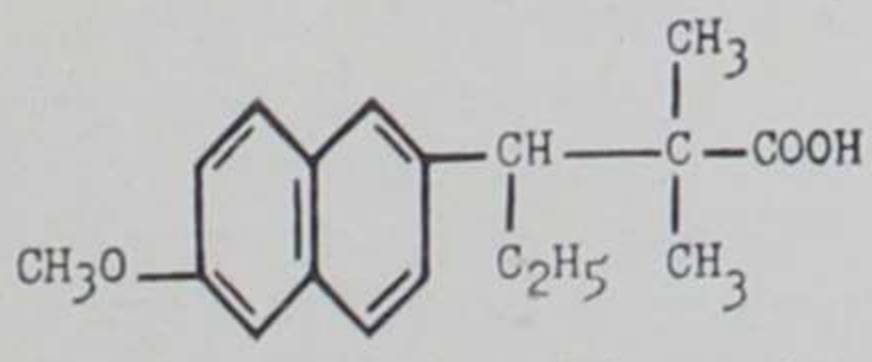


Fig. 82.—3-(6-methoxy-2-naphthyl)-2-2-dimethylpentanoic acid (vallestril). (Courtesy of Sturnick, M. I., and Gargill, S. L.: New England J. Med. 247:829-834, Nov. 27, 1952.)

Vallestril was given orally, usually in doses of 4.5 mg. daily, increased to 6 or 7.5 mg. daily if there was no response. It was necessary to give as much as 9 mg. in two cases. In four patients it was possible to reduce the dose gradually to as little as 1.5 mg. daily and to maintain an asymptomatic state for about a month. Although the dosage necessary to control postmenopausal osteoporosis or prostatic cancer was comparable with that of diethylstilbestrol, which these patients had used previously, the menopausal group required considerably greater amounts of vallestril than of any other synthetic or natural estrogen.

Twelve of the menopausal women had an excellent result, 8 a good response, 5 fair improvement and 3 no relief. The drug was effective in all patients with postmenopausal osteoporosis and did not produce uterine bleeding. It was effec-

(9) New England J. Med. 247:829-834, Nov. 27, 1952.

tive in the patient with prostatic carcinoma without causing gynecomastia, which had been severe while he was taking diethylstilbestrol. One patient became nauseated while taking 7.5 mg. daily. No other evidence of toxicity was encountered and no patient had withdrawal bleeding.

The estrogen produced vaginal cornification, but no consistent correlations were observed between dosage and degree of cornification or between clinical improvement and changes in vaginal epithelium. No alteration in uptake of radioactive iodine by the thyroid gland was observed in two patients who had taken therapeutically effective doses of vallestril for several weeks. Thus, vallestril does not appear to suppress thyrotrophin secretion by the pituitary.

Vallestril compared favorably with other estrogens in effectiveness and seemed superior to most in its lack of side effects. The failure to produce withdrawal bleeding may be due to the fact that the doses were not sufficiently great, yet therapeutic results were satisfactory. It was possible to use vallestril in patients who had had alarming vaginal bleeding from other estrogens. For this reason alone, vallestril is preferentially indicated in therapy of the menopausal syndrome and in other conditions in which estrogens have value.

[Vallestril is a derivative of allenolic acid, which was named in honor of Dr. Edgar Allen who, with Dr. E. A. Doisy, pioneered in endocrine biochemistry. Dr. Doisy's name has also been used as the basis for the name of a group of compounds derived from "doisynollic" acid.—Ed.]

Recent Advance in Estrogenic Therapy: II. Walter J. Reich, Mitchell J. Nechtow, Alvin M. Kurzon and M. Wm. Rubenstein[1] (Chicago) investigated the clinical effectiveness of piperazine estrone sulfate (PES) in giving relief to 100 women with menopausal symptoms and in inhibiting postpartum lactation in 50 patients.

Menopausal patients with mild symptoms received initial doses of 0.75-1.75 mg.; those with moderately severe symptoms received from 1.5 mg. upward daily, and those with severe symptoms, 3-6.75 mg. daily. Therapeutic results are presented in the table. Satisfactory responses were obtained in 95% of the patients with mild and moderately severe manifestations. Despite cyclic therapy, treatment had to be dis-

(1) Am. J. Obst. & Gynec. 64:174-178, July, 1952.

continued in two with severe symptoms because of profuse withdrawal bleeding.

Six patients with severe symptoms who did not respond to treatment with PES alone and an additional 19 with mild to moderately severe menopausal symptoms were treated with combined PES and methyltestosterone. Tablets containing 0.75 mg. PES and 5 mg. testosterone and 1.5 mg. PES and 10 mg. testosterone were used. Only 5 of the previously refractory patients responded and 17 (89.5%) of the 19 additional patients, thus indicating that relief from menopausal symptoms is influenced more by dose than by type or combination of medication and that there is no significant advantage to the PES-testosterone regime.

The women used to study the effect of PES on postpartum

RESULTS OF THERAPY IN 100 MENOPAUSAL PATIENTS

GROUPS	NO.	SATISFACTORY	NOT SATISFACTORY	%
Mild	44	43	1	95.4
Moderately severe	36	33	3	91.6
Severe	20	13	7	65.0
Total	100	89	11	89.0

lactation were given 18-24 mg. PES daily for three days, followed by 12 mg. daily for the next two days. Medication was started within 24 hours of delivery in 25 patients and after onset of lactation in 25. Results indicate that PES will completely relieve 9 out of 10 patients with lactation engorgement if treatment is started within 24 hours of delivery and that this percentage rapidly diminishes as the interval between delivery and therapy increases.

[The dosage and efficacy of this compound are similar to those of conjugated equine estrogens, NNR (premarin,® conestron,® lynoral®). These are extremely useful compounds, for they rarely produce nausea. They have the economic disadvantage of being more expensive than other estrogens; also, some patients are offended by the odor of the naturally occurring conjugated equine estrogens extracted from pregnant mare's urine. This derivative is reportedly free from unpleasant odor.—Ed.]

Topical Estrogens: Clinical Effects and Side Actions. Irving Shapiro[2] (Newark, N. J.) treated 31 men and 52 women with topical estrogens in concentrations of 1.0-2.5 mg./cc. of 70% alcohol or gram of vanishing cream base. Average daily dose was 4 cc. of alcoholic lotion or 4 Gm. of ointment. Only

(2) J. Clin. Endocrinol. 12:751-760, June, 1952.

patients with cutaneous disease resistant to other therapeutic measures were chosen for study.

Results were considered excellent in 10 of 16 females and 6 of 10 males with acne vulgaris who were treated with estrogen cream. Treatment was continued for periods of one to seven months. Good results were obtained in 15 of 26 women and 10 of 18 men when estrogen lotion was applied for 1½-5 months. Applications were made to the face only, leaving chest and back lesions, when present, untreated. In all cases in which the face improved, the other areas remained unchanged.

Of seven patients with premature male-pattern baldness and seborrhea treated, there was cessation of hair loss in two of three men and all four women. Two of three patients with keratoderma climactericum responded well as did three patients with pruritus vulvae.

In 10% of patients clinical improvement was associated with occurrence of pruritus. Gynecomastia in two patients subsided promptly when estrogens were withheld. Withdrawal bleeding, "spotting" and delayed menses disappeared when treatment was stopped. No change was noted in libido, pigmentation, hirsuties, size and frequency of erections or coitus.

Diethylstilbestrol in Treatment of Senile Sebaceous Adenoma. Any substance that increases (or decreases) sebaceous gland secretion is known to do so by increasing (or decreasing) the size of the sebaceous gland. Androgens increase and estrogens decrease the size and number of sebaceous glands. Walter C. Lobitz, Jr., and Donald P. Cole[3] (Dartmouth Med. School) studied these effects in a patient.

Man, 62, had for 17 years noted a gradual increase in number and size of cystic lesions from which cheesy material could be expressed. He had had oily skin with prominent sebaceous gland openings and comedones since puberty. For seven years, the yellow oil from the face had been so profuse that his pillow slip had to be changed daily. Both his father and paternal grandmother had had similar lesions.

When examined, strikingly oily skin on face and neck, upper part of chest and back, dilated sebaceous gland openings umbilicated on their surfaces, mild erythema and telangiectasia were noted (Fig. 83). He was given 1-5 mg. diethylstilbestrol daily by mouth and erythema, telangiectasia, seborrhea and tumor size promptly dimin-

(3) A.M.A. Arch. Dermat. & Syph. 66:358-362, September, 1952.

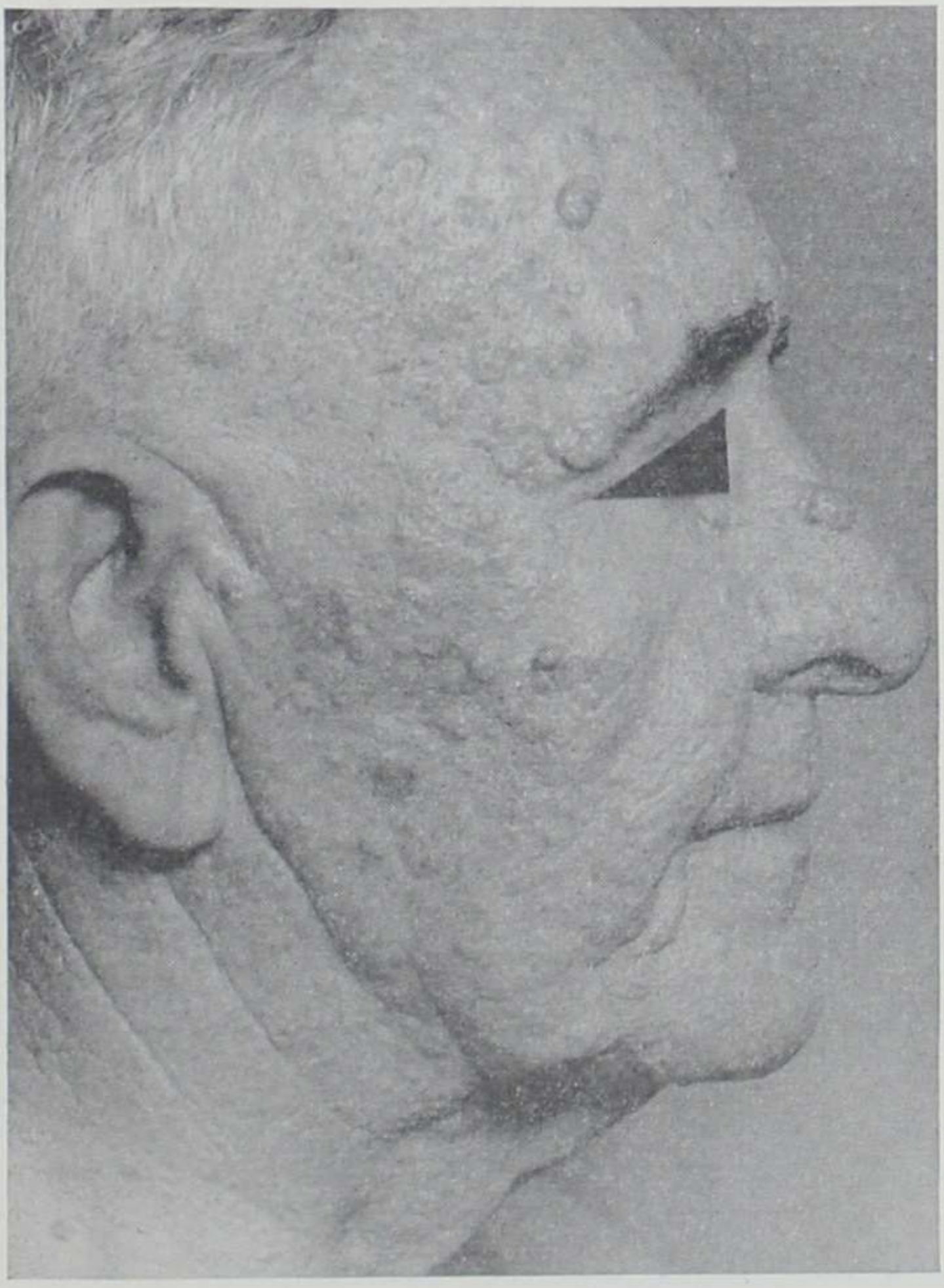


Fig. 83.—Patient with senile sebaceous adenoma before therapy. (Courtesy of Lobitz, W. C., Jr., and Cole, D. P.: A.M.A. Arch. Dermat. & Syph. 66:358-362, September, 1952.)

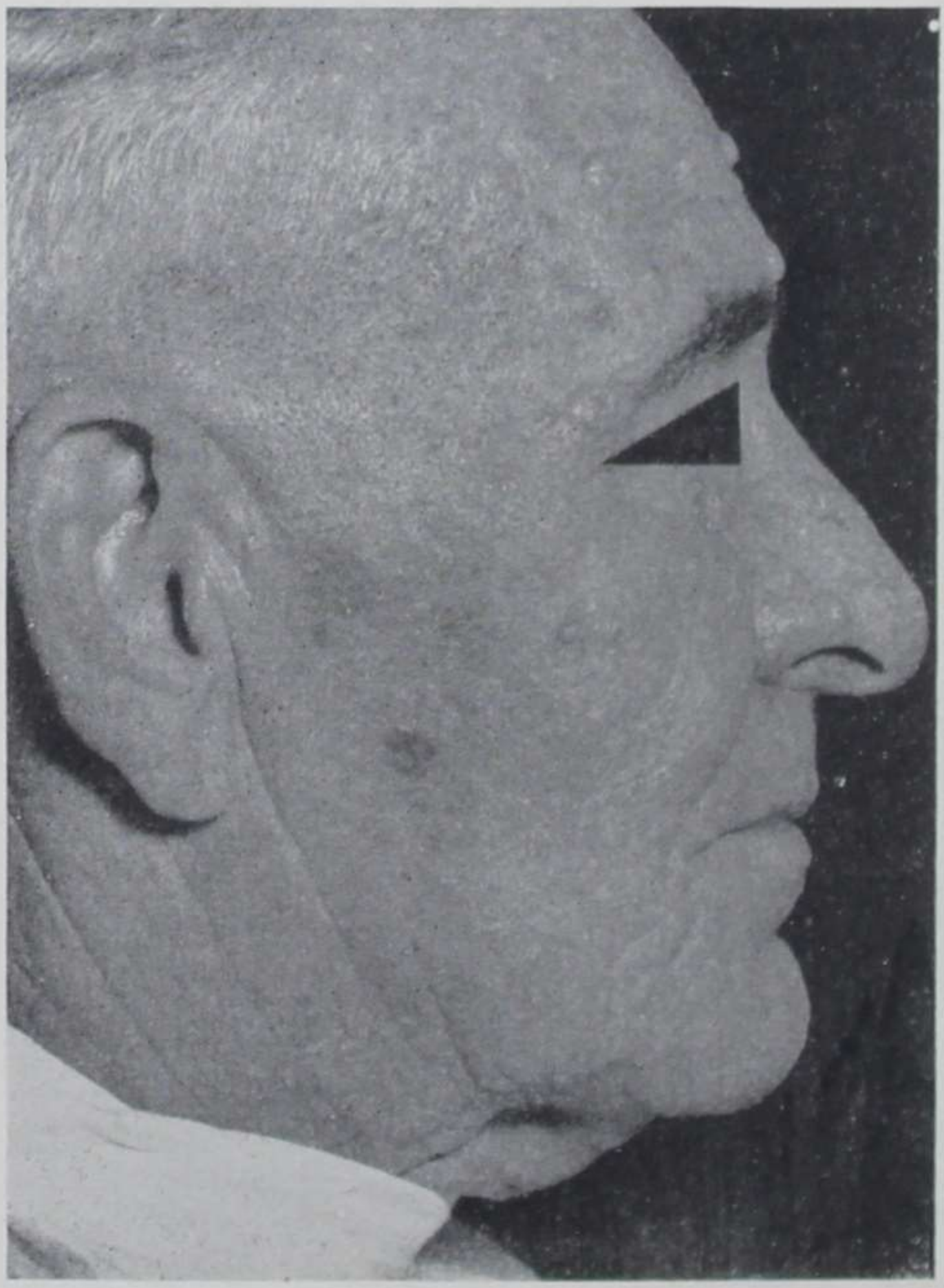


Fig. 84.—Same patient as in Fig. 83, after about 18 months of therapy. (Courtesy of Lobitz, W. C., Jr., and Cole, D. P.: A.M.A. Arch. Dermat. & Syph. 66:358-362, September, 1952.)

ished (Fig. 84). Side reactions included breast soreness and enlargement and a loss of libido and erections. Although reduced, the glands never returned to normal size; the larger ones were therefore destroyed by electrocoagulation. Pillow staining disappeared.

Gynecomastia with Pigmentation in 4 Year Old Male Following Stilbestrol Exposure is reported by Margaret Prouty[4] (Madison, Wis.).

Boy, 4, was examined during an attack of tracheobronchitis. He had been examined repeatedly since birth and had been in good health until this attack. Examination revealed striking enlargement of the breasts. The nipples were well developed, with areolae show-

(4) Pediatrics 9:55-57, January, 1952.

ing the pigmentation of a gravid female near term (Fig. 85). The mother had noted the breast enlargement five months previously. At about the same time, pigmentation of the navel, in the linea nigra and on the scrotum was noted. The hips had the feminine type of fat distribution, and there was a light growth of axillary and pubic hair, the latter in a straight, feminine line. For several weeks before the symptoms developed the mother had been packaging stil-

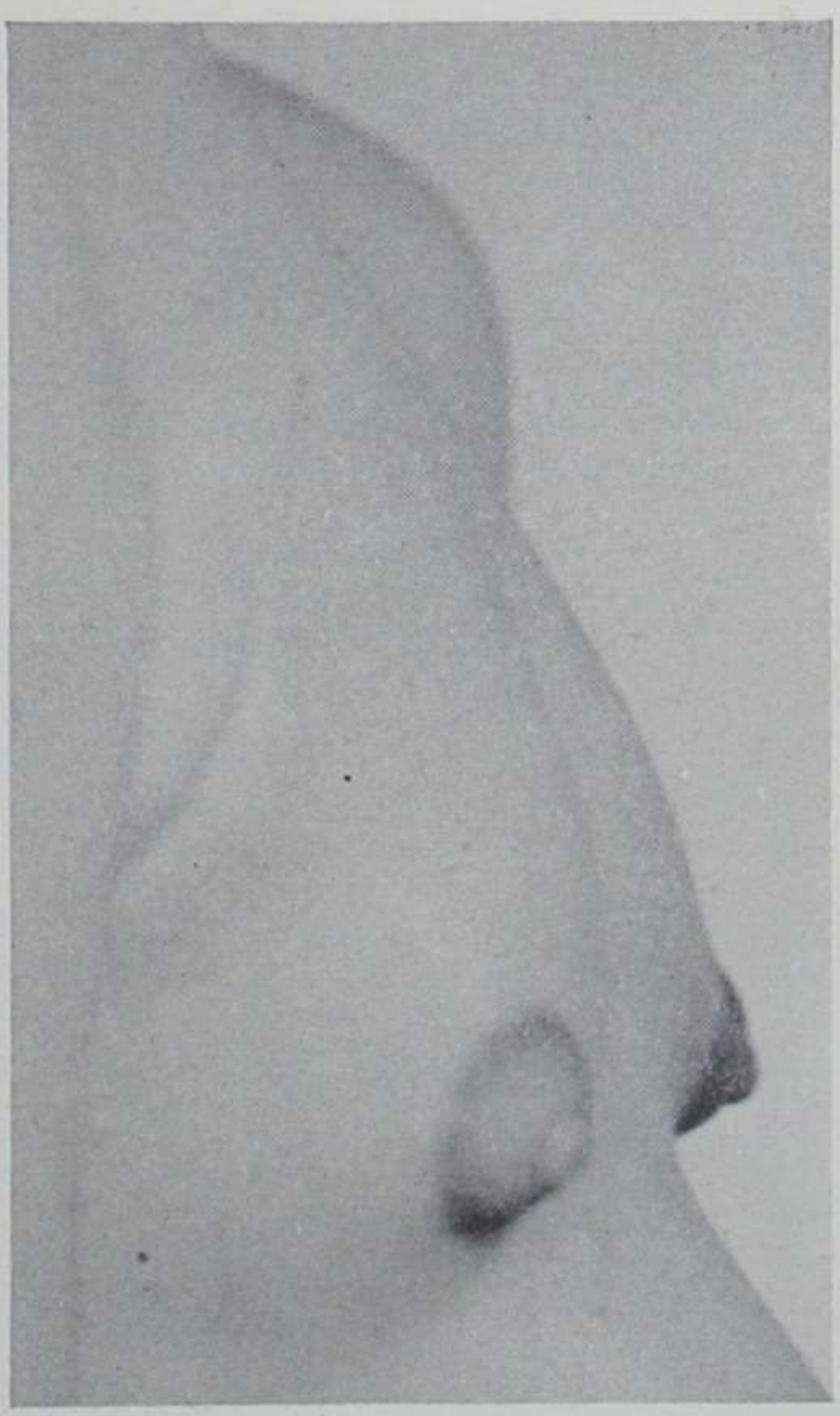


Fig. 85.—Gynecomastia with pigmentation due to stilbestrol exposure in boy, 4. (Courtesy of Prouty, M.: Pediatrics 9:55-57, January, 1952.)

bestrol pellets. She did not change her clothing on leaving the laboratory. At least a month after the breast enlargement was noted, a packaging machine was brought to the home and several thousand pellets were processed daily during rush periods. The child was usually with his mother while she worked. Dust from the stilbestrol was noted in the air repeatedly. At about the same time the mother had severe, continuous rhinitis and irregular and almost continuous menstrual bleeding. A daughter, 10, also showed pigmentation and enlargement of the breasts, and she menstruated.

Physical examination of the boy revealed no abnormalities other than those described. Results of routine blood and urine studies were normal. Gonadotrophin excretion was less than 1 R.U. daily. When the patient was first seen, urinary excretion of 17-ketosteroids was 6.6 mg./24 hours; a week later, 2 mg., and two weeks later, 1.22 mg. The Thorn test showed a total eosinophil count of 250 cells/cu. mm., which dropped to 133 after injection of 15 mg. ACTH. X-rays showed bone age to be normal and the sella turcica regular in outline. There was no evidence of increased intracranial pressure. Retrograde pyelograms and air injection of the peritoneum did not reveal a tumor mass or enlargement of the adrenals, liver or spleen.

The mother was requested to stop working with stilbestrol. She cleaned the house thoroughly. Two weeks later, she no longer had rhinitis and subsequent menstrual periods were regular. The daughter did not menstruate again, and pigmentation of the breasts decreased over four to five months. The patient showed obvious regression of both gynecomastia and pigmentation within three weeks, and at the last examination these conditions were present only in faint degree.

Signs of Sexual Precocity in Male Infant Due to Estrogenic Ointment. Breast enlargement, sometimes of considerable magnitude, is commonly seen in the newborn; it is also observed in boys during puberty. Between these periods it may be seen with a rare adrenal tumor. Lennart Hesselvik[5]

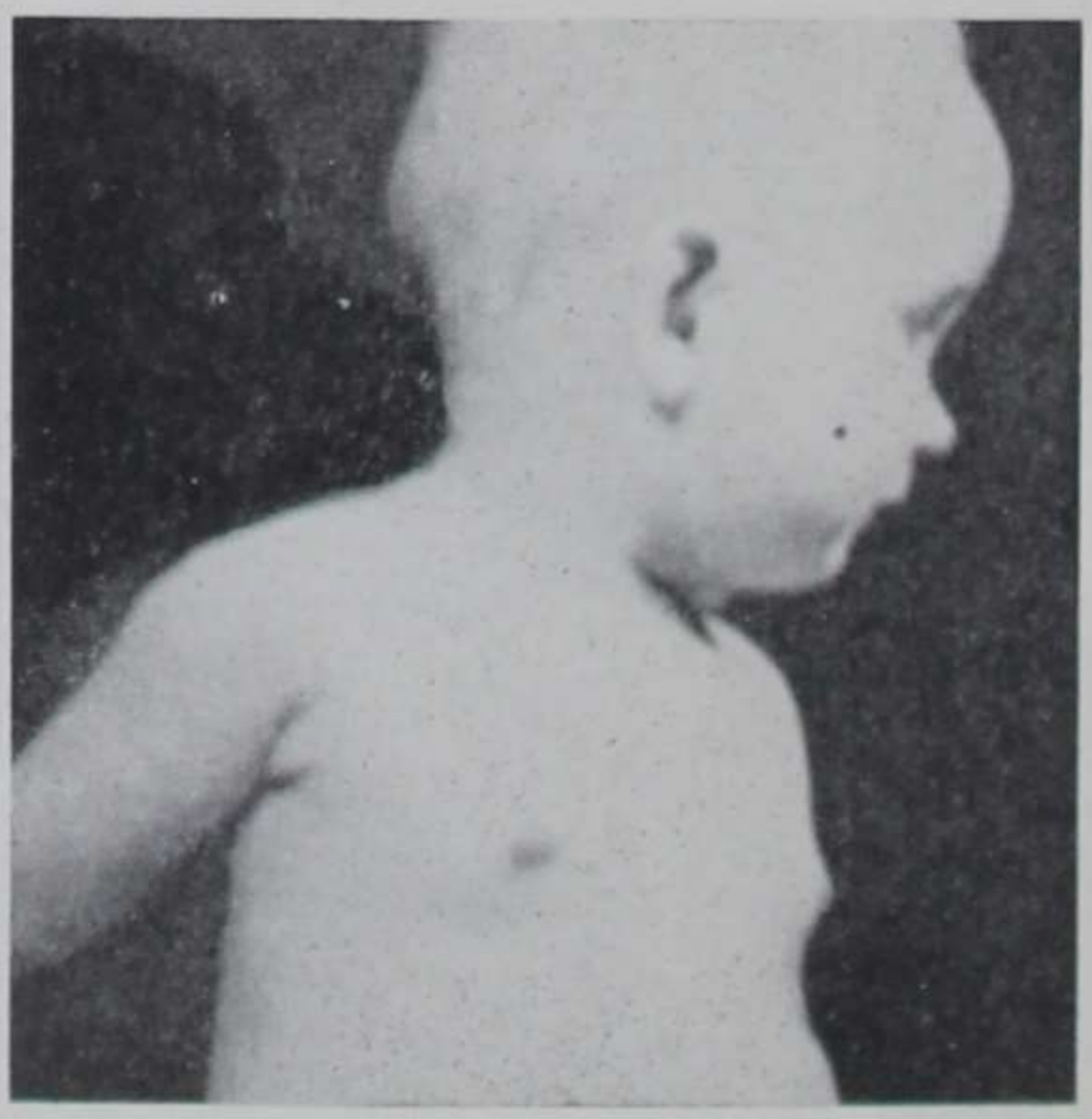


Fig. 86.—Gynecomastia and pigmentation in 10 month old boy. (Courtesy of Hesselvik, L.: Acta paediat. 41:177-185, March, 1952.)

(5) Acta paediat. 41:177-185, March, 1952.

(Uppsala) reports a case of gynecomastia of a different origin.

Boy, aged 10 months, was hospitalized because of considerable growth of the breasts during the preceding five months (Fig. 86). This was associated with increasing pigmentation of the areolae, penis, scrotum, anal area and linea abdominalis. Pubic hair, up to 5 mm. in length, was also present. All laboratory tests, including those of adrenal function, had normal results. The urine contained 0.9 mg. neutral 17-ketosteroids in 24 hours, and no estrogenic substances were found. Skull x-rays and bone age were normal. Since evidence of adrenogenital syndrome was lacking, scrutiny of the home was made. The mother was found to be using an estrogen ointment for eczema of the hands, applying it generously each time she washed her hands before nursing the child. During the previous six months she had used 300 Gm. of the ointment which contained 0.1% diethyldioxistilbene. When she stopped using the ointment, the child's gynecomastia and pigmentation regressed within three weeks, and he was entirely normal after six months.

The experimental daily application of 0.7 Gm. of this ointment to a 5 month old boy with a large myelomeningocele produced increased pigmentation in two weeks, gynecomastia in two months and pubic hair in three months.

[The preceding two cases point out the extreme sensitivity of small children to sex hormones. Judging by his clinical appearance, I should have said that the second patient had heterosexual or pseudosexual precocity rather than sexual precocity, since the stigmas were those of feminization. It must be admitted that androgens can produce gynecomastia; however, in clinical syndromes of isosexual precocity associated with gynecomastia, the excretion of 17-ketosteroids is greatly increased, which was not true in this child.—Ed.]

Metabolism of Estrogens by Human Liver Studied in Vitro. Henry J. Tagnon, S. Lieberman, Phyllis Schulman and Alexander Brunschwig[6] (Sloan-Kettering Inst.) conducted an experiment to determine whether patients with uterine carcinoma have a deficiency of metabolic function of the liver. Liver slices obtained at biopsy on 12 patients were incubated with 17-β estradiol for three hours. Liver slices from patients with cancer and from those with serious liver disease both had a normal ability to metabolize the estrogen. The results indicate that the average human liver (15,000 Gm.) could metabolize enormous amounts of 17-β estradiol/24 hours in vitro. Data regarding rates in vivo are lacking.

[These studies of the metabolism of estrogens by human liver in vitro parallel Zondek's observation that estrogens are conjugated in a normal fashion by patients with severe liver disease (Zondek and Black, J. Clin. Endocrinol. 7:519-534, July, 1947). The isomer of estradiol used in this

(6) J. Clin. Invest. 31:346-350, April, 1952.

study is designated beta-estradiol, using the term of Fieser and Fieser. Unfortunately, in the pharmacologic literature the same isomer is designated alpha-estradiol; in both instances, it is the active estrogenic isomer which is meant.—Ed.]

Estrogen-Induced Regression of Coronary Atherosclerosis in Cholesterol-Fed Chicks. Ruth Pick, Jeremiah Stamler, Simon Rodbard and Louis N. Katz[7] (Michael Reese Hosp.) found that estrogen (estradiol benzoate, 1 mg. daily intramuscularly) reversed previously induced coronary atherosclerosis in cholesterol-fed cockerels, despite the continued presence of atherogenic stimulus in the diet. Aorta atherogenesis remained unaffected. There was clearing of both lipidosis and fibrosis from the coronary vessels. The estrogen-induced regression occurred in the presence of continued pronounced hypercholesteremia, reversal of previously elevated total cholesterol-lipid phosphorus ratios to normal levels and persistent aorta atherogenesis.

The mechanism of this regression is obscure. Several possibilities are suggested. (1) The estrogen may induce lipophage activity which effects movement of lipids toward the adventitia and the perivascular tissue. (2) Estrogen may decrease permeability of the endothelium for lipids. (3) It may alter the plasma lipid-lipoprotein complexes. These possible mechanisms do not explain the lack of effect on the aorta.

Progesterone

Progesterone Metabolism: I. Pregnanediol Excretion in the Menstrual Cycle. Richard H. Fischer, Stanley P. McColgan and Albert L. Chaney[8] (Doctors Hosp., Washington, D. C.), utilizing a new technic for assay of free urinary pregnanediol rather than the pregnanediol complex, studied six women during normal menstrual cycles. The amount excreted ranged from 0 to 49.8 mg./cycle, with a maximum on the 7th or 8th day before onset of the next cycle. Free pregnanediol excretion does not necessarily cease before onset of menstruation, in contrast to Venning and Browne's observations on the pregnanediol complex. Figure 87 illustrates this in a married woman, 23, who had never been pregnant and who had had regular 25 day periods with 5 days of flow since age 12. Pregnanediol

(7) Circulation 6:858-861, December, 1952.
(8) Am. J. Obst. & Gynec. 63:613-619, March, 1952.

first appeared in the urine on day 19 and reached a maximal level of 6.5 mg. on day 24. It was still present in the urine on the day of menstruation. A total of 49.8 mg. was excreted.

There are no clinical data which can explain the discrepancies in the quantity of pregnanediol excreted in some cycles. Another unexplained observation, made on these six women and six additional ones, is that in no instance did the maximal

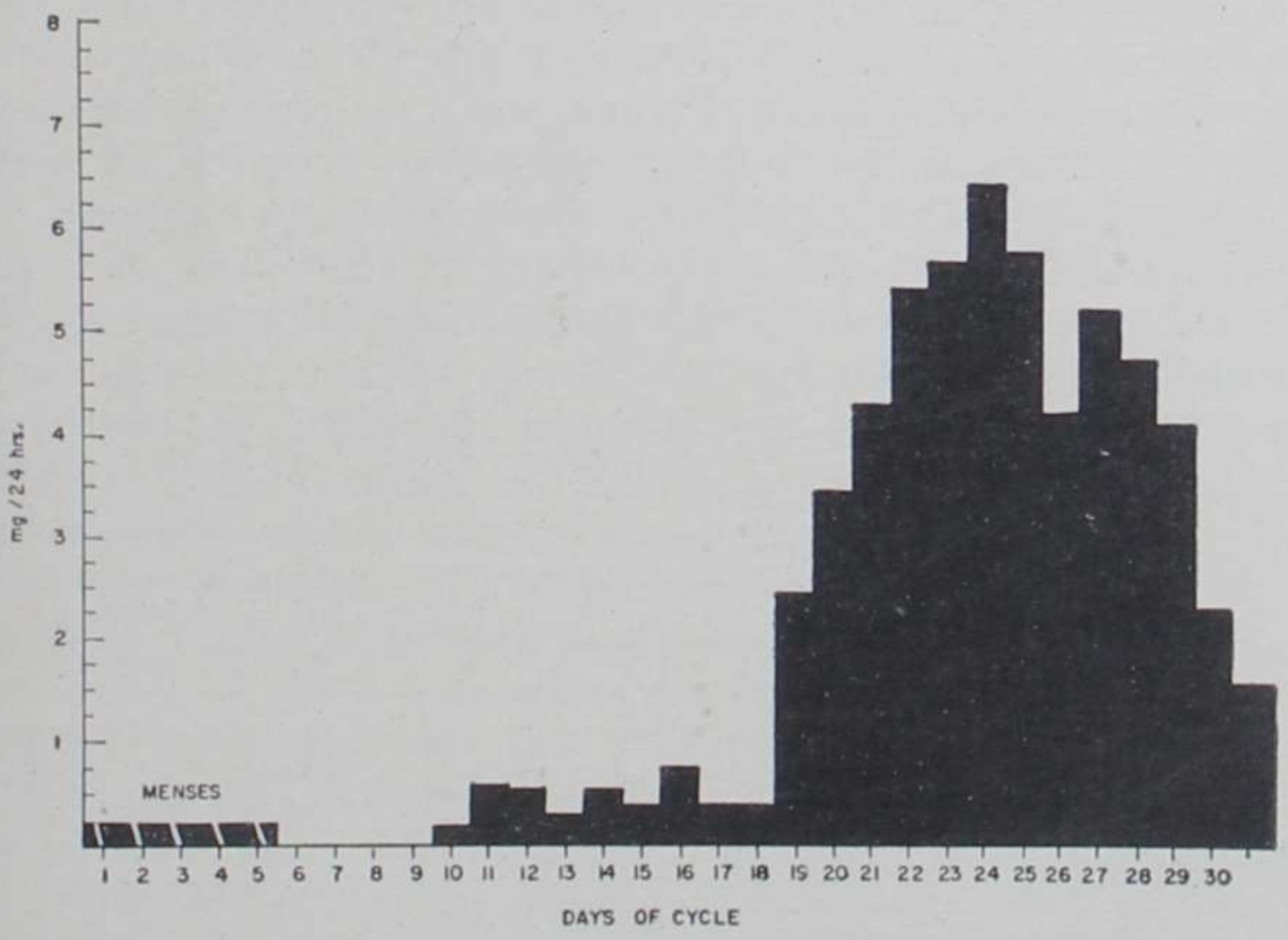


Fig. 87.—Pregnanediol excretion during menstrual cycle of one subject. Base line average was 0.45 mg./24 hours; total excretion, 49.8 mg. (Courtesy of Fischer, R. H., *et al.*: Am. J. Obst. & Gynec. 63:613-619, March, 1952.)

amount of pregnanediol excreted by a single woman approach the minimum excreted by a married woman. Further study is indicated to evaluate possible hormone differences which may result from sexual activity.

Habitual Abortion: Further Observations on Prophylactic Value of Progesterone Pellet Implantation. P. M. F. Bishop (Postgraduate Med. School, London) and N. A. Richards[9] (Chelsea Hosp. for Women, London) treated 40 women who had had two or more successive miscarriages each within the first five months of pregnancy with implantation of six 25 mg.

(9) Brit. M. J. 1:244-246, Feb. 2, 1952.

pellets of progesterone. An earlier series of 45 patients so treated has been reported. If pregnancy proceeded to 28 weeks, the result was defined as successful.

Malpas calculated expected spontaneous cure rate after three abortions at 7-27%, and after four at 0.3-6%. Eastman calculated spontaneous cure rate after three abortions at 16%. Of the combined total of 85 patients treated by the authors, 32 had had at least three miscarriages within the first five months of pregnancy; 23 (72%) produced live children during the treated pregnancy. Figures for three earlier abortions were 76% live births, and for more than three, 67%. This is significantly above estimates of Malpas and Eastman. It parallels Smith's results with 60 patients after three or more abortions, of whom 46 (77%) were successfully treated with diethylstilbestrol, starting with 5 mg. daily at the 6th week and increasing to 115 mg. daily at the 35th. The essential therapeutic mechanism may be the same in both series: whereas Smith attempted to stimulate secretion of placental hormones and especially progesterone by means of extrinsic estrogen, the authors provided progesterone which was intrinsically lacking by extrinsic means.

Of 32 patients with three or more previous abortions reported by Bevis, 26 (81%) gave birth to live children. They were given no effective treatment, but underwent a series of elaborate investigations. Accepting these results and the estimates of Eastman and Malpas, one must logically conclude that 81 minus 16%, or 65%, of patients with more than three previous abortions have aborted for psychologic reasons and that any procedure which wins their confidence may be psychotherapeutic and prove successful. It is emphasized, however, that results of the combined series do not indicate that progesterone pellet implantation in the dosage used is harmful in cases of habitual abortion.

Effect of Chorionic Gonadotrophin in Metropathia Hemorrhagica Cystica: Resistant Cases. Tore Wahlén[1] (Malmö, Sweden) found chorionic gonadotrophin to be effective in induction of ovulatory cycles in 82.6% of 46 women under age 45 with metropathia hemorrhagica cystica. Treatment usually consisted of 600 I.U. of pregnyl on five consecutive days. For

(1) Acta endocrinol. 11:67-73, 1952.

chorionic gonadotrophin to produce the desired result, the ovaries must contain follicles capable of responding to the stimulus received from the hormone, i.e., fairly mature follicles.

Treatment is less effective when given after periods of physiologic anovulation, i.e., menarche and puerperium, or in the premenopausal period, when the follicles are often not sufficiently mature to respond. If chorionic gonadotrophin fails to produce the desired effect on women with metropathia hemorrhagica cystica in other stages of reproductive life, estrogen-producing tumors must be looked for.

Of eight patients who did not respond to chorionic gonadotrophin, two were in the puerperium, one was in the menarche, three were in the premenopausal period, one had retarded follicle development and one had an estrogen-producing tumor.

[In this condition, chorionic gonadotrophin is given to stimulate the endogenous production of progesterone from the ovary. Identical results can be obtained by administering progesterone intramuscularly, buccally or, in very large doses, orally. Recent studies have indicated that anhydrohydroxyprogesterone, also known chemically as ethinyl testosterone or pregneninolone (lutocylol,® pranone,® progesterol®), is a reliable agent which can be administered conveniently by the oral route in daily doses of 60-100 mg. If the endometrium has been primed by estrogens (endogenous or exogenous), these progestational compounds (chorionic gonadotrophin, progesterone, or anhydrohydroxyprogesterone) convert the endometrium from a proliferative to a secretory phase. Then, when the agent is withdrawn, the endometrium is sloughed, just as occurs normally in each menstrual cycle. This technic, termed "medical D & C" by Albright, is a useful procedure for demonstrating the presence of estrogen. It is also of value in the treatment of metropathia hemorrhagica; the agent may be given for five to seven days each month to produce withdrawal bleeding. It is interesting that often after the agent is withdrawn, the patient may have several normal ovulatory cycles without medication before reverting to anovulatory cycles and metropathia. Because these steroids can now be given so conveniently, metropathia hemorrhagica is easy to treat. It should be noted that this condition may be symptomatic of other disorders, particularly hypothyroidism, in which case it is most effectively treated by the administration of thyroid substance.—Ed.]

Effect of Chorionic Gonadotrophic Therapy on Human Ovary: Histologic Analysis of Ovary and Endometrium of Women with Metropathia Hemorrhagica Cystica Treated with Chorionic Gonadotrophic Hormones is presented by Per Bergman and Tore Wahlén[2] (Malmö, Sweden, Gen'l Hosp.). Women with this condition have anovular cycles, an indication of continuous estrogenic stimulation without progesterone

(2) Acta endocrinol. 9:69-78, 1952.

action. Ten women with essential uterine hemorrhage with typical endometrial pattern (cystic glandular hyperplasia) were given chorionic gonadotrophin intramuscularly before laparotomy (the operation was usually performed for coexistent uterine myoma). Daily dosage was 600-1,500 I.U. for two to five days to a total 1,800-6,000 I.U. Therapy was begun three to five, and in one instance two, days before operation. Operative specimens were examined histologically for presence and phase of development of corpora lutea. The ovaries of 10 controls with the same condition and endometrial picture but without preoperative therapy were also examined.

In eight women given chorionic gonadotrophin a recent corpus luteum was found in one of the ovaries. The endometrium showed signs of initial secretory changes in two of three women with corpora lutea in the vascularization phase; no secretory changes were noted in those with recently ruptured follicles. In none of the controls was a recent corpus luteum found. These findings suggest that chorionic gonadotrophin is an effective agent for inducing ovulation and corpus luteum formation in women with anovular cycles.

THE TESTES

Probably the most interesting developments in the field of male reproductive physiology in the past year deal with the use of long-acting testosterone preparations. The efficacy of this type of therapy is now established. The chief advantage is that injections are minimized to as few as one a month. These compounds are particularly useful when it is desirable to exert anabolic or androgenic effects if there is little likelihood that the action of the androgen will have to be terminated abruptly.

Potent androgens can now be administered by a variety of routes, including methyltestosterone by the oral route (i.e., swallowed); methyltestosterone or the less effective unesterified testosterone by buccal or sublingual administration; testosterone propionate or unesterified testosterone by intramuscular injection; long-acting testosterone compounds by intramuscular injection, and pellets of testosterone or of testosterone propionate by implantation. In rare cases it may be desirable to produce androgenic or anabolic effects in youngsters by inunction of testosterone compounds. This wide variety of preparations and choice of methods of administration provide the physician with a good many useful tools, all with their proper uses; for example, pellets may be best for a patient who can be seen only every six to nine months; intramuscular administration of long-acting compounds may be best for hypogonadal patients who must be seen at monthly intervals; swallowed or sublingually administered methyltestosterone may be best when hair-trigger control is required

(e.g., when large doses are used and edema or hypercalcemia may be precipitated).

Endogenous secretion of testosterone or a similar hormone can be stimulated by administration of chorionic gonadotrophin. This compound acts similarly on the gonadal interstitium of the two sexes, stimulating the production of progesterone in the female and androgen in the male. Although theoretically the use of chorionic gonadotrophin is the most physiologic means of treating patients with hypogonadotrophic eunuchoidism, practically it accomplishes nothing that cannot be accomplished as well with methyltestosterone administered sublingually, or long-acting testosterone compounds given by monthly intramuscular injection. Chorionic gonadotrophin has also been found to cause antibody formation, with resulting refractoriness. In addition, because it appears to stimulate secretion of estrogens, it is now considered to exert a potentially damaging effect on the testes.

Although infertility is usually not of endocrine origin, the influence of testosterone compounds on spermatogenesis is coming more and more into the realm of office therapeutics. Massive doses of unneeded testosterone compounds undoubtedly suppress spermatogenesis, reduce the sperm count, and produce histologic evidence of damage to the testes. Apparently, however, the damage is only transient, and withdrawal of the agent results in a rebound augmentation of spermatogenesis and an increase in the sperm count. This reaction may be nonspecific, for a similar rebound occurs after withdrawal of estrogens and after the depression of spermatogenesis which occurs in febrile diseases or radiation injury. However, this phenomenon is reported to have value in the treatment of infertility. It should not be assumed that small doses of testosterone compounds also interfere with spermatogenesis. The studies of Beller and Turner (J. Clin. Endocrinol. 9:666, July, 1949) showed that small amounts of testosterone propionate do not decrease, and often increase the sperm counts of healthy young men. When testosterone compounds are administered for anabolic or androgenic effects to patients with deficient testicular secretion, it must be assumed that they act as substitutes for the androgen of the normal testis, which certainly does not damage spermatogenesis.

The search for anabolic steroids devoid of androgenic activity continues, but the perfect compound, one that is as anabolic as testosterone compounds but completely devoid of androgenic activity, has not been found. Several promising compounds have been identified (methylandrostenediol; androstadiene delta 1-2, 4-5, 3, 17 dione; androstadiene delta 4-5, 6-7, 3, 17 dione; androstane 3, 17 diol; testololactone). Methylandrostenediol, which is weakly androgenic and about half as anabolic as methyltestosterone, is the only one to have been given extensive clinical trial. This compound is useful but not ideal. It is to be anticipated that better compounds will eventually be found. As indicated in the section on the Female Reproductive System, the simultaneous administration of estrogens and androgens does not prevent the virilizing effects of the androgen.

The use of testosterone compounds to counteract the catabolic effects of cortisone or corticotrophin is discussed in the section on Cortisone, Hydrocortisone and Corticotrophin; effects of androgens on 17-ketosteroid excretion, in the section on the Adrenal Cortex; their value in the treatment of anterior pituitary insufficiency, in the section on the Pituitary Gland; their use in the treatment of osteoporosis and osteogenesis imperfecta in the section on Parathyroids, Calcium Metabolism and Metabolic Bone Diseases, Interstitial cell tumors of the testis are

included in the section on Sexual Precocity. The effects of chorionic gonadotrophin on 17-ketosteroid excretion in the female are discussed in the section on the Female Reproductive System. The use of testosterone compounds and of methylandrostenediol in the treatment of advanced mammary carcinoma is discussed in the section on the Endocrine Treatment of Neoplastic Diseases.—Ed.

Spermatogenesis

Rebound Phenomenon of Spermatogenic Activity of Human Testis Following Administration of Testosterone Propionate. Norris J. Heckel and James H. McDonald[3] (Chicago) confirm previous observations that although testosterone propionate produces an initial depression of spermatogenesis (often to zero), a rebound phase may follow discontinuation of therapy, so that both sperm count and testicular biopsy

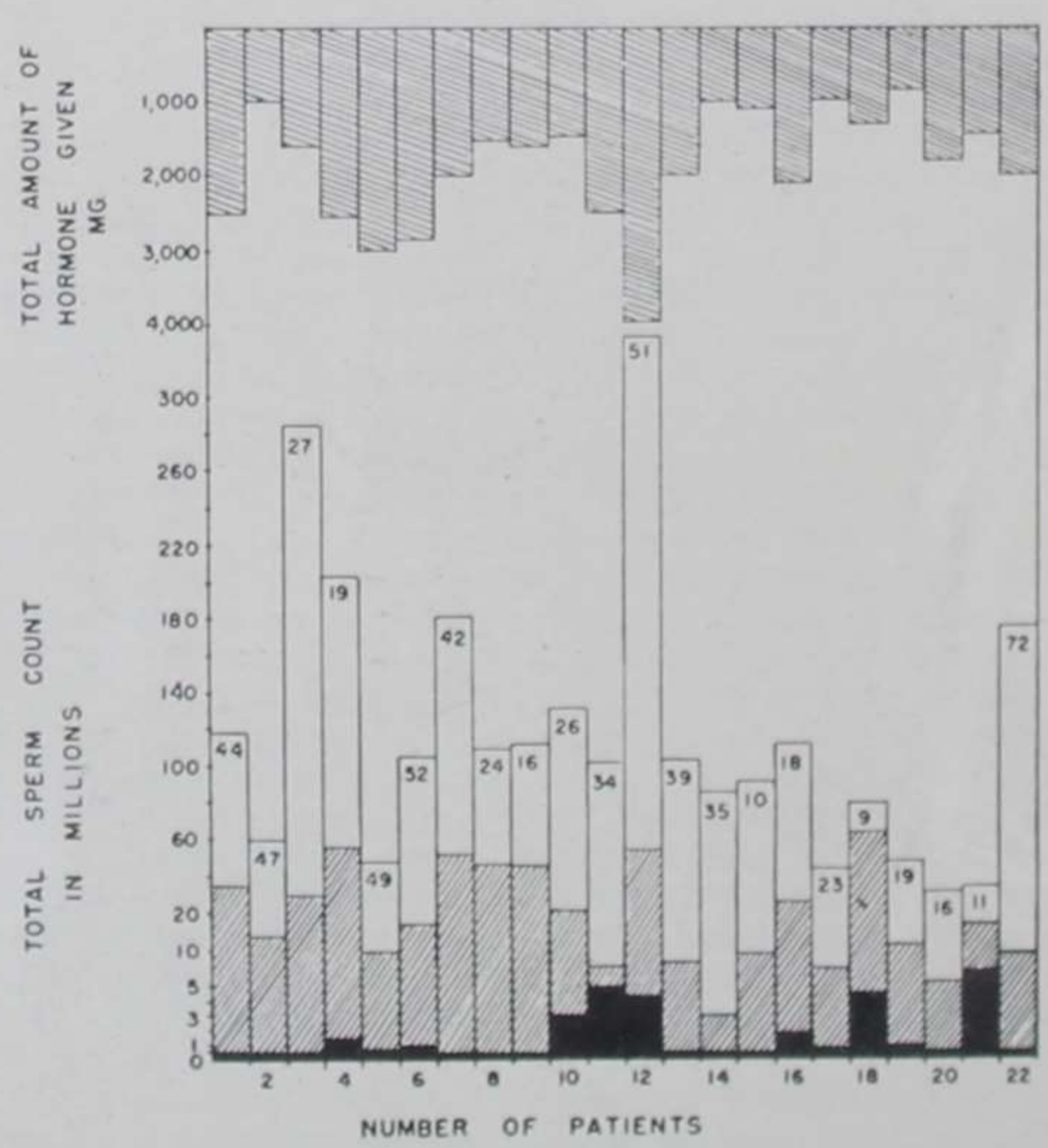


Fig. 88.—Data on 22 patients with rebound phase after treatment with testosterone propionate, 150 mg./week. Total sperm count: before testosterone therapy (shaded), level to which count was depressed (black) and height of rebound after initial depression (white); numbers in columns indicate time in weeks for count to reach rebound height after initial depression. For data on twenty-third patient, see Figure 90. (Courtesy of Heckel, N. J., and McDonald, J. H.: Fertil. & Steril. 3:49-61, Jan.-Feb., 1952.)

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(3) Fertil. & Steril. 3:49-61, Jan.-Feb., 1952.

become more normal than before treatment. Sixty-four men with oligospermia (count below 75,000,000) but otherwise normal were studied by a prefreatment testicular biopsy and several semen analyses. Testosterone propionate or testosterone cyclopentylpropionate was injected intramuscularly three times a week in 50 mg. doses. When sperm counts (made every six to eight weeks) approached zero, therapy was stopped. Of

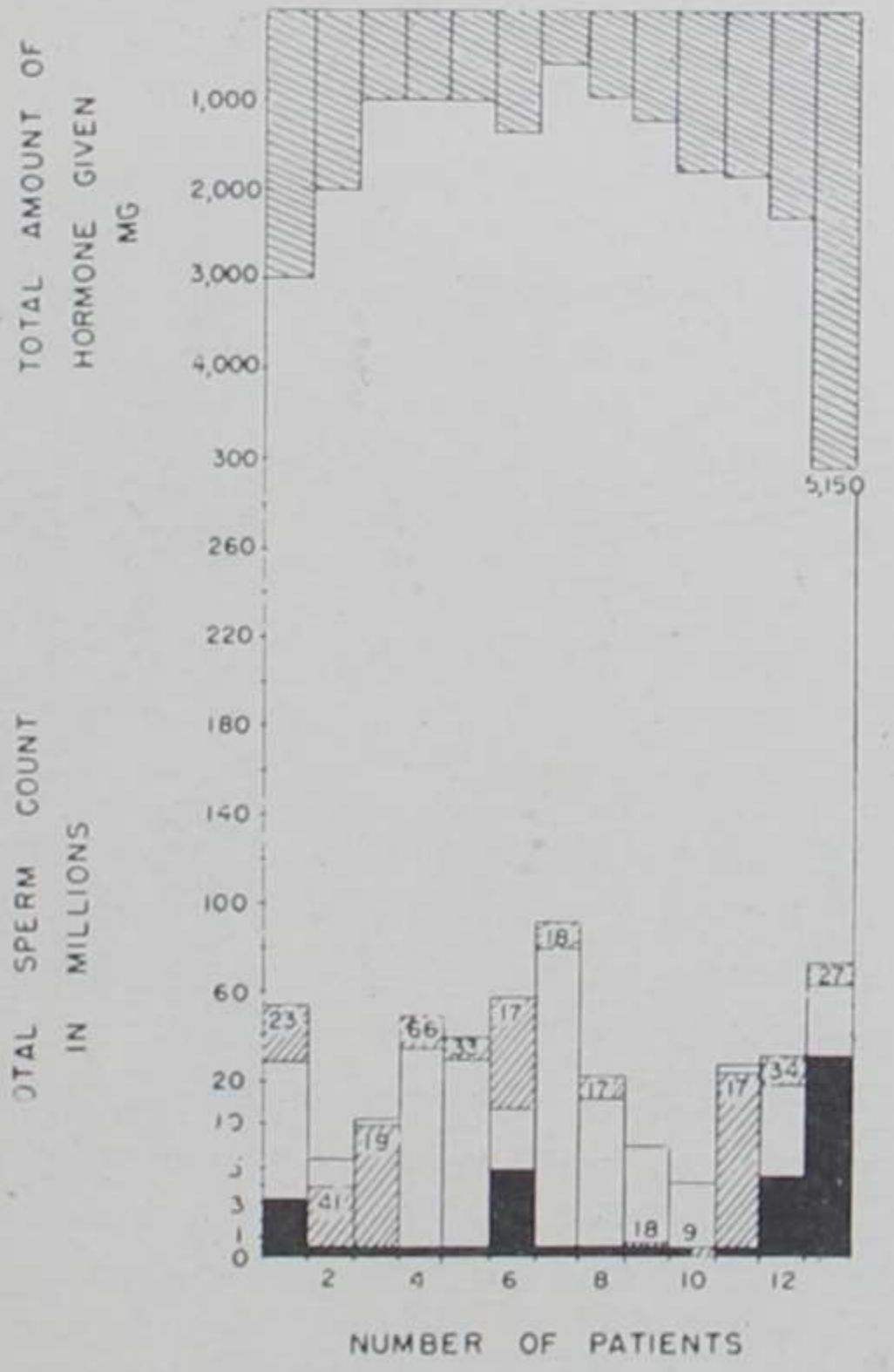

Fig. 89.—Data on 13 patients without significant response after testosterone propionate therapy, 150 mg./week. Total sperm count: before therapy (white), level to which count was depressed (black) and height of rebound after initial depression (shaded); numbers in columns indicate time in weeks for count to reach rebound height after initial depression. (Courtesy of Heckel, N. J., and McDonald, J. H.: Fertil. & Steril. 3:49-61, Jan.-Feb., 1952.)

36 men adequately followed, 23 had a rebound sperm count exceeding pretreatment levels (Fig. 88). It may take as long as 72 weeks for the rebound to occur. This delay may explain some of the 13 failures (Fig. 89). Biopsy has not been helpful. One azoospermic patient whose testicular biopsy was considered to show an irreversible condition had a sperm count of 41,000,000 during therapy. Contrary to the usual rebound,

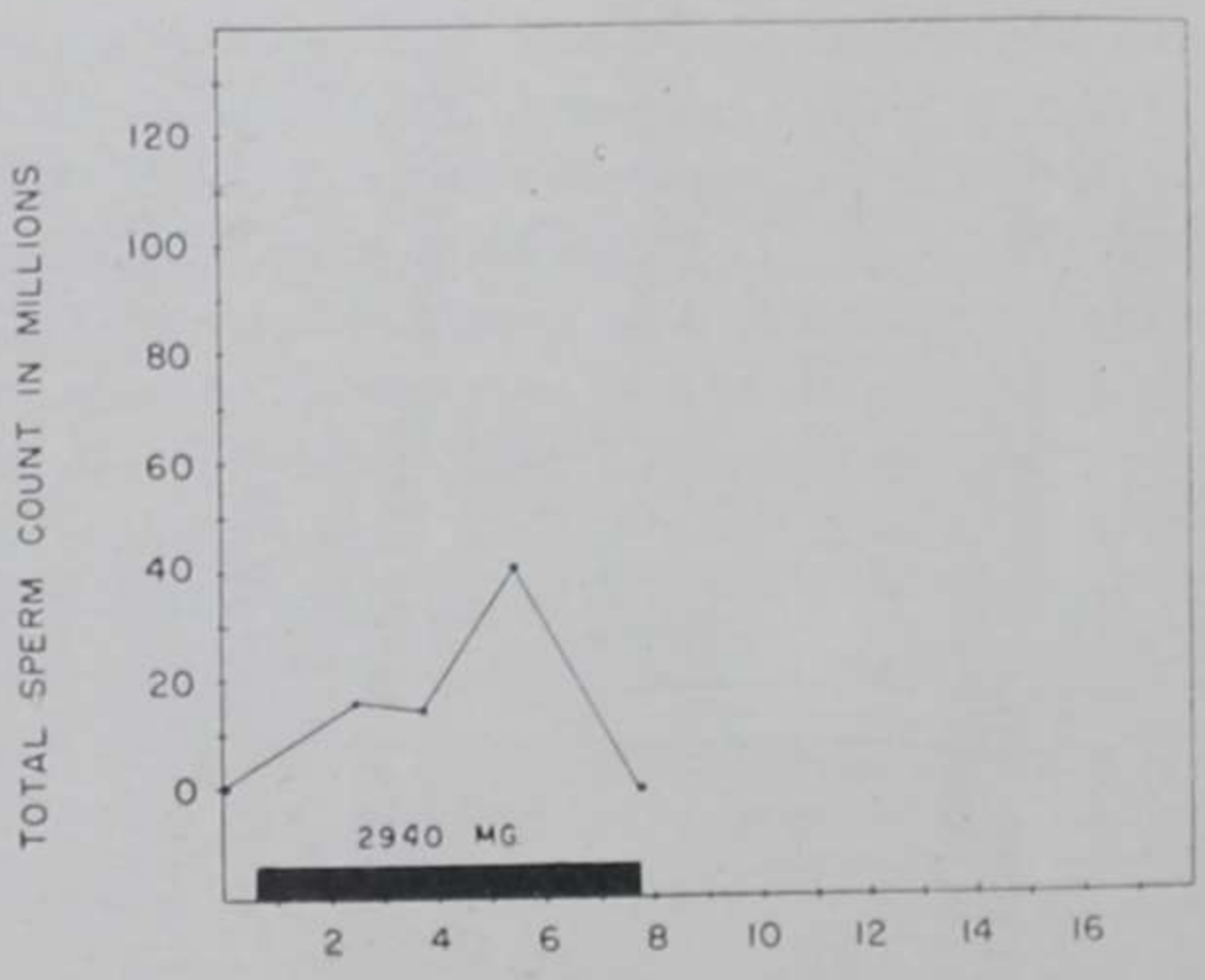

Fig. 90.—Spermiograph of one patient, showing initiation of spermatogenesis during therapy, followed by return to azoospermic stage. (Courtesy of Heckel, N. J., and McDonald, J. H.: Fertil. & Steril. 3:49-61, Jan.-Feb., 1952.)

azoospermia returned when testosterone was discontinued (Fig. 90). The mates of 5 of the 23 men with favorable rebound have become pregnant.

Improved Spermatogenesis after Nutritional-Liver Regimen with and without Testosterone is reported in 17 infertile subjects with oligospermia by S. J. Glass and Murray Russell[4] (Cedars of Lebanon Hosp., Los Angeles).

Method.—After three or more months of diet therapy alone (with 2 Gm. protein/kg. body weight, 50,000-100,000 units of vitamin A, natural concentrates of vitamin B complex and edible or desiccated whole liver in capsules daily), if spermatogenic response was inadequate (12 patients), 500 mg. testosterone propionate was given intramuscularly in 50 mg. doses three times weekly. Desiccated thyroid was sometimes also prescribed. This regimen was continued for 6-24 months. Infertility factors in the wives of nine patients were treated concurrently.

Among 17 patients, 12 had satisfactory spermatogenic responses as indicated by 50-100% or more improvement in all seminal values or significant improvement in motility and morphology without increase in numbers of the spermatozoa. There were five pregnancies during the study: three in wives

(4) Fertil. & Steril. 3:167-178, Mar.-Apr., 1952.

of patients on the liver regimen alone and two after combined liver-testosterone therapy. Two of the pregnancies occurred with seminal values below accepted normal standards. Significant suppression of spermatogenesis did not follow treatment with testosterone, possibly because of the relatively small dose or because the liver regimen affords protection to the germinal epithelium. In one patient testicular tissue was obtained by biopsy before (Fig. 91) and again five months after his wife became pregnant; this followed seven months of

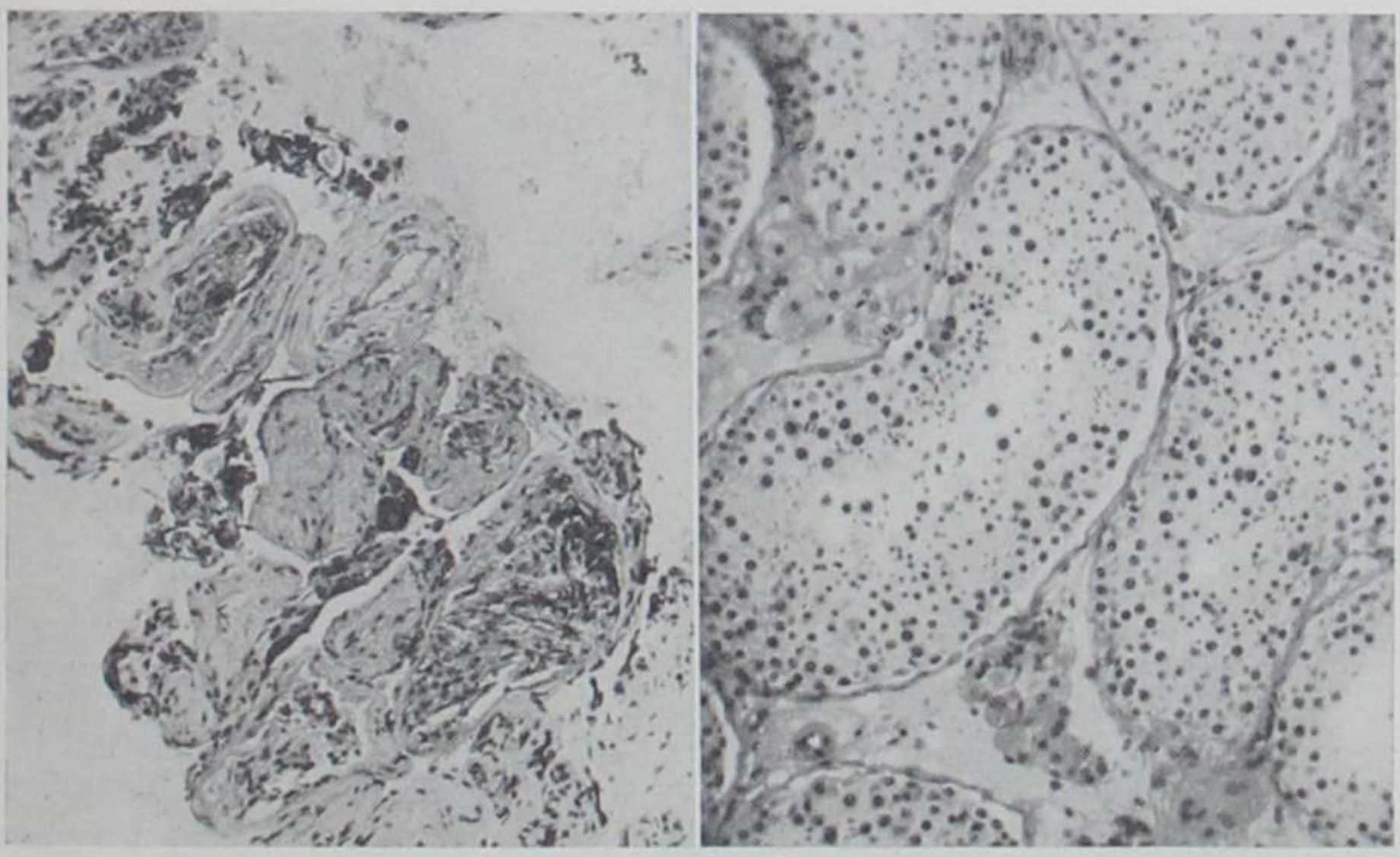

Fig. 91 (left).—Biopsy specimen before therapy, showing hyalinized tubules and atrophy.

Fig. 92 (right).—Same case after therapy and successful impregnation of the wife, showing recovery of spermatogenesis.

(Courtesy of Glass, S. J., and Russell, M.: Fertil. & Steril. 3:167-178, Mar.-Apr., 1952.)

combined therapy with the liver regimen and testosterone (Fig. 92). Testicular architecture was restored to normal, although spermatogenesis was proceeding at a relatively low level of efficiency after the sharp rise induced by testosterone. In five subjects with extensive testicular damage shown on biopsy before therapy, therapeutic responses, if any, were slight; response might have been favorable after more aggressive treatment with testosterone.

The authors believe that the nutritional-liver regimen,

carefully continued for long periods, may suffice for minor spermatogenic failure and that testosterone therapy should be used only after three or more months of intensive nutritional priming have failed to produce adequate spermatogenic response or if there is severe oligospermia.

[The difficulties in assessing the efficacy of any type of treatment of infertility are well known. It will be noted that in the experiment of Heckel and McDonald, in which testosterone alone was used, withdrawal of the steroid was apparently effective in 5 of 23 infertile couples. In the study of Glass and Russell, in which testosterone propionate, vitamin B, liver and sometimes thyroid substance were given to the husbands and the wives of 9 were also treated, five pregnancies occurred among 17 previously infertile couples. From these results, one might surmise that whatever the treatment, a cure rate of 20-30% is inevitable. The subjects of these reports, however, were probably refractory couples who had run the gamut of earlier treatment without results; accordingly, these successes may really be *post hoc, propter hoc*.—Ed.]

Effects of Chorionic Gonadotrophin (A.P.L.®) in Male "Eunuchoidism with Low Follicle-Stimulating Hormone": Aqueous Solution vs. Oil and Beeswax Suspension. Male eunuchoidism with low follicle-stimulating hormone (FSH) is characterized by hypogonadism with virtual absence of secondary sex characteristics, normal somatic growth except for changes attributable to delayed epiphyseal closure, testicular tissue either characteristic of the normal prepuberal state or differing therefrom by thickening of the tunica propria and low or absent urinary FSH titers. Urinary 17-ketosteroids are present in subnormal amounts. Therapy with chorionic gonadotrophin will produce secondary sex characteristics, raise the 17-ketosteroid excretion and produce partial maturation of the Leydig cells and tubules. It has been denied that spermatogenesis is influenced.

F. C. Bartter, R. C. Sniffen, F. A. Simmons, F. Albright and R. P. Howard[5] (Harvard Med. School) compared effects of intramuscular injections of an aqueous solution of A.P.L.® and the same material suspended in peanut oil and beeswax in nine eunuchoids with low FSH. The urinary 17-ketosteroid excretion, serial testicular biopsies and repeated sperm counts were used to evaluate therapy. Results showed that the effects of A.P.L.® in water given at short intervals (daily) may be achieved by giving A.P.L.® in oil and beeswax at intervals of as long as a week. However, the oil preparation was not found

(5) J. Clin. Endocrinol. 12:1532-1550, December, 1952.

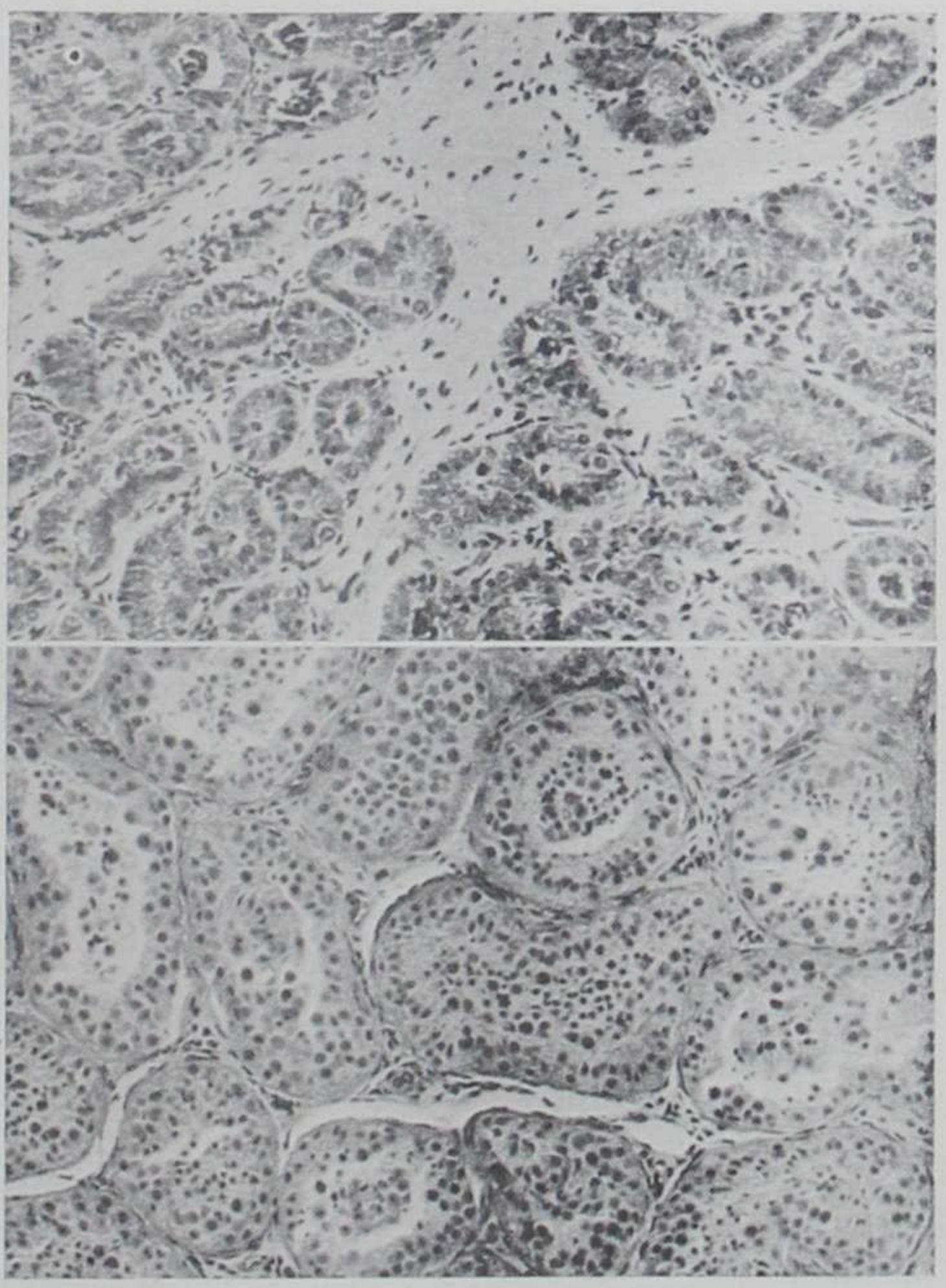

Fig. 93 (top).—Testicular biopsy specimen before starting therapy.
Fig. 94 (bottom).—Testicular biopsy specimen after 21 months of therapy, showing almost complete maturation; note presence of spermatozoa.
(Courtesy of Bartter, F. C., *et al.*: J. Clin. Endocrinol. 12:1532-1550, December, 1952.)

more effective than the aqueous solution when both were given at four to seven day intervals.

Prolonged therapy with A.P.L.® in two patients produced mature testes and active spermatozoa (Figs. 93 and 94). The wife of one of the patients became pregnant. The changes regressed when therapy was stopped. In a third patient, prolonged therapy with methyltestosterone linguets® was given following A.P.L.® therapy, with concomitant development of mature testes and normal numbers of active spermatozoa

which persisted when testosterone was stopped. However, the initial testicular biopsy in this patient showed considerable maturation.

It is emphasized that effects of treatment cannot be evaluated unless they regress when treatment is stopped. Only on this basis may the contribution of endogenous gonadotrophins be ruled out. In delayed puberty there is the possibility that therapy may initiate puberty which then proceeds spontaneously. Another group of eunuchoid patients with low FSH are those whose testicular biopsies show some maturation. These patients respond to chorionic gonadotrophin and, when treatment is stopped, continue to mature spontaneously. They are distinguished from the delayed puberty group only by the histologic appearance of the testes. It is these groups which contribute cases of "cured" eunuchoidism. Eunuchoidism with low FSH and complete testicular immaturity is a syndrome which responds to chorionic gonadotrophin by progressing toward maturation, but when therapy is stopped, the changes regress.

In the seven patients in whom follow-up was long enough to evaluate regression of effects after discontinuance of therapy, all but the one with considerable maturation on initial biopsy showed decrease of libido, loss of potentia with inability to obtain ejaculum and fall in 17-ketosteroid excretion; in two, regression was demonstrated by biopsy. Thus it may be concluded that A.P.L.® directly stimulated maturation of all elements of the testicular tissue, including spermatogenesis.

Sertoli Cell as Related to Age of Man and Experimental Alteration of Pituitary-Gonad Axis in the Animal, with Consideration of Its Role in Spermatogenesis. Kenneth M. Lynch, Jr., and William Wallace Scott[6] (Johns Hopkins Univ.) report studies of frozen sections of testicular tissue obtained from 197 human males, aged 2 months premature to 84 years, and young adult 200 Gm. albino rats of the Sprague-Dawley and Wistar strains, stained for demonstration of Leydig and Sertoli cell lipid by Oil-Red-O and acid hematoxylin counterstain. The effect of various manipulations on Leydig and

(6) Fertil. & Steril. 3:35-48, Jan.-Feb., 1952.

Sertoli cell lipid was studied in the testicular tissue from the animals.

In the human testicular tissue, Leydig cell lipid appeared at age 12 and Sertoli cell lipid at age 15. Spermatogenesis was not present until lipid appeared in the Sertoli cells, which suggests that both androgen from the Leydig cells and pituitary FSH are required for proper tubular function. Maximal spermatogenesis occurred during ages 17-35, when the Leydig cell lipid was estimated at 4 plus and Sertoli cell lipid at 1-2 plus. With increasing age and decreasing spermatogenesis, Leydig cell lipid decreased and Sertoli cell lipid increased to a 4:1 ratio in old age.

In the normal rat testis, a characteristic lipid pattern was found. Tubules in the "resting" phase with no spermatozoa present contained droplets of lipid at the basement membrane, presumably in the Sertoli cells. As the sperm matured, these droplets became smaller and migrated toward the tubular lumen to disappear when the sperm were released. This suggests that Sertoli cells have a nutritive function and that the lipid may be the nutrient. Hypophysectomy, inanition to loss of 50% of body weight and artificial cryptorchidism resulted in degeneration of the germinal epithelium, absence of spermatogenesis and accumulation of lipid in the Sertoli cells. Following injections of estradiol benzoate, the most conspicuous changes resembled those following hypophysectomy; the least marked were merely an increased number of tubules in the "resting" phase. Injection of testosterone propionate produced changes similar to estrogen plus atrophy of the Leydig cells and lipid accumulation in an occasional interstitial cell nest. The effect of both the transabdominal and scrotal approaches to vas deferens ligation was studied. The testes of animals subjected to vas ligation through scrotal incisions remained normal, suggesting that degeneration of the germinal cells following vas ligation by the transabdominal approach is due to accidental production of cryptorchidism.

These studies indicate, in addition, that the Sertoli cell lipid accumulates in the cell, probably because it is not utilized, when spermatogenesis is impaired.

[Little is known about the functions of the Sertoli cells. Sertoli cell tumors in dogs result in estrogenic phenomena. Whether tne Sertoli cells of the normal human testis also secrete estrogen is not established, nor is it certain whether the second hormone of the testis is estrogen (not water-soluble) or "inhibin" (a water-soluble substance). It will be noted in the following article that Goldzieher and Roberts have succeeded in demonstrating the presence of estradiol in the human testis.—Ed.]

Testicular Hormones

Identification of Estrogen in Human Testis is reported by Joseph W. Goldzieher and Irene S. Roberts[7] (New York City). Although estrogenic substances have been extracted from testes of many mammals, the authors were unable to find any factual reports of an estrogen assay on human testicular tissue. By subjecting 8.75 kg. of such tissue to an extraction procedure designed to isolate steroids, they were able to identify estradiol by both bioassay and paper chromatography. Estrone (present in large quantity in stallion testes) and estriol were not found.

Experimental Production of Gynecomastia with Chorionic Gonadotrophin. Gynecomastia is often seen in patients with chorioepitheliomas of the testes, teratomas or seminomas associated with a high urinary chorionic gonadotrophin level. Less common are estrogen-producing tumors of the testes or adrenal cortex which may cause gynecomastia by direct stimulation. The mechanism whereby chorioepithelioma stimulates mammary growth is unknown. Gerald Klatskin and Paul L. Munson[8] (Yale Univ.) studied this problem by injecting large doses of human pregnancy urine chorionic gonadotrophin for two months, producing gynecomastia in two cirrhotics, one with testicular atrophy, the other with pituitary deficiency. A rise in urinary 17-ketosteroid and estrogen excretion was measured but bioassay showed no increase in androgen. The observations suggest that chorionic gonadotrophin affects the male mammary gland by stimulating adrenal cortex estrogens. When colostrum-like secretion and mammary alveolar development accompany gynecomastia, they are probably due to simultaneous stimulation by progesterone derived from the tumor or the adrenal cortex.

[Histologically, the gynecomastia produced by estrogen and by androgens cannot be differentiated. These studies suggest that the gyne-

(7) J. Clin. Endocrinol. 12:143-150, February, 1952.
(8) Yale J. Biol. & Med. 24:474-497, June, 1952.

comastia resulting from chorionic gonadotrophin is mediated by estrogen rather than by androgens, since the androgen content of the urine was not increased. It should be noted that a rise in urinary estrogen excretion may also result from the normal metabolism of androgens, a mechanism which was apparently excluded in these studies. Incidentally, increased 17-ketosteroid excretion with no change in androgen content strongly suggests an effect of chorionic gonadotrophin on the adrenal cortex.—Ed.]

Clinical Application of Testosterone Preparations with Long Lasting Action was studied by Henriëtte A. VanGilse, A. A. H. Kassenaar and A. Querido[9] (Leiden) in 11 males, 17-48, with primary or secondary hypogonadism. Tablets containing 100 mg. crystalline testosterone and similar tablets of testosterone propionate (TP) were implanted subcutaneously in the back. Dosage ranged from 300 to 800 mg. but was usually 600 mg. Some implants (20 of 138) were expelled in all patients; the weight of the extruded tablets gave a measure of absorption. In four patients given both testosterone and TP, no difference in clinical activity or incidence of expulsion was noted. Clinical improvement usually began on the 2d or 3d day, reached a maximum in 2-8 weeks, where it remained for 2-3 months, and lasted 3-6, sometimes 9-10, months. All patients who had had testosterone in other forms preferred implantation because it was uniformly effective and was infrequently administered. Almost always 17-ketosteroid excretion rose, was maximal in the 2d or 3d week and lasted 20-26 weeks. Fibrosis of implantation site was noted in two patients whose clinical improvement and 17-ketosteroid excretion were also diminished.

Three patients were given 50-150 mg. aqueous TP emulsion intravenously. Clinical effectiveness varied greatly. In one patient no subjective or objective difference between implantation and injection (50 mg./12 days) could be detected, but such differences are difficult to establish. In two patients 17-ketosteroid excretion reached a maximum in the first 24-48 hours and remained high for three to four days after 50 mg. and for three to six days after 100 and 150 mg. The increased excretion consisted of androsterone and etiocholanone in constant proportions.

(9) Nederl. tijdschr. geneesk. 96:314-324, Feb. 9, 1952.

Comparison of Effectiveness of Three Testosterone Preparations in Man and Rats. E. Perry McCullagh, J. B. R. McKendry and C. A. Schaffenburg[1] (Cleveland Clinic) compared a long-acting androgen, testosterone β-cyclopentylpropionate

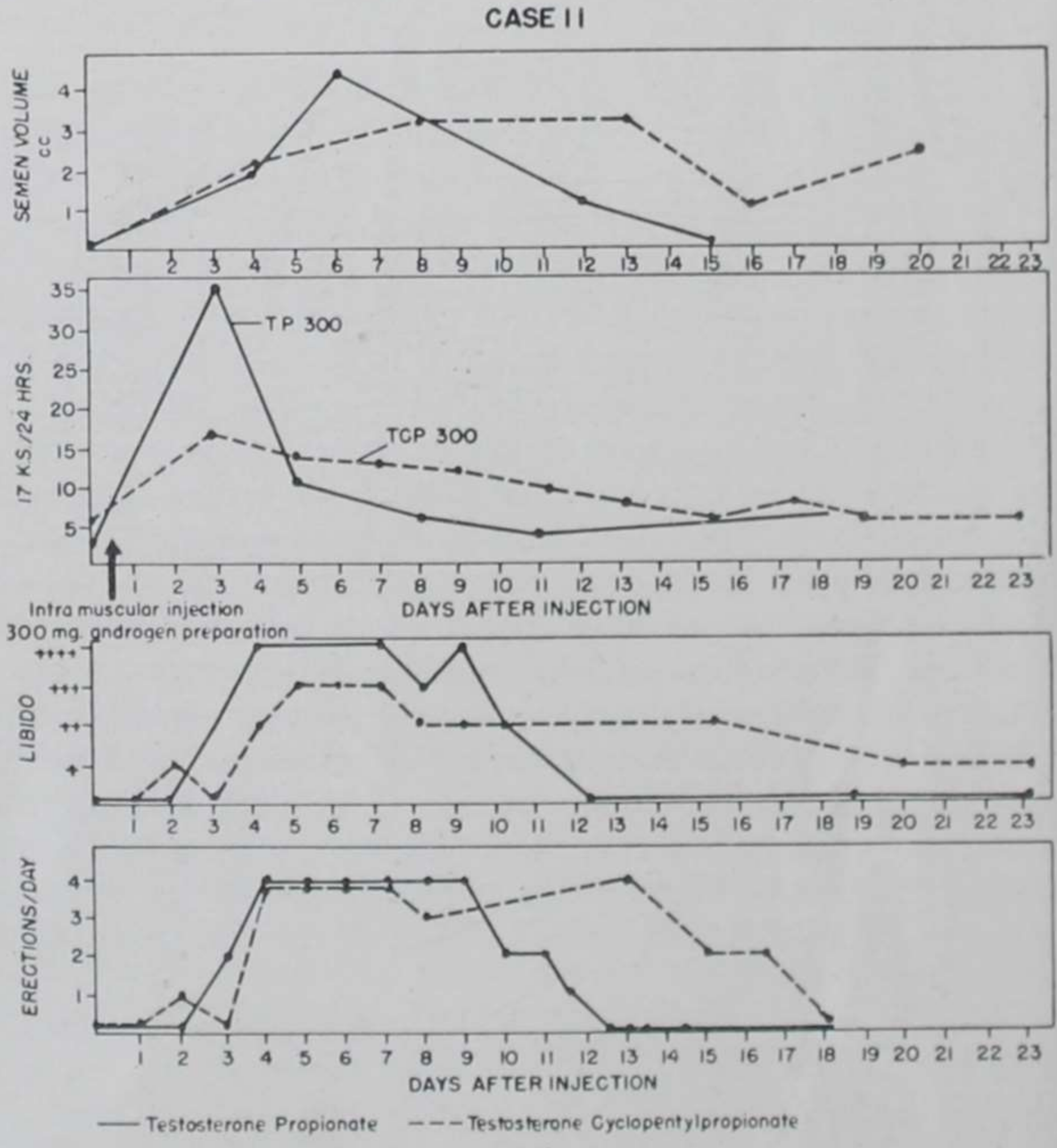

Fig. 95.—Effects of testosterone propionate (solid line) and testosterone cyclopentylpropionate (broken line). (Courtesy of McCullagh, E. P., *et al.*: J. Clin. Endocrinol. 12:3-14, January, 1952.)

(TCP), testosterone propionate (TP) in oil and unesterified testosterone in aqueous suspension. Seven patients with primary hypogonadism were given comparable single doses of 50-300 mg. of each preparation with 4-12 weeks between each administration. Fluctuations in potentia and libido and uri-

(1) J. Clin. Endocrinol. 12:3-14, January, 1952.

nary 17-ketosteroid excretion were followed and in two instances semen volume and fructose concentration. The following case is illustrative.

Man, 33, with primary hypogonadism was observed because of delayed puberty. He had received chorionic gonadotrophin and testosterone for many years and recently had been given 50 mg. testosterone propionate intramuscularly three times a week. Eight days after this was discontinued, the first test dose of 300 mg. testosterone propionate was given. Twenty-four days after testosterone propionate was stopped, TCP was started. The patient noted no sharp qualitative difference in their effects. However, the duration of activity of TCP exceeded that of the propionate by more than a week. Effects which lend themselves to quantitative measurement are shown in Figure 95. Semen fructose concentration ranged from 210 to 540 mg./100 cc.

Urinary 17-ketosteroid excretion was more prolonged after TCP than after TP or testosterone in aqueous suspension. The effect of a single injection of TCP on semen volume, libido and potentia was less than that following an equal dose of TP. These observations were confirmed in 45 castrated male rats. Comparison of weights of prostate and seminal vesicles the 3d, 6th and 8th day after a single injection of 1 mg. androgen showed that TCP had a more prolonged effect than the other two testosterone preparations.

[These observations confirm those reported last year by Lloyd and Fredericks (J. Clin. Endocrinol. 11:724-727, July 1951) as well as some I have made. Long-acting testosterone compounds greatly simplify the treatment of male hypogonadism in patients who can conveniently visit a physician at monthly intervals. Similar maintenance can be obtained in patients who need not be seen so frequently by administration of methyltestosterone tablets buccally or sublingually, or by implantation of pellets whose action lasts five to nine months. Practically, the use of long-acting depot compounds and administration of methyltestosterone sublingually remain the methods of choice in male hypogonadism. If the dose is not established or the patient's condition may fluctuate, use of the long-acting compound is contraindicated, e.g., in the treatment of mammary carcinomatosis with osteolytic metastases.—Ed.]

Testosterone Therapy for Pruritus of Obstructive Jaundice. H. G. L. Lloyd-Thomas and Sheila Sherlock[2] (Postgrad. Med. School, London) report results of methyltestosterone therapy (25 mg. daily sublingually) in seven patients with chronic obstructive jaundice who had had severe pruritus for six weeks to three years. Three had primary biliary cirrhosis; two, inoperable carcinoma of the main hepatic ducts; one, a gallstone impacted in the common bile duct, and one,

(2) Brit. Med. J. 2:1289-1291, Dec. 13, 1952.

a traumatic stricture of the common bile duct. All complained of itching and showed excoriations on the skin due to scratching. The hormone relieved the itching four to seven days after beginning of treatment. In all five patients for whom serial serum bilirubin determinations were made testosterone seemed to increase the rate of rise of serum bilirubin. The jaundice tended to increase. Serum total cholesterol diminished under hormone therapy, especially when the pretreatment rates were high. Masculinization occurred in three of the six women but diminished when the dose was reduced. Testosterone propionate by subcutaneous implantation was not so effective as sublingual therapy, probably because of inadequate absorption.

It is not known how testosterone relieved the pruritus in these cases.

[These studies confirm the surprising observation of Ahrens *et al.* (Medicine 29:299, 1950) that methyltestosterone relieves the pruritus of jaundice. This report is of particular interest in that it demonstrates the usefulness of methyltestosterone in liver disease, which some authors have considered a contraindication to use of the methyl ester of testosterone. The objections were based on an alleged entity called "methyltestosterone jaundice." I have serious reservations about the existence of such a condition for several reasons. (1) It has not occurred in the large number of patients to whom I have given methyltestosterone therapeutically or experimentally. (2) It has not occurred in the practice of any of my colleagues in the Endocrine Clinic of the University of California, who also give this agent to many patients. (3) It has been attributed to the creatinuria induced by methyltestosterone, which could possibly and theoretically cause loss of lipotrophic agents, *but* liver biopsy in afflicted persons shows no fatty infiltration of the liver. (4) In the reported cases, jaundice has subsided despite continued administration of the agent. The last reason alone strongly militates against a causal relation.—Ed.]

Clinical Report on Use of Testosterone in Psychiatric Syndromes. Edward L. Margetts[3] (McGill Univ.) has found this hormone a useful adjunct to other treatment, particularly psychotherapy and electric shock, in psychiatric syndromes. Electric shock is the treatment of choice for patients with manic-depressive psychosis, particularly if they have suicidal potentialities. However, testosterone can be used for those with mild depressions who do not have suicidal tendencies and for those in whom convulsion therapy is contraindicated. Testosterone was helpful in lifting a depression in a man with manic-depressive psychosis who had previously benefited from

(3) Canad. M. A. J. 67:251-254, September, 1952.

electric shock and who could not have any more treatments because of pulmonary infarct. His energy increased and libido improved. Testosterone was also helpful in increasing the sex desire in a woman with manic-depressive psychosis who had been treated with electric shock. It was of value in increasing the energy and sex desire in a man with manic-depressive psychosis who sustained a fractured maxilla while undergoing electric shock therapy.

Electric shock is useful in involutional melancholia, but it may sometimes precipitate an acute paranoid psychosis. It is best to use testosterone if this undesirable syndrome shows any likelihood of developing.

The treatment of choice in psychoneurotic depressions is intensive psychotherapy, but testosterone may be of benefit in some cases to stimulate symptomatic improvement. A patient with a depression with a somatic effect (asthma) was greatly improved after treatment with electric shock and testosterone. The asthma disappeared, energy increased and sexual interest increased. A eunuchoid man with feminine behavior and homosexual tendencies was relieved of a psychoneurosis with somatic effect under testosterone therapy.

The male climacteric syndrome rarely exists alone and is often superimposed on a chronic, autonomic instability or frank psychoneurosis. The male climacteric is characterized chiefly by depression (feeling of subjective sadness, difficulty in concentrating, insomnia, fatigability, slowing of physical and mental activity), anxiety (tremulousness, nervousness, fears, apprehensions), cardiovascular symptoms (similar to the female—hot flashes and perspiration) and genital dysfunction (impaired libido sexualis and impotency). Heller's diagnostic criteria of the male climacteric include: elevation of gonadotrophin level in the urine; gonadal atrophy or degeneration as revealed by biopsy of the testis, and favorable response to the therapeutic test of treatment with testosterone. Testosterone was helpful in lifting the depression and increasing libido in a man who was not benefited by electric shock and psychotherapy. It was also useful in relieving the depression and impotency of a man with the climacteric and chronic psychoneurosis.

Testosterone has been found useful in increasing the sex

drive of both men and women. It is of greater value in the latter. It stimulates the sex drive in the same direction to which the patient has been accustomed. This explains why testosterone is not useful in the treatment of homosexuality. The drug is of some use in treating depressions of the aged. It appears to act as an energy- and mood-raising agent and as such can be useful as supportive therapy.

[Testosterone compounds produce a feeling of well-being which is quite different from the ebullient euphoria induced by cortisone or corticotrophin. Hypogonadal patients given these compounds note increased ability to concentrate and to make decisions, as well as increase in libido and potentia. Androgens do not alter the libido or potency of normal men nor do they produce erections in patients with psychogenic impotence. Nor do they cure homosexuality. (It will be recalled that eunuchoids are rarely homosexual.) Although testosterone increases the libido of many women, it is not a cure for severe frigidity, where the barrier is psychic and must be dealt with accordingly. It is likely that the ability of these compounds to induce a feeling of well-being may render them useful adjuvants to psychotherapy in some cases.—Ed.]

Relationship of Protein Intake to Protein Anabolic Activity of Testosterone Propionate was studied by Charles D. Kochakian and William van der Mark[4] (Univ. of Rochester).

TECHNIC.—Male rats, 300-500 Gm., were castrated and brought to nitrogen and body weight equilibrium on an 18% protein diet. They were then divided into three groups and given 18%, 28% and 43% protein diets by replacing part of the carbohydrate of the diet by an isocaloric amount of casein for 60 days before and during 21 days of daily subcutaneous administration of a 10 mg./ml. solution of testosterone propionate in sesame oil.

The increases in protein intake had no effect on maximal daily nitrogen retention, total nitrogen retention or the body-weight-stimulating effect of the androgen. Increases of testosterone dose to 25 and 50 mg./day did not have any greater anabolic effects at either the 28 or the 43% level of protein intake.

[This study demonstrates that increase of protein intake over the optimal 18% does not increase the amount of protein anabolism stimulated in the rat by testosterone propionate. The same is true for growth hormone, the optimal protein intake for Long-Evans rats being 24% (Gordan *et al.*: Endocrinology 42:153-160, 1948). On the other hand, lower concentrations of protein may be insufficient for adequate protein synthesis (Gordan *et al.*: Proc. Soc. Exper. Biol. & Med. 65:317-319, 1947). "No bricks without straw."—Ed.]

Methylandrostene Dipropionate for Weight Gain. M. Albeaux-Fernet, J. Robert and J. Berton[5] administered the drug

(4) Proc. Soc. Exper. Biol. & Med. 79:74-75, January, 1952.
(5) Ann. endocrinol. 13:635-639, 1952.

to five patients with intractable substandard weight sublingually (four 25 mg. tablets daily), by intramuscular injection of oily solutions (25 mg. daily) or by injections of aqueous suspensions (25 mg. daily). The drug was well tolerated except that the suspension produced local pain. Euphoria and appreciable weight gain were noted in all patients without the benefit of additional medication, dietary measures or psychotherapy. Urinary output was maintained at about 1 L./24 hours in all patients. No effect was noted on temperature, pulse or blood pressure and no clinically apparent edema nor virilizing effects were noted.

[Again the anabolic efficacy of this weak androgen is confirmed. I do not know why the dipropionate was used; presumably it would be even more slowly absorbed than the unesterified steroid. The sublingual or buccal route is preferred for the administration of this agent because of shorter action and thus better control, and convenience.—Ed.]

Nonvirilizing Antiestrogenic Steroids in Ovariectomized Woman. The direct antiestrogenic effects of testosterone and methyltestosterone are well known, and in many instances they justify the therapeutic use of these substances in women. However, administration is often accompanied by side effects such as excessive hair growth and appearance of acneiform lesions. J. Férin[6] (Univ. of Louvain) believes that the frequency with which these side effects occur far exceed the 1% sometimes given, when the monthly dose of testosterone propionate intramuscularly is between 200 and 300 mg. Laboratory experiments carried out in an effort to find steroids capable of replacing testosterone and methyltestosterone have already shown that various substances, such as Δ-5-pregnenolone, methylandrostenediol and 17-ethylandrostane, although having little or no androgen activity, are able to inhibit certain estrogenic effects. Antiestrogenic action is, therefore, not merely a part of androgen action but an expression of a particular pharmacodynamic activity.

Férin attempted to determine the minimal dose of methylandrostenediol and methylandrostane-3-on-17-ol required to inhibit the endometrial growth caused by a standard dose of estrogen in ovariectomized women. The figures obtained were compared with those recorded for methyltestosterone in the same experimental conditions.

(6) Ann. endocrinol. 12:1082-1086, 1951.

Two women with clinically normal corticoadrenal function, whose sensitivity to estrogens was known from multiple earlier treatments, were selected for study. One, aged 51, had been castrated for 12 years; the other, aged 31, for 3 years. They were given a constant daily dose of 0.025 mg. ethinyl estradiol, the first receiving it for 14 days by the gastrointestinal route and the second for 20 days perlingually. Variable doses of the steroid being tested were also given perlingually. The various treatments were separated by intervals of about a week. Controls carried out during the experiment showed conclusively that a recognizable, lasting modification of endometrial receptivity is not to be expected after administration of the various steroids, at least under the conditions of the experiment; endometrial growth was noted on each occasion after the control treatments.

It was found that methylandrostenediol and especially methylandrostane-3-on-17-ol have a direct antiestrogenic activity; they are, however, less active than methyltestosterone. The fact that they had no effect from the sexual viewpoint indicates the slightness of their virilizing action in women. In the United States, methylandrostenediol has already been used successfully in place of methyltestosterone in various gynecologic syndromes. Férin was able to duplicate these successes in certain cases of functional dysmenorrhea and premenstrual mastopathy and tension, using a dose of 50 mg. daily for 20 days from the end of menstruation.

Miscellaneous

Testicular Changes of Myotonic Myopathy (Steinert's Disease). In addition to neuromuscular disturbances, myotonic myopathy is often associated with various dystrophies, the reciprocal relationships of which are obscure. Of these, cataract, baldness and testicular atrophy are the most frequent. Jacques Decourt, J. Lereboullet, R. Henry and G. Tinel[7] point out that because this condition often develops rather late, many patients are able to produce children before testicular lesions is debatable, but authorities agree that the seminal sets in. Regression of libido occurs, but is often delayed until the testicular lesions are well established.

(7) Ann. endocrinol. 12:1046-1051, 1951.

Atrophy of the testes results in a great reduction in their size, loss of firmness and sensitivity to pressure. The penis may also be slightly atrophied, and progressive oligospermia may end in total azoospermia. The exact nature of the testicular lesions is debatable, but authorities agree that the seminal system is always affected, although in a topographically irregular manner. Urinary 17-ketosteroid excretion is generally greatly reduced. Estimation of the hypophyseal gonadotrophin is especially interesting in the pathogenic interpretation of testicular changes, because this hormone is not found in the urine in testicular atrophy secondary to hypophyseal insufficiency but is found in excessive quantities in primary testicular disturbance. Widely varying levels have been reported in myotonic myopathy, some normal and some elevated. In five cases reported by the authors there was a marked reduction of 17-ketosteroids. One patient, whose illness was severe and of long standing (32 years) and whose general condition was poor, had an extremely low rate—1.5 mg./24 hours. The same patient had an equally low gonadotrophic hormone excretion rate, less than 5 mouse units. In no case was the rate higher than normal. Testicular biopsy carried out in one case showed uneven hyalinization of the semeniferous tubes and absence of Leydig's cells in the specimen examined.

Attempts have been made to relate the testicular and other changes occurring in Steinert's disease to hypophyseal deficiency, but the hypophyseal lesions noted are neither constant nor characteristic. The testicular lesions themselves, like the muscular ones, are most uneven, differing from one point to another. They cannot be identified with those in the syndrome described in 1942 by Klinefelter, Reifenstein and Albright. At present, therefore, it seems impossible to establish a link, other than the clinical one, between the various manifestations of myotonic myopathy, each of which apparently follows its own line of development. Of all the theories advanced, that which attributes the different elements of the disease to a primary disturbance in the trophic nerve centers or in the sympathetic system itself seems to be the most satisfying.

Turner's Syndrome in a Male Infant. Theodore James[8] (Manchester, England) points out that although Turner's syndrome has been described in more than 100 females, only 5 examples are known in males in addition to 1 reported here. He believes that the apparent rarity of the syndrome will decrease as familiarity with it increases. The classic triad of Turner's syndrome is congenital webbed neck, cubitus valgus or an increased carrying angle at the elbows and infantilism manifested by retardation of sexual and osseous development

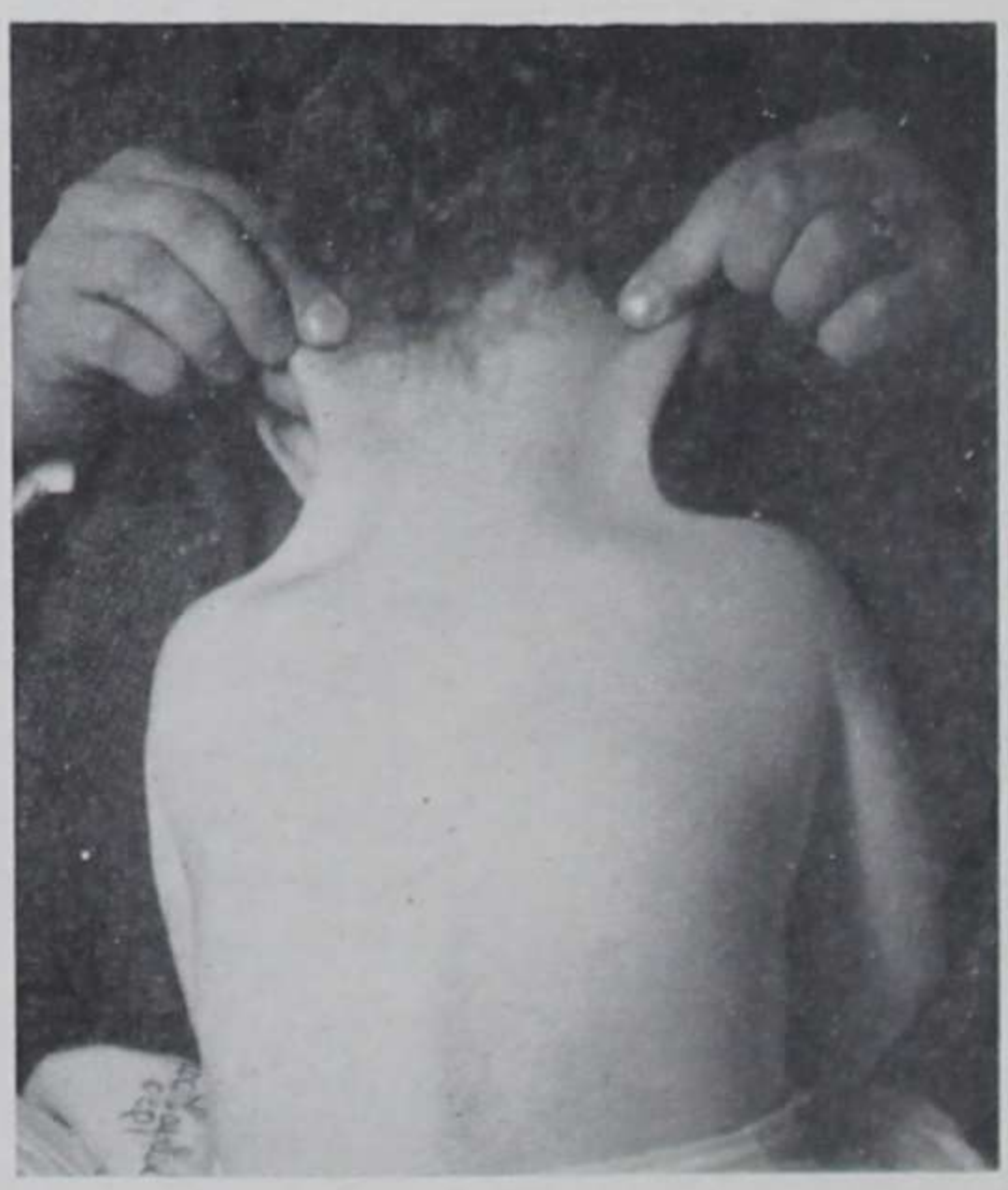

Fig. 96.—Webbing of neck produced by slight traction on skin over mastoid processes. (Courtesy of James, T.: Edinburgh M. J. 59:344-354, July, 1952.)

comparable to that of hypopituitarism. Other congenital defects, including coarctation of the aorta, may also be present.

Boy, 2, was brought to the physician because of failure to grow physically and mentally. Siblings and parents were normal and he had had no accidents or illnesses. Examination revealed a flabby, placid child with open mouth and protruding tongue. The skin was dry. By bending the neck to either side, the folds of a latent pterygium colli could be seen (Fig. 96). The lower portion of the sternum was depressed and a loud systolic bruit was present. The penis was small, but the testes were of usual size and could be pulled into the scrotum. Muscle power was poor and all joints had abnormal flexibility. The fingers showed slight webbing. All laboratory

(8) Edinburgh M. J. 59:344-354, July, 1952.

studies gave normal results except for urinary 17-ketosteroid excretion of 1.6 mg./day (abnormally low) and gonadotrophin excretion of 3½ mouse units/day (abnormally high). These findings exclude pituitary origin of this case and are in agreement with Albright's description of 11 cases in females.

CARBOHYDRATE METABOLISM AND DIABETES MELLITUS

General Aspects

Important advances continue to be made, both in the knowledge of carbohydrate metabolism and in the prevention, recognition and treatment of the complications of diabetes mellitus. It is well established that rigorous treatment of diabetes, with zealous attempts to keep the body chemistry within normal bounds, pays off in the avoidance of degenerative complications of this disorder. Diabetics now live longer than was previously thought possible; consequently, it is extremely important to keep them free from degenerative lesions of the cardiovascular, renal and nervous systems.

Rigid control of the diabetes and close collaboration of internist, obstetrician and pediatrician enable the diabetic woman to go through pregnancy with negligible risk to herself and with only a fraction of the risk to the fetus that existed 25 years ago.

Although difficult, it is worth while to persuade the diabetic patient of the necessity for strict adherence to diet and the importance of keeping a balance between the two factors essential for the burning of carbohydrate—exercise and insulin. As one physician (H. C. Shepardson) has said, it is too bad that diabetes does not hurt, since then the patient could be persuaded to treat himself rigorously to avoid pain. Unfortunately, when pain does appear, it usually denotes that neuritic or cardiovascular complications are already far advanced.

The wide range of insulin preparations now available makes it possible to pick one, or a combination, whose time of action is most appropriate for the individual patient.

The studies of Sanger and his group at Cambridge University have established the amino acid composition of the insulin molecule (F. Sanger and E. O. P. Thompson: Biochem. J. 52:111, 1952). Insulin appears to have a molecular weight of 12,000. It is not clear whether the entire molecule is essential for the action of insulin or whether a moiety may be the active principle. If the latter were true, it might be possible to synthesize this important hormone. Investigation along these lines is greatly needed, since the present demand for insulin almost equals the supply. Therefore stockpiling of insulin against the event of national or international emergencies might be important. A synthetic compound, of course, would greatly increase the supply of this vital agent.

The number of patients thought to be epileptic or psychotic who are cured when an astute physician pins the cause of erratic behavior on a pancreatic islet cell tumor is highly gratifying. These tumors are by no means as rare as was once thought. A high index of suspicion on the part of the physician will salvage many patients with this disorder.

Hypoglycemia, of course, occurs in other conditions, namely, pituitary insufficiency (see section on Pituitary Gland), adrenal insufficiency, liver disease, including chronic passive congestion of the liver (S. M. Mellinkoff and P. A. Tumulty: New England J. Med. 247:745-750, 1950), and after sudden cessation of treatment with cortisone or corticotrophin.

Diabetes mellitus in acromegaly is discussed in the section on the Anterior Pituitary Gland. Effects of adrenal corticoids on glyconeogenesis and the carbohydrate metabolism of adrenalectomized patients are discussed in the section on the Adrenal Cortex.—Ed.

Metabolic Effects of Total Pancreatectomy in Man. In the 25 recorded cases of total pancreatectomy, only 10 patients have survived long enough to allow adequate study of metabolic effects. A. G. W. Whitfield, A. Gourevitch and Garfield Thomas[9] (Univ. of Birmingham) report studies on a man, 55, two years after total pancreatectomy. Small doses of pancreatin (1.5 Gm. per day) caused absorption of only 38% of the fat intake, whereas 11.5 Gm. per day increased fat absorption to 83%. However, protein absorption and nitrogen balance could not be improved. The patient required only 20-60 units of insulin, depending on the diet. Mild hypoglycemic reactions occurred occasionally, as in ordinary diabetics. Defective absorption may well be an important reason why depancreatized human beings need so little insulin, but this alone does not explain the small insulin requirement. Therefore it seems likely that the current view that islet cell deficiency is not wholly responsible for diabetes is correct.

[In severe diabetes mellitus, the insulin requirement may exceed 100 units a day. The diabetes mellitus which follows pancreatectomy is usually milder and may be controlled by less than 40 units of insulin a day. Two explanations for this fact have been offered: (1) intestinal absorption is decreased following pancreatectomy, thereby reducing the absorbed caloric intake; (2) the alpha cells of the islets of Langerhans secrete a glycogenolytic hormone. There is evidence favoring both of these hypotheses, and probably both mechanisms play a part.—Ed.]

Effect of Age on Intravenous Glucose Tolerance Test. Norman G. Schneeberg and Israel Finestone[1] (Mount Sinai Hosp., Philadelphia) report that normal subjects over 40 have a depressed tolerance to glucose given intravenously. They compared 48 healthy volunteers aged 16-39 with 49 volunteers aged 40-90, most of them from a home for the aged and free of any pathologic condition that might affect carbohydrate tolerance. Neither group was placed on a high carbohydrate diet before the test but the diet (by history) had

(9) Lancet 1:180-183, Jan. 26, 1952.
(1) J. Gerontol. 7:54-60, January, 1952.

been adequate. Glucose, 0.3 Gm./kg. in a 50% solution was injected intravenously in 3-5 minutes; capillary blood was taken at 15, 30, 60, 75, 90 and 120 minutes. The aged group had a mean fasting level of 72.4 (standard deviation 17.7) as against 60.1 for the younger group (standard deviation 12.6). The aged had significantly higher values throughout the test.

Attempts to attribute these findings to liver dysfunction, deficient stores of liver glycogen or previously low carbohydrate diet among the aged revealed none of these factors.

Acetone in Breath: Study of Acetone Exhalation in Diabetic and Nondiabetic Human Subjects was undertaken by Margaret J. Henderson, Beatrice A. Karger and Gerald A. Wrenshall[2] (Univ. of Toronto). They used a collection method which depends on the condensation of exhaled vapors in liquid air traps and then analyzed the condensate chemically and by mass spectrometry.

In 106 normal subjects, mean acetone exhalation was 4.6 μg./Gm. condensate/sq. m. body surface, range 1.3-12.7, as against 9.1, range 2.3-42.6, in 70 treated diabetics. Both groups were tested under resting, nonfasting conditions. Discovery of acetone in the exhalation of all normal subjects indicates that it is a normal metabolic product. Females exhaled greater amounts than males. No relation to age was noted in the normal subjects. Serial tests at weekly intervals over one to four months in six normal subjects revealed that a weight increase was accompanied by an increase in acetone exhalation. In three subjects who ingested no carbohydrate for one to seven days, acetone exhalation in each increased fivefold after one day and 100-fold in one after seven days. In one subject, termination of the carbohydrate-free diet by glucose resulted in a decrease in acetone exhalation to about half the pre-glucose value within three hours. Statistically, the diabetics, despite treatment, exhaled significantly more acetone than the controls. The highest values were noted in diabetics under 40.

Effect of β-Hydroxybutyric Acid on Glucose Oxidation in Insulinized Animals. Douglas R. Drury and Arne N. Wick[3] (Univ. of Southern California) studied the ability of rabbits to burn ketone bodies and glucose simultaneously in the pres-

(2) Diabetes 1:188-193, May-June, 1952.
(3) J. Biol. Chem. 196:129-133, May, 1952.

ence of insulin. Insulin caused the rapid disappearance of glucose into the cells with the expected fall in blood sugar despite injection of β-hydroxybutyric acid. However, the rate of glucose oxidation (measured by using C^{14} glucose) was significantly reduced by the competing ketone. Thus, the primary action of insulin appears to be the transfer of glucose into the cell. Its stimulation of glucose utilization is secondary, since other fuels can easily reduce it by competition. Even when the supply of glucose is forced to a maximum by insulin, the tissues will readily burn β-hydroxybutyric acid.

[Since glucose and beta-hydroxybutyric acid are eventually oxidized through a common metabolic pathway, it seems likely that the large amounts of beta-hydroxybutyric acid produced in diabetic acidosis may in themselves interfere with the oxidation of carbohydrate.—Ed.]

Early Diagnosis of Diabetes Mellitus is stressed because of the reversibility of early pathologic changes in the pancreatic islet cells and increase in complications following delayed diagnosis. Martin H. Reinberg, Paul O. Greeley and Mary S. Littlefield[4] (Los Angeles) tested 3,132 college students.

Method.—A routine physical examination was followed by obtaining urine specimens and a venous blood sample. The students returned fasting the next day and 50 Gm. dextrose in 300 cc. lemon-flavored water was ingested. Two hours later venous blood was sampled. Blood sugar content over 130 mg./100 cc. was considered positive in both tests. Patients with positive blood sugar result or glycosuria were recalled for a three hour oral glucose tolerance test with 100 Gm. glucose and another urinalysis. The three hour test was considered positive when the blood sugar peak was over 150 mg./100 cc., with the two hour level above 100 mg. A high fasting blood sugar level or glycosuria was not considered diagnostic in itself. The purpose of the random blood sugar screening test was to see how many diabetics would be missed by this method alone.

Twelve new diabetics, six prediabetics and eight previously known diabetics were discovered. Prediabetics are defined as those who had any abnormal elevation of sugar on any of the samples. Only 4 of the 12 newly discovered diabetics would have been found by urinalysis alone and 3 by the blood sugar screening test alone. By the method of diabetic screening outlined, an incidence of 0.45% newly discovered diabetics and 0.71% total diabetics may be expected in a college age group.

(4) J.A.M.A. 148:1177-1181, Apr. 5, 1952.

Importance of Life Stress in Course and Management of Diabetes Mellitus. In any person, stress situations which lead to a diminution in the carbohydrate and protein intake or to a relative increase in the energy expenditure will lead to an increased utilization of body fat and impaired glucose tolerance. Evidence is accumulating to indicate that significant alterations occur in the metabolic processes of patients with otherwise well controlled diabetes when they react to environmental stresses. It is known that physical stresses increase insulin requirements. Lawrence E. Hinkle, Jr., and Stewart Wolf[5] (New York Hosp.-Cornell Univ. Med. Center) paid special attention to the circumstances in the lives of 64 diabetics which surrounded onset of the disease and exacerbations and remissions. Ages ranged from 12 to 81 and all grades of severity were included.

During quiet resting, blood ketone and glucose levels and urinary output of nondiabetics changed little during the morning of a fast but, with continued fasting, the glucose level gradually fell to about 40-50 mg./100 cc. while the ketone level rose. Urinary output usually increased. Similar changes occurred under stress in nondiabetics and diabetics, but to much greater degree in the latter. In the diabetic, if the stress continued, blood glucose level ceased to fall and even rose at times. In labile diabetics, the initial fall was sometimes severe enough to produce hypoglycemic symptoms. A diabetic with a relatively high blood sugar level and established glycosuria may under stress have a rapid rise in blood ketones and increased urinary excretion of water, glucose, ketones and chlorides.

The authors conclude that there is a causal relationship between stresses and fluctuations in the control of diabetes. During periods of resentment, rebellion and hopelessness, patients might stop taking insulin, eat a great deal of food (or stop eating entirely) or expose themselves to illness by such maneuvers as neglecting to sterilize syringes. Life stress therefore may lead to ketosis by a variety of mechanisms, although direct metabolic response appeared to be the most important.

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(5) J.A.M.A. 148:513-520, Feb. 16. 1952.

General Practitioner Treats the Uncomplicated Diabetic. Everett O. Bauman[6] (Newark, N. J.) describes a simple and practical method. Diagnosis is based on classic symptoms, pronounced glycosuria and fasting blood sugar level over 130 mg./100 ml. Only when symptoms are equivocal, glycosuria minimal and fasting blood sugar content normal is a two hour glucose tolerance test with 100 Gm. glucose indicated. The patient must have received an adequate carbohydrate intake for a week before the test. A blood level above 130 mg./100 ml. two hours after glucose ingestion indicates impaired tolerance; diabetes may be diagnosed if intracranial, thyroid, adrenal and liver disease can be ruled out. Urine tests are made at one and two hours to detect a low renal threshold.

Dietary regimen should be based on certain high carbohydrate foods that must be taken in definite amounts and at definite times. These are 8 oz. milk at each meal and at bedtime, 2 slices bread at each meal, 30 Gm. dry weight of cereal (3 level tablespoonsful of oatmeal) at breakfast and 4 oz. fruit juice at each meal. This supplies 203 Gm. carbohydrate, 30 Gm. fat, 55 Gm. protein and 1,300 calories. These foods have been chosen because of general appeal and availability. Foods with equivalent food values and absorption speeds which may be substituted include: 8 oz. beer or buttermilk for 8 oz. milk; 1 small potato, 1/3 cup cooked spaghetti or 7/8 cup corn flakes for 1 slice of bread; 1 large orange, 1 medium pear, 1½ cups strawberries or 1 medium banana for 4 oz. fruit juice, and so on. These are then supplemented by desired amounts of low carbohydrate foods (meat, poultry, fish, eggs, vegetables—except potatoes, corn, lima beans and peas—cheese, butter, cream, etc.) that may be taken at any time. Both "free" and "must" foods may be limited by other factors, particularly obesity. The final criterion of control is adequate carbohydrate utilization. At first this is achieved by checking postcibal urines and adjusting carbohydrate foods to produce minimal glycosuria. This is finally checked by balancing carbohydrate intake against 24 hour excretion. The metabolism of 150-200 Gm. carbohydrate will prevent acidosis and probably reduce vascular degenerative processes.

When this cannot be accomplished by diet adjustment

(6) J. M. Soc. New Jersey 49:91-98, March, 1952.

alone, insulin is necessary. It is also generally required with urgent symptoms of diabetes, clinical or laboratory evidence of ketosis and severe infections. Insulin dosage can usually be determined on an outpatient basis and should be achieved as quickly as possible with as few injections of the smallest amount of insulin necessary. In Bauman's method, a small dose of regular insulin (RI) is given before breakfast and gradually raised until the Benedict reaction of the after-lunch urine is green or less. The after-lunch urine is more reliable, as RI given before breakfast does not at first have its maximal effect on the breakfast. After two to three days of stabilization, if the two hour after-supper urine is not improved, small doses of RI are given before supper or protamine zinc insulin (PZI) is given before breakfast until the after-supper specimen gives a green or blue reaction. This dose of insulin must be raised cautiously to prevent reactions during the night. When urine reactions before breakfast and after lunch and dinner are blue or green, the amount of RI given before dinner and the amount of PZI is given as PZI in conjunction with but separately from the dose of RI before breakfast. After control is again ascertained, a single injection can be given by converting half the PZI units into RI; total RI and remaining PZI are combined in a single syringe. When the ratio of RI to PZI is 2:1, an equivalent amount of NPH insulin may be used instead.

Complications of Diabetes

Metabolic Study of Disturbances Taking Place during Diabetic Coma and Its Treatment, with Special Reference to Changes in Potassium Metabolism. A. F. Willebrands, J. Groen and M. Frenkel[7] (Amsterdam) studied five patients treated for diabetic coma by a conventional method consisting of insulin (190-680 units in the first 24 hours) and intravenously administered saline (1-4.5 L.) supplemented on occasion by sodium bicarbonate or lactate. On the first and second days no solid food was given but after this, for periods ranging from one to six days, a special diet of rice, butter and sugar was given. It contained 2 Gm. protein, 50 Gm. carbohydrate, 15 Gm. fat, 10-15 mg. potassium and 350 calories. After this

(7) Acta med. scandinav. 141:331-351, 1952.

trial period, the dietary intake of potassium and nitrogen was varied, and subsequently a standard diabetic diet was given.

In all cases, the sodium and chloride levels in the serum were practically normal during coma and remained so during treatment and recovery. The potassium level, which at the time of hospitalization was increased in the more severe cases, dropped with treatment to levels below normal. The lowest levels were reached in one to three days and low levels persisted for several days even though considerable quantities of potassium were provided. Urinary excretion of potassium was high during coma but fell rapidly during treatment to almost zero. The excretion remained low for several days, decidedly lower than the intake, even with increased potassium intake. During the treatment all the patients showed potassium retention, in some estimated to be roughly 10-12 Gm. As the serum potassium remained low during this period of potassium retention, most of the retained potassium must have passed into the intracellular space. In no case did signs of hypopotassemia occur, probably because the serum level did not drop low enough. During coma, all patients had negative nitrogen balance. When nitrogen was supplied in the food the nitrogen balance rapidly reached equilibrium. The phosphate metabolism showed a picture analogous to that of potassium, with the difference that only slight phosphorus retention was observed and that the phosphate balance returned to equilibrium earlier than the potassium balance.

Intravenous infusions of potassium are not generally needed in the treatment of diabetic coma, but potassium-rich foods should be taken orally.

Diabetic Coma—Therapeutic Problem. Garfield G. Duncan[8] (Pennsylvania Hosp., Philadelphia) calls attention to the importance of early diagnosis of diabetic coma. Such a diagnosis is possible in the home by simply finding grade 4 reactions for glycosuria and ketonemia by qualitative tests in a subject with clinical evidences of ketosis. Initial therapy with insulin, fluids and sodium chloride should be started at once. Regular insulin, 100 units, and 8 oz. of a salty broth should be given. The patient should then be brought to the hospital where blood sugar level, CO_2-combining power, hematocrit,

(8) Ann. Int. Med. 37:1188-1196, December, 1952.

blood specific gravity and urea nitrogen level are determined. The urine is tested for sugar, acetone, culture and sediment, an ECG is made and blood pressure is recorded. For clinical purposes glycosuria and a 4 plus reaction for acetone in the plasma are the criteria for diagnosis. The qualitative tests for hyperketonemia on undiluted plasma and on various dilutions give more reliable indications of the gravity of the ketosis and the prospective need for insulin than does a knowledge of the CO_2-combining power or sugar content of the serum. The CO_2-combining power may give false information in the presence of renal failure or hypoventilation.

At Pennsylvania Hospital, when a grade 4 reaction for plasma ketones is found, a sample of plasma is diluted 1:1 with normal saline; if this dilution still gives a grade 4 reaction for acetone, ketonemia is of severe degree and large amounts of insulin will be tolerated at the beginning of therapy. This diluted mixture is further diluted 1:1 with normal saline, and if a grade 4 reaction is still elicited ketosis is of a profound degree. In such cases the apparent effectiveness of insulin is greatly impaired, and as much as 300 units of regular insulin is given as the initial dose. If the patient has a grade 4 reaction for acetone in the undiluted plasma but only grade 3 or 2 on the first dilution, he is more sensitive to insulin, and 100 units of regular insulin is given, 40 units intravenously and 60 units subcutaneously, with 25 units at one hour intervals until the undiluted plasma gives less than a grade 4 reaction. Thus, 100 units of regular insulin is given as the initial dose if the grade 4 reaction for plasma acetone is obtained only in the undiluted plasma, 200 units if it is also obtained in the first dilution, 300 units if it is observed in the second dilution and 400 if it occurs in the third dilution. A decrease in the ketone content of the plasma is detectable before any apparent reduction in ketonuria. When this occurs there is a rapid return of sensitivity to insulin and the amount is reduced and only given every four to six hours. If there is no reaction with the qualitative tests for ketonemia and glycosuria subsides, glucose is administered and insulin therapy withheld until glycosuria returns.

Adults in diabetic coma are given fluids intravenously until the blood pressure and hematocrit are normal. No attempt

is made to correct deficits of electrolytes during the first few hours of therapy. Intravenous administration of fluids is discontinued as soon as the patient can take adequate fluids orally. Hypopotassemia can be detected quite early by the ECG, and the clinical danger of hypopotassemia is postponed several hours. After six hours of therapy, potassium can be given orally or intravenously if renal function is good and urine output is adequate. Patients in profound ketonemia can be given a solution of multiple electrolyte composition intravenously. Glucose solutions are not necessary parenterally while extreme degrees of hyperglycemia persist. Glucose can be given parenterally when the blood sugar is below 300 mg./100 cc. It will protect against the danger of a rapidly developing hypoglycemia in patients who become sensitive to insulin rapidly at a time when their glycogen stores are depleted; it alleviates tissue starvation and is important in reducing excessive ketone production.

The disappearance of excessive ketoacids and the release of base that accompany therapy make the routine use of alkali unnecessary. But if the degree of ketosis is extreme and the patient is greatly hyperpneic, sodium-R-lactate in an amount calculated to raise the CO_2-combining power 10-15 vol. % and no more can be used.

Treatment of Diabetic Ketosis. D. N. Nabarro, A. G. Spencer and J. M. Stowers[9] (Univ. College Hosp., London) make recommendations based on balance studies in patients recovering from ketosis. An average loss of 3 L. extracellular water, 500 mEq. sodium, 400 mEq. chloride, 3 L. intracellular water, 350 mEq. potassium, 150 mEq. phosphorus and 40 mEq. magnesium was shown. Therapy strives to replace these losses and restore normal carbohydrate metabolism. Adequate soluble insulin must be given early. In moderately severe ketosis 100 units should be given initially. When normal insulin requirement exceeds 60 units daily or when there is severe infection, dehydration, circulatory collapse or coma, 200 units should be given initially. Blood sugar level should be estimated as soon as possible; if it is above 600 mg./100 ml., 100 units more is given. Because poor circulation delays absorption, four fifths of the insulin should be given intramus-

(9) Lancet 1:983-988, May 17, 1952.

cularly and the rest intravenously. A blood sugar estimate made 90 minutes after initial insulin dose should guide further treatment; if the level has risen, the dose is doubled; if the same, the dose is repeated; if falling, no insulin is given and the level is re-estimated 90 minutes later. Blood sugar level should be estimated every two hours since urine sugars do not reflect changes above 300 mg./100 ml. When blood sugar values approach renal threshold, urine may be checked every three to four hours and insulin dosage adjusted accordingly.

Sodium and chloride losses in the extracellular fluid should be replaced in the same ratio that they are lost, i.e., 1.3:1. Attempts to correct acidosis with excessive lactate and bicarbonate may cause large amounts of sodium to enter the cells and, as ketonemia diminishes, may result in alkalosis. A solution suitable in most cases contains 5.85 Gm. sodium chloride and 3.36 Gm. sodium lactate/L.; it supplies 130 mEq. sodium, 100 mEq. chloride and 30 mEq. lactate/L. and more closely approximates extracellular fluid composition than isotonic saline. Because gastric atony is common, fluids must be given intravenously and the first 2 L. should be given as rapidly as age and condition of heart and lungs allow. Circulatory collapse must be combated with transfusions of blood or plasma. Solutions containing glucose should be given only two to six hours after start of treatment and when blood sugar values have begun to fall. Maintenance of high blood sugar levels from outset of therapy produces cellular dehydration and osmotic diuresis with continued loss of fluids and electrolytes. As diabetic acidosis develops, there is cellular dehydration and catabolism with potassium, magnesium and phosphorus losses of the aforementioned magnitude. Dehydration and depressed renal function lead to initially elevated serum levels of these electrolytes.

With fluid replacement and glycogen formation incident to therapy, the elements re-enter the cells and serum levels fall rapidly. If urinary flow is adequate, it may be assumed that when blood sugar level begins to fall, potassium level is showing a similar trend and administered fluids should contain the necessary intracellular ions. A suggested solution for cellular repair contains 1.17 Gm. sodium chloride, 0.87 Gm. dibasic

potassium phosphate, 1.49 Gm. potassium chloride, 0.24 Gm. magnesium chloride and 50 Gm. glucose to a liter of solution. This solution contains 30 mEq. potassium and should be given no faster than 1 L. in four hours. Intravenous therapy may be discontinued when fluids are well tolerated orally. A mixture containing 50 Gm. glucose and 2 Gm. dibasic potassium phosphate in 500 cc. orange juice-flavored water has helped to restore intracellular potassium and may be given in amounts to 2 L. daily for two or more days. This is followed by milk feeding and return to normal foods with high protein intake as soon as possible.

[Of course, the most important measures in the treatment of diabetic acidosis or coma are the administration of insulin and the replenishment of fluids and electrolytes by intravenous infusion of saline solution. It should be emphasized that these measures in themselves will cause a depletion of the body potassium store. Consequently, the cautious administration of potassium has been life-saving, thus greatly lowering the rate of death from diabetic coma. With most patients, potassium can be given by mouth at the time it is needed, which is after insulin has been given and the intravenous infusion of saline solutions has been continued for several hours. Potassium depletion is indicated by the presence of hypoactive reflexes, muffled heart sounds and the typical ECG abnormalities.

Controversy over the administration of glucose in the treatment of diabetic acidosis is largely semantic. It is recognized that carbohydrate stores are greatly reduced, but it seems useless to administer glucose until it is needed, i.e., when the urinary Benedict reaction comes down the scale from red through orange and yellow to green. At this stage, most patients can take bland carbohydrates by mouth, e.g., in the form of ginger ale.—Ed.]

Degenerative Complications of Diabetes. Howard F. Root[1] (Harvard Med. School) discusses four of the major degenerative sequelae.

1. Vascular disease. The characteristic lesions in smaller blood vessels, i.e., arterioles, venules and capillaries, are specific for diabetes. All these small vessels may be affected in long-standing diabetes with poor control. Three types of arterial degeneration occur: atherosclerosis, calcification of arterial walls and arteriolosclerosis. Although atherosclerosis is clinically important since it is the chief cause of death in diabetes, it is the hyaline change in arteriolar walls which is distinctive in diabetics. The human species seem inherently susceptible to atherosclerosis, but there is an increased incidence in diabetics. This may be related to altered lipid metabolism and lipid transport. Instability of the solution of cholesterol in the

(1) J. Clin. Endocrinol. 12:458-479, April, 1952.

blood rather than increased level of cholesterol concentration itself is the condition required for its deposition in the arterial wall. This stability in turn depends on the relation of cholesterol level to other substances in the blood such as phospholipids and lipoproteins. Hypercholesteremia is frequently seen in poorly controlled diabetics and is best combated by correction of obesity and a moderately high carbohydrate diet with necessary insulin for adequate utilization. Despite past controversies, evidence exists that even in normal individuals serum cholesterol concentration will fall if intake of fat is sufficiently restricted.

2. Neuropathies. Degenerative changes caused by diabetes may involve the higher centers of the brain, the spinal cord, the sympathetic nervous system or the peripheral nerves. The more severe types of diabetic neuropathies are seen almost entirely in patients whose diabetes has not been under adequate control for considerable periods. In early or mild forms, symptoms are often generalized, beginning with vague aches, pains and paresthesias which are more marked at night and on exposure to cold. Relief is obtained by walking, in contrast with pains of arthritis or impaired circulation which are made worse by exertion. Vibration sense can be diminished and may be differentiated from that in pernicious anemia by the absence of lateral column degeneration. The response of diabetic neuropathy to control and regulation of diabetes by insulin and diet is consistent with the concept that the lesions are chiefly of the central nervous system rather than of the peripheral nerves alone. In treatment of acute diabetic neuropathy, bed rest and control are essential. Vitamin B_{12}, 30 mg. intramuscularly daily, has been recommended. BAL in doses of 100-200 mg. daily for 7-14 days caused improvement in 12 of 22 patients who had previously failed to respond to other forms of treatment.

3. Diabetic nephropathy. Renal lesions which complicate diabetes are: (*a*) presumably reversible metabolic phenomena, e.g., glycogen and fat deposits in tubules; (*b*) arteriolorsclerosis (nephrosclerosis); (*c*) intercapillary glomerulosclerosis; (*d*) acute and chronic pyelonephritis, including necrotizing renal papillitis, and (*e*) arteriosclerosis. Glycogen deposits in the tubules merely indicate glycosuria. Fat deposits in the tubules

indicate injury to the tubular epithelium and commonly occur in coma. Arteriolosclerosis appears earlier and is more common in diabetes than in other diseases. The last four lesions listed often occur together, especially in younger patients with diabetes of long duration. Intercapillary glomerulosclerosis is an important complication in diabetes of 10 years' or more duration, with onset in youth or childhood. The typical lesion is a round or globular mass in the central portions of the glomeruli, appearing between the capillaries. Specificity of this lesion was demonstrated by its production in dogs made diabetic with anterior pituitary extract. The associated clinical syndrome may begin with progressive albuminuria followed by edema not necessarily related to albumin levels and then hypertension. Renal dysfunction, uremia and anemia are common. Of 43 patients with intercapillary glomerulosclerosis, 36 were aged 20-30. None had good control of diabetes, 45% had poor control and the rest fair control. It is impossible to relate the lesions to severity of diabetes since measurement of severity depends usually on insulin requirements, and it is characteristic that as renal failure advances insulin requirements fall.

4. Retinitis. Many patients who have been diabetic for a long time may have small punctate and irregular retinal hemorrhages. Use of special stains has shown many of the hemorrhages are actually clusters of microaneurysms. There may be associated dilatation and tortuosity of veins and hard white exudates. In some patients a further stage is characterized by many newly formed vessels and growth of a connective tissue membrane from the retina into the vitreous (retinitis proliferans). Retinitis may progress rapidly in women coincident with onset of pregnancy and in some cases may be sufficient reason for termination of pregnancy. Some workers regard premature vascular disease and retinitis as inevitable in diabetes and due to the duration of the disease; they advocate a free diet and insulin given only to the extent of preventing acidosis and actual symptoms. Opposed to this view are many who believe that every effort should be made to restore physiologic conditions, including freedom from glycosuria and hyperglycemia as far as practicable. A review of a large series of diabetics with onset of the disease at age

18-30 revealed that (*a*) no patients with excellent or good control showed advanced retinitis or calcification of arteries even after 20-34 years; (*b*) diabetic nephropathy did not develop in patients with good or excellent control for 20-34 years. In 62 patients maintained under poor or fair control, nephropathy developed. Root concludes that whatever the specific etiologic factors causing diabetic degenerative lesions may be, regulation of diabetes controls these factors and thus that regulation becomes more important than duration of diabetes in their prevention.

Charcot Joints and Infectious-Vascular Lesions of Bones in Diabetes Mellitus. Barkley Beidleman and Garfield G. Duncan[2] (Pennsylvania Hosp., Philadelphia) report that patients with diabetes mellitus may have destructive lesions of the

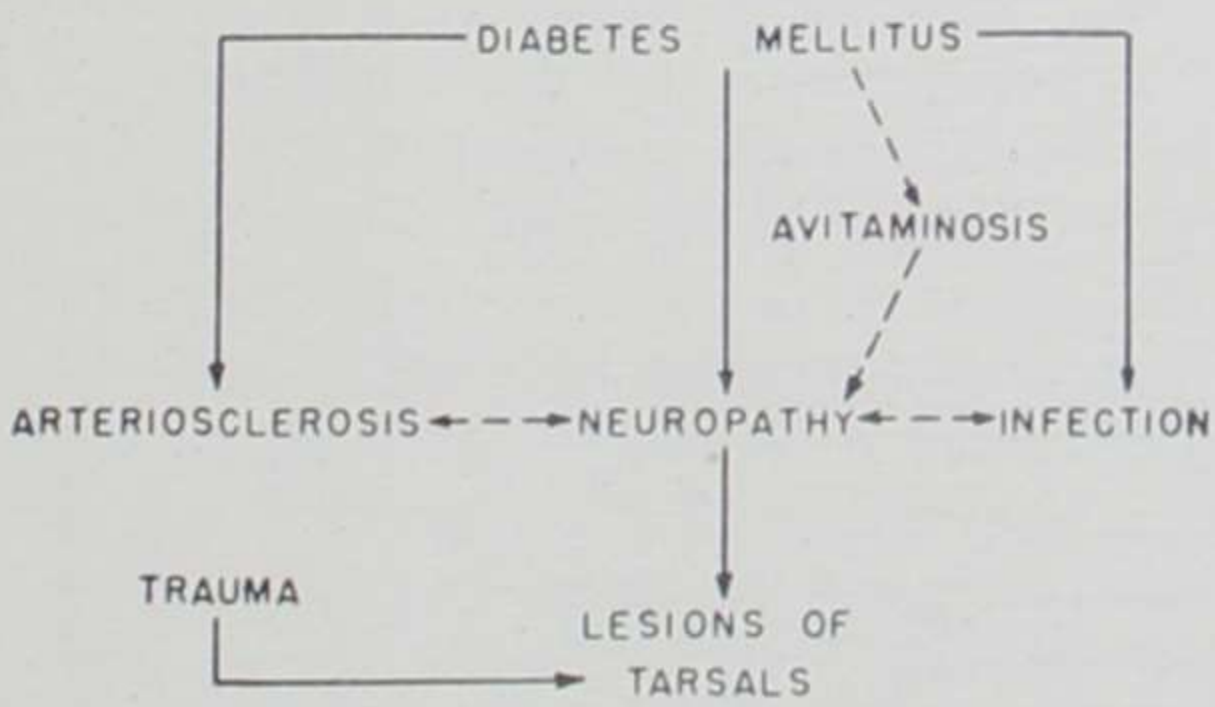

Fig. 97.—Pathogenesis of Charcot type of bony lesion in feet of diabetics. Solid lines indicate well established relationships; broken lines, more tenuous ones. (Courtesy of Beidleman, B., and Duncan, G. G.: Am. J. Med. 12:43-52, January, 1952.)

bones of the foot, demonstrable by x-ray. These are of two types. One consists of gradual dissolution of the tarsal bones and their articulations (Charcot joints) in patients with diabetic neuropathy, with associated sensory loss in the legs and feet. Presumably the pathogenesis is the same as in Charcot joints associated with syphilitic tabes or syringomyelia—a loss of protective pain and proprioceptor sensibility in a joint which has intact motor power and is subjected to repeated minor trauma. The role of arteriosclerosis, avitaminosis and infection is tenuous, as shown in Figure 97.

The second type of bone lesion consists of rarefaction of the phalanges and metatarsals secondary to chronic infection

(2) Am. J. Med. 12:43-52, January, 1952.

in the adjacent soft tissues and to arterial insufficiency. In these cases, diabetes may be of short duration, there may be no diabetic neuropathy and the evidence of infection or vascular insufficiency is usually apparent, thus distinguishing the condition from diabetic Charcot joints.

The authors report four cases of Charcot joint in diabetes mellitus, in two of which the second type of bone lesions also was present. No type of treatment used, including regulation of the diabetes, appeared to have any effect on the bone lesions.

Postmortem Study of Vascular Disease in Diabetics. E. T. Bell[3] (Univ. of Minnesota) presents a quantitative comparison of death rate from vascular disease in diabetics and nondiabetics by a review of 1,559 autopsies performed between 1910 and 1951. Histologic material was available in 75%. Less than 5% belonged to the preinsulin era. In reports on survival from known onset, the percentage of long term survivors decreases as age of onset increases. When diabetes began before 40, about 45% lived over 10 years and 17% over 20 years. When diabetes began between 40 and 60, 31.5% lived over 10 and 7% over 20 years.

There is a convincing relation between age at death and fatal vascular disease. Diabetes clearly shortened life expectancy. No diabetic under 20 died of vascular disease. In the third and fourth decades combined, 22.8% died of vascular lesions, commonly of renal arteriosclerosis. In the fifth and sixth decades combined, 45.6% were vascular deaths and after 60, 56.5%. In order of frequency, vascular lesions consisted of coronary disease, gangrene, encephalomalacia, renal arteriosclerosis, myocardial failure, intracerebral hemorrhage and atherosclerotic aneurysm. In 4,419 autopsies on nondiabetics, vascular death was rare before age 40, but one third of the deaths after 60 are due to vascular disease. A comparison of the incidence of different types of vascular disease in nondiabetics and in diabetics is shown in the table. In the third and fourth decades, deaths from vascular lesions were four times as common and in the sixth decade twice as common in diabetics.

The influence of diabetes in promoting atherosclerosis is

(3) A.M.A. Arch. Path. 53:444-455, May, 1952.

COMPARISON OF DEATH INCIDENCE FROM VASCULAR DISEASE IN DIABETICS AND NONDIABETICS OF CORRESPONDING AGE

Age at Death, Yr.		Total No. of Patients	Percentage Dying of Vascular Disease: Coronary Disease	Encephalomalacia	Intracranial Hemorrhage	Myocardial Failure	Gangrene	Aneurysm	Renal Arteriosclerosis	Total
1- 20	Nondiabetic	273	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Diabetic	34	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
20- 40	Nondiabetic	548	1.1	0.5	1.8	0.4	0.0	0.0	1.8	5.7
	Diabetic	140	6.4	0.0	0.0	1.4	1.4	0.0	13.6	22.8
40- 60	Nondiabetic	1,334	10.9	2.6	4.5	2.8	0.0	0.6	1.5	22.9
	Diabetic	423	14.9	5.4	2.8	4.0	10.2	0.5	7.8	45.6
60-100	Nondiabetic	2,264	16.1	6.9	3.3	5.0	0.5	0.7	0.5	32.9
	Diabetic	958	22.4	7.2	1.7	5.9	16.0	0.1	3.1	56.4
40-100	Nondiabetic	3,598	14.2	5.3	3.7	4.2	0.3	0.7	0.9	29.2
	Diabetic	1,381	20.3	6.7	2.0	5.4	14.2	0.2	4.5	53.1

striking and much more pronounced in younger than in older persons. When diabetes begins before age 40, vascular lesions seldom appear during the first 10 years of the disease; thereafter most patients die of vascular lesions. However, vascular disease is not inevitable even after 30 years of diabetes. Among 93 persons who lived over 20 years after onset of diabetes, no serious vascular disease was found at autopsy in 28; absence of vascular disease in them could not be attributed to better control of diabetes.

Classification according to severity of diabetes showed no significant difference in incidence of vascular disease in patients with mild and those with moderately severe or severe diabetes. The danger of vascular complication was as great in mild as in severe diabetes. In seven subjects with hemochromatosis, autopsy revealed no vascular complications.

Coronary Arteriosclerosis in Diabetics. Richard W. Thaler and Christian George Wornas[4] (Boston) studied the effect of careful control of diabetes on prevention and postponement of angina pectoris and myocardial infarction in 50 patients (35 women) with average duration of diabetes of 18.1 years in whom angina pectoris and/or myocardial infarction developed. Age range was 50-82, except for one aged 33 and one 46. Degree of control was estimated as good, fair or poor, based on the criteria of frequency of urine and blood sugar determinations, urine and blood sugar levels, rigidity of dietary control, regularity of insulin administration, regularity of medical supervision and incidence of coma. In 15 patients control was considered good, in 12 fair and in 23 poor.

Of the 50 patients, 92% had a history of obesity, 84% had had hypertension, 67% of the 15 men and 91.4% of the 35 women were hypertensive, in 90% angina pectoris developed and 34% had myocardial infarctions. Average age at onset of angina pectoris in the 45 patients was 60.7 and of myocardial infarction in the 17 affected patients was 57.1. In the 15 patients with good diabetic control, average age at onset of coronary artery disease was 65.6, in contrast to 56.1 in the 23 with poor control and a group average of 60.2 (56.4 years for the 15 men; 61.8 for the 35 women). Average age at onset of coronary artery disease in 10 patients with poorly controlled

(4) Am. J. Digest. Dis. 19:33-37, February, 1952.

diabetes of 10-15 years' duration was 60.2 years, 53 years in 13 with poorly controlled diabetes of 16-38 years' duration, and 67 years in 13 with good control of diabetes of 16-38 years' duration. Since only 41.2% of the patients who had myocardial infarcts and 30% with angina pectoris were male, diabetes appears to cancel the female's relative "immunity" to severe coronary arteriosclerotic disease.

The better controlled patients required an average insulin dosage of 39 units and those poorly controlled, 49 units. Among 12 of the poorly controlled patients who initially took 20 units of insulin or less daily, average age at onset of coronary disease was 57.7 as against 54.4 years in the 11 other poorly controlled patients who initially took more than 20 units daily. Among 28 patients with a known history of familial cardiovascular disease, average age at onset of coronary artery disease was 55.3.

These data show that prolonged good control of diabetes mellitus is an important factor in postponement of the manifestations of coronary arteriosclerosis.

Vascular Complications of Juvenile Diabetes. Harriet G. Guild, Wilson Grubb, Mildred Y. F. Chu and James B. Sidbury, Jr.[5] (Johns Hopkins Hosp.) present an analysis of 40 patients who had had juvenile diabetes for 10 years or more. The degree of diabetic control during the years was considered good in 14, fair in 17 and poor in 9. Vascular complications, especially retinal, may be found relatively early in this disease. Although the incidence of these complications increases with time, the time of appearance, severity of the lesions and rapidity of progression are modified by the degree of diabetic control. Vascular lesions were present in only 4 of the 14 patients with good control, 10 of the 17 with fair control and all of the 9 with poor control. They included retinal changes, renal abnormalities, calcification in the arteries of the leg and sporadic cholesterol elevations. Patients with only fair or poor control may show lesions as early as 10 years after onset and rarely escape some evidence of vascular damage by the time the disease has been in progress for 15 years. Patients consistently well controlled may remain free from lesions for as long as 18 years and may show no more than minimal

(5) J. Pediat. 41:722-739, December, 1952.

changes of doubtful significance as long as 22 years after onset. Good control is more easily established and maintained in children in whom diabetes develops during the preschool period than in those in whom it occurs at a later date, when habits are more fixed and there has already been a taste of freedom.

Every effort must be made to achieve and maintain as good control as is humanly possible in children with diabetes and at the same time to guard their general health and make them normal and well adjusted with a psychologically healthy attitude toward their disease. Regularity of attendance at a clinic or the physician's office, so that careful supervision and systematic training in the diabetic way of life is possible, is an important factor in maintenance of good control. Adequate social service assistance is an essential adjunct to a diabetic clinic if the goal of satisfactory regulation is to be achieved in the greatest possible number of patients.

Serum Lipoproteins and Cholesterol Levels in Normal Subjects and in Young Patients with Diabetes in Relation to Vascular Complications. Nils R. Keiding, George V. Mann, Howard F. Root, Eleanor Y. Lawry and Alexander Marble[6] (New England Deaconess Hosp., Boston) determined the levels of serum cholesterol and lipoproteins of the S_f 12-20, S_f 21-35 and S_f 35-100 classes in 218 diabetic patients and compared the values with those for 691 normal subjects. Results indicated that the severity of diabetes as measured by insulin dosage and duration of diabetes are not important factors in determining these levels in patients under insulin treatment for up to 25 years.

Classification of 144 young patients with diabetes for over 10 years on the basis of control revealed higher mean levels of serum lipids in those with poor control. Levels of the S_f 12-20 lipoproteins exceeding 50 mg./100 cc. were found in 32% of patients with poor control, 17% with fair control and 10% with good control. In 26 patients with diabetic nephropathy, all of the serum lipid components were decidedly elevated as compared with values for the 118 subjects without renal disease.

A significant observation was the relation between pres-

(6) Diabetes 1:434-440, Nov.-Dec., 1952.

ence of retinitis and elevated values of the S_f 12-20 lipoproteins. Arterial calcification showed a much less striking relation to this lipoprotein. The lipoprotein levels alone were significantly associated with retinitis.

Lipoprotein Molecules, Cholesterol and Atherosclerosis in Diabetes Mellitus. Joseph H. Barach and Alexander D. Lowy[7] (Univ. of Pittsburgh) present a preliminary survey on what will eventually be a series of 1,000 patients with diabetes mellitus. Studies are being carried out to determine the relation of blood cholesterol and S_f 12-20 lipoprotein molecules to age, sex, color, occupation, duration of disease, overweight, size of heart, calcification of thoracic and abdominal aorta, femoral and tibial vessels, blood pressure and diabetic control. Hyperlipemia in diabetes is believed related to the increased incidence of atherosclerosis in this disease. So far in these studies the frequency of hypercholesteremia and increase in S_f 12-20 lipoprotein molecules indicates that a diabetic has a constant tendency toward increased lipids in the blood stream.

The incidence of increased blood cholesterol and lipoproteins was higher in females, those in whom the disease was of longest duration, those who were overweight, those with abnormal-sized hearts, those with hypertension, those with poor diabetic control and those with severe calcification of the blood vessels. A distinct relation between hyperlipemia and the complications of diabetes mellitus was apparent.

It is not possible to compare values of blood cholesterol and of lipoproteins in the same patients. Of 601 patients so studied, both values were abnormal in 60%, but in the other 40% they showed opposite trends. While one was above normal level, the other was below in the same blood sample. In these cases the level of one would not have indicated the actual value of the other.

Follow-up Study of Juvenile Diabetics is reported by Robert B. Kerr, Gordon D. Brown and Norman Kalant[8] (Univ. of Toronto) to shed light on the course and outcome of this disease and to ascertain the effects of treatment. A group of 81 patients, who became diabetic before age 16, was studied for degenerative complications. The group was di-

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(7) Diabetes 1:441-446, Nov.-Dec., 1952.
(8) Canad. M. A. J. 66:97-104, February, 1952.

INCIDENCE OF COMPLICATIONS RELATED TO DIABETIC CONTROL AND DURATION OF DIABETES IN 81 PATIENTS

Duration of diabetes	*0 - 9 years*		*10 - 14 years*		*15 - 19 years*		*Over 20 years*		*Total*	
Diabetic control	good	poor	good	poor	good	poor	good	poor	good	poor
Number of cases	6	12	10	9	6	10	10	18	32 100%	49 100%
Retinopathy	0	2	2	5	4	7	6	15	12 38%	29 59%
Cardiac	0	0	0	0	0	1	1	5	1 3%	6 12%
Renal	0	1	0	0	0	3	2	5	2 6%	9 18%
Vascular calcification	0	0	0	1	0	0	2	10	2 6%	11 22%
Neuropathy	0	0	0	1	0	2	1	4	1 3%	7 14%
Skin	0	2	0	1	0	3	0	2	0 0%	8 16%
Other	0	0	1	1	0	0	0	1	1 3%	2 4%
No. of patients with complications	0	4	3	6	4	8	6	18	13 41%	36 73%
No. of patients free from complications	6	8	7	3	2	2	4	0	19 59%	13 27%

vided in two based on an estimate of the quality of control maintained throughout the history of diabetes. The first group included well controlled patients; the second, those with only fair or poor control. Only 40% of the patients qualified for the first group.

Complications were demonstrable in 49 of the patients; 41 had retinopathy, 7 cardiac disease, 11 renal disease, 13 vascular calcification, 8 neuropathy, and 8 skin lesions. Tabulation clearly demonstrated that the total number of complications and the incidence of each type of complication increased with increased duration of diabetes (table). Of the 49 patients with complications, 24 had had diabetes over 20 years.

Incidence of complications increased with the lack of good control. After 15 years or more of diabetes, 6 of 16 well controlled patients showed no clinical evidence of degenerative change, whereas only 2 of 28 poorly controlled patients were in this fortunate condition.

Of 23 pregnancies in 9 diabetic women, 11 living children were born. However, 9 of 10 pregnancies in 4 well controlled mothers resulted in living children.

The importance of striving constantly for physiologic control of diabetes, instead of for mere freedom from symptoms, in an effort to postpone the development of complications, is stressed.

[Once again, this study shows how worth while it is to attempt to gain the patient's co-operation and to strive for strict control of diabetes mellitus.—Ed.]

Significance of Atheroma of Renal Arteries in Kimmelstiel-Wilson Syndrome. G. M. F. Hall[9] (King's College Hosp., London) reports pathologic study of the kidneys of 135 diabetics. Diabetic glomerulosclerosis was encountered in 51 patients. Three characteristic lesions were noted: (1) the nodular lesion of Kimmelstiel and Wilson in the glomerular tuft, (2) the exudative lesion, often of crescent shape at the glomerular margin, and (3) efferent arteriolosclerosis.

Eight patients in the group are of special interest since they all died of uremia and had gross atheroma of the renal arteries which gave the kidney a distinctive gross and histologic appearance with ischemic obliteration of vast numbers of glomeruli. This malignant type of renal change is to be contrasted with 43 other instances of diabetic glomerulosclerosis with no evidence that the renal lesion, without renal artery atheroma, was responsible for death.

(9) J. Path. & Bact. 64:103-120, January, 1952.

More Glomerular Changes in Diabetics. From review of 290 autopsies, H. J. Barrie, C. L. Aszkanazy and G. W. Smith[1] (Univ. of Toronto) report changes which differ fundamentally from those described by Kimmelstiel and Wilson, affecting the glomerular tuft, capsule and possibly the basement membrane of the tubules.

The glomerular change was found in 16 autopsies. In sec-

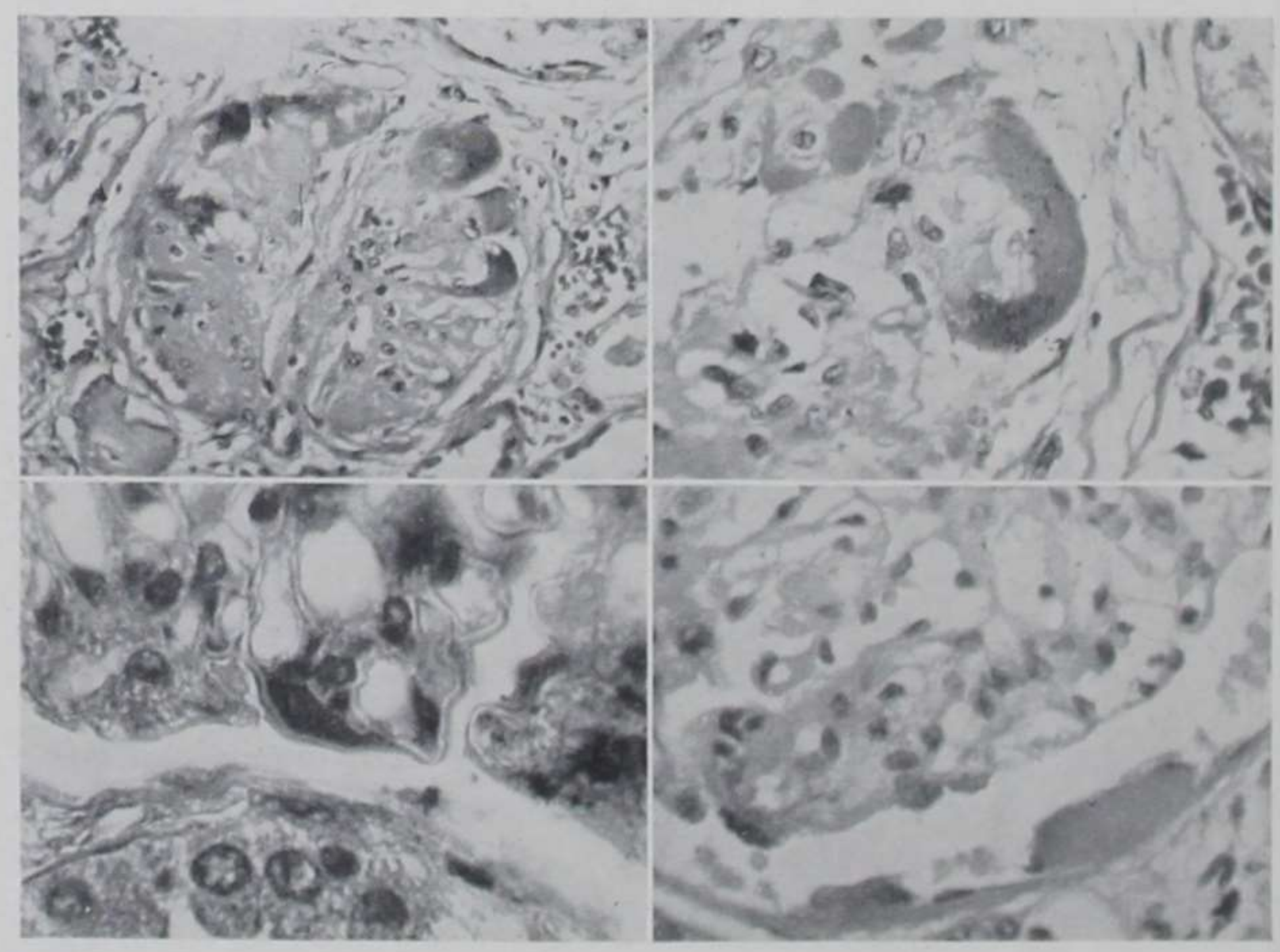

Fig. 98 (top left).—Crescents forming fibrin cap in diabetic glomerulus. Hematoxylin-eosin; reduced from × 256.

Fig. 99 (top right).—Fibrin cap, showing its position outside endothelial cells of glomerular tuft. Hematoxylin-eosin; reduced from × 538.

Fig. 100 (bottom left).—Early formation of fibrin cap between basement membrane and endothelial cell of glomerular tuft. Phosphotungstic acid-hematoxylin; reduced from × 900.

Fig. 101 (bottom right).—Capsular drop in diabetic glomerulus. Hematoxylin-eosin; reduced from × 538.

(Courtesy of Barrie, H. J., *et al.*: Canad. M. A. J. 66:428-431, May, 1952.)

tions stained with hematoxylin and eosin (Figs. 98-100), the convex outer borders of the capillary loops are capped by a crescentic, glossy, bright pink homogeneous deposit called the fibrin cap. It is always associated with severe arteriosclerosis, occurs with or independently of intercapillary sclero-

(1) Canad. M. A. J. 66:428-431, May, 1952.

sis and about half as often but has exactly the same age incidence and relation to high blood pressure.

Similar lesions develop between the epithelium and the basement membrane of the capsule, forming a capsular drop (Fig. 101). At first they are localized, droplike swellings staining pale pink with hematoxylin-eosin. Unlike the fibrin cap, secondary changes occur rapidly, with cell invasion through breaks in the basement membrane transforming the pink material into fibrous tissue which stains green with the Masson stain.

The capsular exudate may involve the tubules by extension between the basement membrane and the epithelium of the first convoluted tubule. Minor degrees of exudate are seen elsewhere in the convoluted tubules and seem to be replaced by fibrous tissue at a later stage.

Individually, these changes are not specific for diabetes, since the fibrin cap was found in 11 of 15 cases of glomerulonephritis. However, no capsular drops were found. None of these changes were found in 15 cases each of benign hypertension, malignant hypertension, atherosclerotic nephrosclerosis and pyelonephritis. The fibrin caps found in diabetes were larger than those in glomerulonephritis and the combination of fibrin caps, capsular drops and hyaline changes in the extraglomerular part of the arterioles is probably at least as specific for diabetes as is the Kimmelstiel-Wilson lesion.

Kimmelstiel-Wilson Syndrome. Among 376 patients hospitalized at Cordoba, Argentina, Sixto Sonzini Astudillo, F. Loza and A. Romero[2] found 21 diabetics, 3 of them with all of the elements of the Kimmelstiel-Wilson syndrome and two others with an incomplete syndrome. The characteristic edema, albuminuria, retinitis and arterial hypertension are found in various combinations, chiefly in older patients. The basic lesions affect the glomeruli, and the intercapillary hyaline deposits which differentiate the condition from glomerulonephritis have given it the name of intercapillary glomerulosclerosis. The fact that it may appear in the diabetic despite the maintenance of normal blood sugar level for years indicates that it is not a complication of diabetes, but rather a result

(2) Presse méd. 60:922-924, June 18, 1952.

of the same basic disturbance which caused the general disease. The intrinsic disturbance presumably leads to filtration of blood proteins through the glomerular capillaries and their precipitation in the basal capillary membranes or in the mesenchyma; the same process is found in arteriolar hyalinosis. Of the two patients with incomplete syndrome, one had hypertension and albuminuria but no nephritis or renal insufficiency; in the other, generalized edema and signs of a nephritic syndrome preceded death.

One patient with the complete syndrome, given ACTH in the hope of reducing edema, had prompt relief, but blood sugar content rose substantially, then returned to its former level when the hormone was withdrawn; hyperglycemia of this kind does not involve any danger of acidosis. In another patient, renal decapsulation apparently brought cure.

Woman, 43, after diabetes for five years, suffered a psychic trauma during the menopause six months before hospitalization. Hyperthyroidism (Basedow's) ensued and edema, initially involving the feet, appeared. Ocular symptoms were complete, and there was accompanying hypertrophy of the left ventricle. Diuresis was within normal limits; urine gravity ranged from 1.015 to 1.018, depending on albumin content, which ranged from 1.86 to 3.2 Gm./L.; sugar content ranged from a trace to 15 Gm./L. The BMR in May was plus 28%, but declined to plus 9% on June 21 after treatment with Lugol's solution. A month later, it was again plus 22%, but was again successfully reduced with Lugol's solution and sedatives. Sedimentation rate on May 4, when she was in poor general condition, was 81 in the first hour and 114 in the second; on July 5, when she was improved and blood sugar level was normal, the rate for the first hour was 37; on September 15, it was only 12. Eye examination showed diabetic retinitis and arteriolar sclerosis. Diabetic control was established, but the renal condition progressed and decapsulation was decided on. The operation (September 22), performed on one side only because of the hyperthyroidism and renal insufficiency, was well tolerated and led to improvement of all symptoms. Urine gravity was 1.020-1.022 and there was no detectable albumin; edema disappeared, and blood sugar and urea levels became normal. Two months later, edema and albuminuria reappeared, but she felt well and refused further operation.

Biopsy of renal tissue removed during the decapsulation showed characteristic Kimmelstiel-Wilson lesions. The favorable postoperative progress suggests that the syndrome has a functional element other than the renal lesions which can be modified by decapsulation. A review of the literature indicates

that this is the first time this syndrome has been treated by renal decapsulation.

[These reports present two novel concepts. To my knowledge, the Kimmelstiel-Wilson syndrome has never before been attributed to renal atherosclerosis. The use of renal decapsulation in the treatment of this condition is also new. It will be interesting to see if equal success with this procedure is reported in other studies.—Ed.]

Orthostatic Hypotension in Diabetes Mellitus. Jørgen H. Berner, Jr.[3] (Rikshosp., Oslo) found that of seven patients with long-standing diabetes associated with retinopathy and nephropathy, but no evidence of neuropathy, five had a definite fall of systolic pressure when they changed from the recumbent to the standing position. Of seven patients with long-standing diabetes and definite signs of neuropathy, all had a fall in both systolic and diastolic pressure when they stood up, with, simultaneously, no or only a slight increase in pulse rate. Postural hypotension is supposed to be caused by a disturbance of the autonomic nervous system. All patients in the last group stated that they often felt dizzy on rising from bed, particularly in the morning. Three patients had an abnormal pupillary reflex, five had disturbances of bowel function and two had paresis of the bladder, signs indicative of damage to the autonomic nervous system.

Charcot Spine Due to Diabetic Neuropathy. Gary Zucker and Maxwell J. Marder[4] (Beth Israel Hosp., New York City) report a case which was confirmed at autopsy.

Woman, 47, had swelling of ankles and eyelids, dyspnea and dry cough. She was known to have had diabetes for 14 years. X-rays of the spine taken because of a fall at age 45 did not show fracture, but pain and limitation of flexion of the spine required a back brace. Examination showed right retinal hemorrhage, distended neck veins, moist râles at both lung bases, enlarged liver, thoracic kyphosis, posterior knuckling of the lumbar spine, hypoactive knee reflexes, no ankle reflexes and loss of vibration and position sense below the knees. The Westphal, Abadie and Romberg signs were present. Hyperglycemia and glycosuria were found. She was believed to have congestive heart failure due to hypertensive and arteriosclerotic heart disease (blood pressure was 172/110). She improved when given digitalis, oxygen, mercurial diuretic agents, salt restriction and bed rest. The diabetes was controlled with difficulty. X-ray studies revealed a neuropathic spine (Fig. 102). Spinal puncture showed normal pressure and results of manometric studies were normal. About five months later, she was rehospitalized for patho-

(3) Acta med. scandinav. 143:336-340, 1952.
(4) Am. J. Med. 12:118-124, January, 1952.

logic fracture of the right leg, which was anesthetic. She eventually died of cerebral hemorrhage.

Autopsy showed a bony mass at the lumbar vertebrae, the middle three compressed and the third almost obliterated. There was a small subarachnoid hemorrhage in the right frontal lobe. Atherosclerosis was found in the aorta and vessels of the vertebral mass, and arteriolosclerosis and intercapillary glomerulosclerosis (Kimmel-

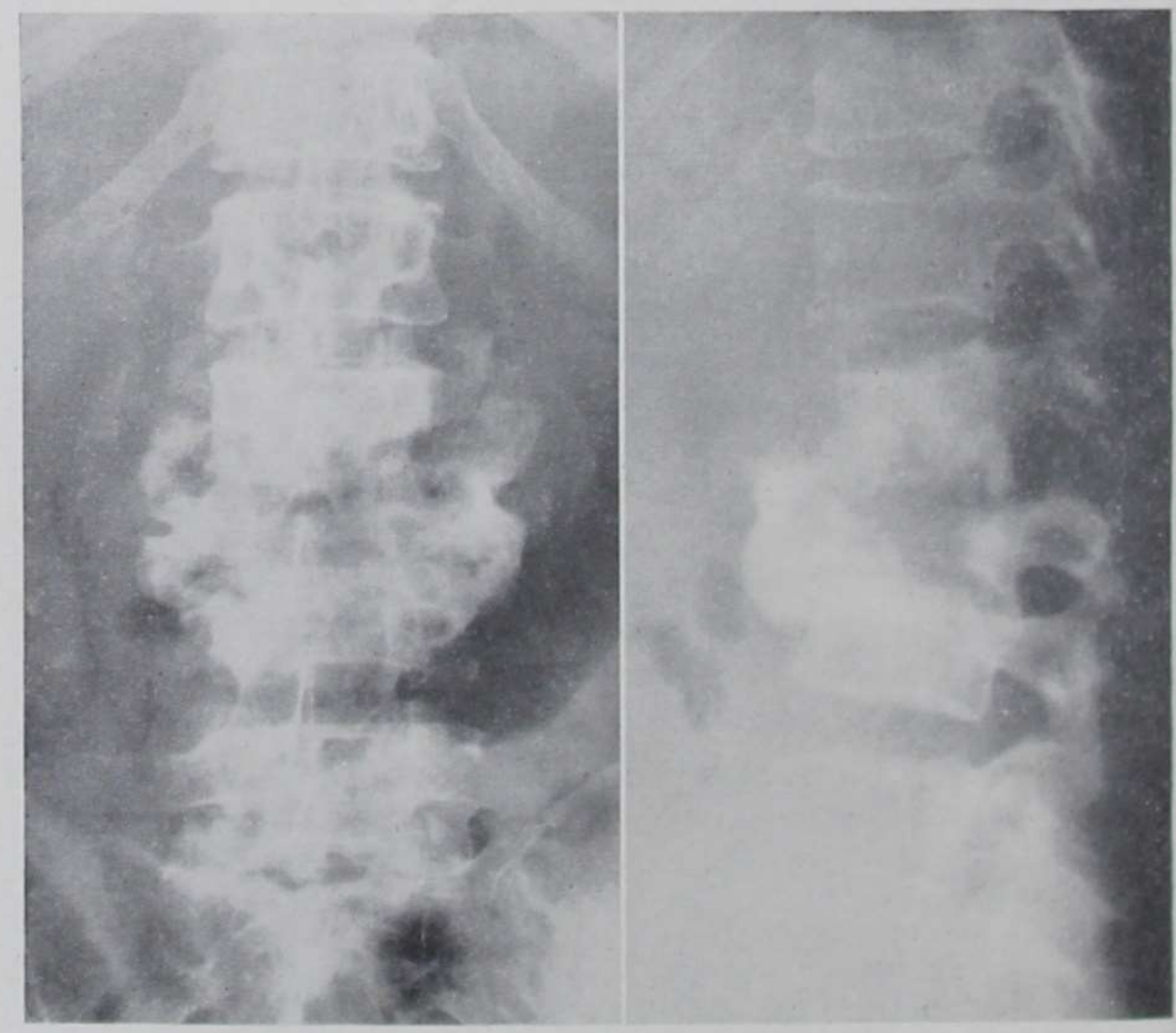

Fig. 102.—Charcot spine involving second, third and fourth lumbar vertebrae. Note almost complete destruction of third lumbar vertebra and new bone formation in this area. There is no sclerosis in first or fifth lumbar vertebra. (Courtesy of Zucker, G., and Marder, M. J.: Am. J. Med. 12:118-124, January, 1952.)

stiel-Wilson lesion) in the kidneys. The tibial nerve showed extensive degeneration of myelin sheaths. Great thickening of the walls of the vasa nervorum was seen; this was noted in the lumbar posterior roots and cauda equina also. Patchy, asymmetrical degeneration of the fibers of the fasciculus gracilis was apparent, increasing as the cord was ascended.

Histologic observations were clearly not those of tabes dorsalis but of advanced diabetic neuropathy. The unique localization of the Charcot joint is attributable to the severe

back injury, for it is now agreed that such joints result from a combination of trauma and loss of deep joint sensibility. No effective treatment is known.

[Diabetic tabes is outstripping tabes dorsalis as a cause of Charcot joints, probably because of the decreased frequency of neurologic complications in patients with syphilis. The neurologic lesions from either cause may be identical, including Argyll Robertson pupils, tabetic crises, difficulty with gait, loss of position sense and Charcot joints.—Ed.]

Experience with New Liver Extract for Treatment of Diabetic Neuropathies is discussed by I. M. Rabinowitch[5] (Montreal). The extract, prepared from pregnant mammalian liver by W. S. Collens and his associates, is clear, amber colored, free from cortisone and ACTH, contains only traces of folic acid and B_{12} and is nontoxic. The dose has been 5 cc. daily intramuscularly, except recently when 10 cc. doses have also been used.

Two women, aged 68 and 70, with diabetic cord bladder were given the extract. Both had numbness and tingling of fingers and toes, no tendon reflexes and decreased vibration sense in the lower extremities. The diabetes was deliberately allowed to escape control to exclude control as a factor in evaluating extract effects. Incontinence of urine disappeared after four days of treatment, and within a week paresthesias disappeared. Another woman, 58, had diabetic neuritis complicated by ulnar nerve palsy due to pressure. She was promptly relieved of the neuritis, and there was improvement in the ulnar palsy. One man, 68, with diabetic neuritis, had complications of advanced generalized vascular disease, indolent ulcer, nocturnal fecal incontinence and severe edema of both feet. Extract gave immediate relief from pain, the ulcer healed and the edema disappeared. However, extract had to be discontinued because of appearance of an allergic rash. In a man, 71, diabetic for 13 years, the extract rapidly relieved pain present for four years, and a partial footdrop disappeared, as did urinary incontinence. Fifteen other patients had typical diabetic neuritis with numbness, tingling, formication, hyperesthesia and severe nocturnal pain. Relief was obtained with 4-22 injections regardless of status of diabetic control; there was no control in most.

Besides these initial 20 patients, Rabinowitch treated 16

(5) Am. J. Med. 12:59-65, January, 1952.

more with the extract. Only three patients with diabetic neuritis had not improved. The extract was tried ineffectually on two patients with far advanced retinitis. The author believes it should be tried in early diabetic retinopathy and in diabetic patients with sexual impotence.

New Liver Extract Derived from Pregnant Mammalian Liver: I. Its Effect on Peripheral Neuropathy. A water-soluble extract from liver was prepared by William S. Collens, James D. Zilinsky, Jerome J. Greenwald and Arthur B. Stern[6] (Maimonides Hosp., Brooklyn) in the hope of isolating the materials which appeared to make liver useful in treating diabetic neuropathy. Long term toxicity studies in rabbits and rats revealed no ill effects from the extract, which is most potent when obtained from pregnant mammals. The extract contains only minute quantities of vitamin B_{12} and folic acid and does not cause reticulocytosis. The patients to whom the extract was given had neuropathic symptoms for at least two months. No other medication was used during study; placebos were given to some patients without the knowledge of either the patient or the person giving the injection. Patients were unaware that the injections were given to test their effect on the neuropathic symptoms.

Treatment consisted of daily intramuscular injection of 5 cc. pregnant mammalian liver extract (PMLE), usually for two weeks. PMLE was given to 127 diabetics with neuropathy; 84% had good to excellent and 10% had fair results; 6% showed no response. Three patients had mild local allergic reactions after a week of injections.

Disturbances in tendon reflexes and muscle atrophies were not reversed by treatment, but sensory changes and subjective symptoms were. Diarrhea, a manifestation of visceral neuropathy, was relieved in a week. Two weeks of treatment usually caused remission lasting two to six months. When relapses tended to occur, one injection a week sufficed to maintain the remission. Some remissions have lasted two years.

Case 1.—Woman, 39, who sought relief from pain in the left leg, was found to have diabetes. The diabetes was well controlled with protamine zinc insulin, but leg pain continued in paroxysms and became unbearable. Examination revealed generalized hyporeflexia and weakness of the left lower extremity. No sensory changes

(6) Am. J. Med. 12:53-58, January, 1952.

were found. A year later, the pain was so severe as to require narcotics. Liver extract was given daily for two weeks. Following the seventh injection, improvement began; a month after beginning treatment the patient had no symptoms. She was still in complete remission 1½ years later without further treatment.

Case 2.—In man, 30, diabetes of four years' duration was well controlled with diet and protamine zinc insulin. Because of severe burning pain in the toes, unaccompanied by abnormal neurologic findings except moderate decrease in vibratory perception, he was given PMLE injections. After the third injection, the burning of the feet disappeared. Five more injections were given. Complete remission was still present 2½ months later.

Case 3.—Woman, 54, had diabetes for 10 years, treated only by diet. When control was undertaken by a new diet and protamine zinc insulin, tingling of the hands, toes and anterior aspect of the chest wall developed. Except for reduction in perception of vibration, neurologic examination was within normal limits. Tingling in the left hand was greatly alleviated 24 hours after the first of seven intramuscular injections of PMLE. After the sixth, the hands and feet felt normal and remained so for the following six months.

Case 4.—Man, 37, diabetic for 13 years, had bouts of abdominal cramps and diarrhea without organic cause for 10 years. After a particularly severe attack, he was given PMLE. After the third injection, the diarrhea stopped for the first time in three months. A four day period of constipation came after two weeks of treatment, and then normal bowel habits returned.

Case 5.—Man, 37, diabetic for seven years, complained of severe shooting pains in both legs and tingling pain in the toes. There was diminished pain, touch and vibration sensibilities in the lower extremities, with reduced knee and ankle jerks. The diabetes was controlled with diet and insulin. After two weeks of PMLE injections, the tingling lessened. Injections were then given twice a week for a month, with disappearance of the shooting pains. Toe tingling persisted another month. After all symptoms had abated, treatment was stopped. Remission was still present six months later.

Case 6.—Woman, 64, was diabetic for 12 years. Obliterative arteriosclerosis developed in the lower extremities, with an ischemic neuritis in the toes. This failed to respond to three weeks of daily intramuscular injections of PMLE.

Case 7.—Woman, 51, with diabetes for 12 years, was found to have reduced vibratory sense in both feet, when examined because of numbness in the right foot. After three injections of PMLE, all symptoms disappeared; after completion of a week's course, she has been in remission for a month.

Case 8.—Woman, 63, had numbness and pain in the right side of the face although diabetes was well controlled with diet and insulin. This neuritis of the middle branch of the right fifth nerve subsided with PMLE injections and has not returned.

Case 9.—Man, 30, diabetic since age 21, had been asymptomatic

with diet and 100 units of insulin daily until sudden onset of numbness of the right fingers. The only neurologic finding was reduction of vibratory sense in all extremities. Twenty-four hours after the first of seven injections of PMLE, all complaints of numbness vanished. Five months later remission was still complete.

Case 10.—Man, 61, had diabetes for three years, controlled with diet and insulin. Shooting pains in the thighs and burning of the toes appeared four months before. Examination revealed reduction in pain, touch, vibration and tendon reflexes in both lower extremities. Following the third of 10 injections of PMLE, all neuropathic symptoms disappeared. Four months later there had been no recurrence.

[It is to be hoped that the success obtained with this form of treatment, now confirmed by two extremely competent independent observers, will alter the outlook for victims of this severely incapacitating complication. —Ed.]

Course of Diabetes during Pregnancy. Jørgen Pedersen[7] (Rigshosp., Copenhagen) reviews 205 pregnancies among 152 diabetics; he followed 20 patients throughout pregnancy. Severe acidosis and precoma occurred in 16% of pregnancies, usually during the sixth and seventh months. Dietary indulgence, failure to take insulin or infection was rarely the cause. No maternal deaths resulted but fetal mortality was 30%. Insulin shock occurred in 14%, usually in the second or third month with no fetal mortality.

Insulin requirement increased in 67%, usually during the seventh and eighth months, whereas in 13% insulin requirement decreased, usually during the second and third months. Half of the patients with improved carbohydrate tolerance early in pregnancy had decreased tolerance later. Carbohydrate tolerance does not change during the last six weeks of pregnancy. Fetal insulin production and carbohydrate consumption cannot explain these changes.

Management of diabetes during pregnancy must depend on blood sugar control, not on urinary sugar, because of a low renal threshold. The patients are checked each week until hospitalization eight weeks before term and labor is induced three weeks before term.

The Pregnant Diabetic. Paul Pedowitz and Edmund L. Shlevin[8] (State Univ. of New York, Brooklyn) describe 184 consecutive pregnancies in diabetics during 1932-50. Before the advent of insulin, infertility in diabetic women usually

(7) Acta endocrinol. 9:342-364, 1952.
(8) Bull. New York Acad. Med. 28:440-453, July, 1952.

prevented pregnancy, but when it occurred the fetal loss was 50% and maternal mortality 25-30%. By contrast, this series of 118 patients had 156 viable pregnancies, 22 spontaneous and 6 therapeutic abortions. The viable fetal loss was 20.5%, and there were two maternal deaths. In 45 patients with 92 pregnancies before diabetes was recognized, there was an infant loss of 20.5% and most infants weighed over 3,500 Gm. In known diabetics, toxemia occurred in 17.9%, five times the incidence in nondiabetics. Abortion occurred at the normal rate of 11%. The newborn were treated as prematures, regardless of weight. Congenital anomalies were noted in 3.2%—six times normal incidence.

Management depends on early discovery of diabetes, which must be suspected in any patient with glycosuria, unexplained intrauterine death or an infant over 4,000 Gm. Unless the diabetes is carefully controlled by insulin, silent episodes of ketoacidosis result in fetal loss. The patient must be followed every 10 days, alternating between internist and obstetrician until the third trimester, when she must be seen weekly. Urine must be tested daily for acetone as well as sugar if silent ketosis is to be avoided. If ketoacidosis cannot be controlled or pre-eclampsia occurs, the pregnancy should be terminated as early as the 33d week if the fetus is deemed viable. Elective cesarean is the procedure of choice. Hormonal therapy is not warranted since its rationale is not established and it does not reduce fetal loss below that reported in this study.

Retinal Findings in Pregnancy Complicated by Diabetes Mellitus and Toxemia. Stuart S. Snyder[9] (New York Hosp.-Cornell Univ. Med. Center) presents data on 37 patients with both pregnancy toxemia and diabetes who were followed ophthalmoscopically as a guide to management. Six patients with normal eyegrounds and mild pre-eclampsia gave birth to four living and two dead babies; nine with grade 1 eyegrounds, to seven living and two dead babies, and seven with grade 2 arteriolar changes, to two living and five dead babies.

In more severe toxemias the prognosis is worse and development of retinopathy indicates need for immediate termination of pregnancy if the fetus is viable. If only grade 1 eyegrounds are present in mild pre-eclampsia, the patient may

(9) Am. J. Ophth. 35:831-836. June, 1952.

be allowed to go to term. If grade 2 changes appear, intervention is necessary; in the first trimester, abortion may be indicated. Type and severity of diabetes do not seem to have as much effect on fetal mortality as does the severity of toxemia. Daily eyeground examination is recommended in following these patients.

[Vigorous treatment of the diabetes and frequent examination of the patient during gestation, under the co-ordinated care of the obstetrician and internist, together with prompt pediatric care after birth, has greatly reduced the infant mortality in diabetes mellitus. Whether the added use of hormones during pregnancy, as advocated by Priscilla White and the Smiths, aids in lowering the incidence of fetal mortality is not statistically established. The development of retinopathy, particularly retinitis proliferans, calls for immediate interruption of the pregnancy. The principles described in this and the two preceding reports are now generally accepted as standard practice.—Ed.]

Survey of Tuberculosis among Diabetics, based on comparison of 3,106 clinic and private diabetic patients with a control group of 71,767 apparently healthy industrial workers, is presented by Edward S. Dillon, Katharine R. Boucot, David A. Cooper, Paul Meier and Russell Richardson[1] (Philadelphia). Of the diabetics, 86% were over age 40, 28% were nonwhites and 69% were females. Controls were grouped to correspond to age, race and sex distribution in the diabetics. Tuberculosis was present in 4.3% of the controls and in 8.4% of the diabetics (12.3% of the male and 6.7% of the female diabetics). Incidence was almost 10% in the white diabetics and 4.3% in the Negroes. Presumably tuberculosis runs a more acute course in the Negro diabetic and results in an earlier mortality. The films of 31% of the tuberculous diabetics were classified as showing an active lesion (three times the frequency in the controls). The prevalence of active tuberculosis increased greatly with severity of the diabetes, as gauged by insulin requirements, and was greater in those having had diabetes 10 years or more and in those under age 40. Body weight had a decided influence on the prevalence of tuberculosis in both diabetic and control groups, being twice as prevalent in those under as in those over standard weight. In the diabetics, this influence of body weight was present in both the younger (under age 40) and in the older group. A history of gangrene, amputations, boils, or carbuncles bore no obvious relation to the prevalence of tuberculosis in the

(1) Diabetes 1:283-289, July-Aug., 1952.

diabetics. The clinical impression that tuberculosis in the diabetic is characterized by midlung and basal lesions is apparently related to the higher proportion of active lesions among diabetics. When active tuberculosis alone was considered, there was no difference in the site of the lesions in diabetic and control groups.

The Tuberculous Diabetic Patient is discussed by Michael A. Ferrara[2] (Norwich, Conn.). Of 3,178 patients admitted to a tuberculosis hospital because of pulmonary lesions, 68 (2.1%) also had diabetes mellitus. It is the impression of many that diabetes predisposes to tuberculosis and to reduced resistance to the disease. The average life expectancy of a tuberculous patient with diabetes is said to be barely half that of a patient without diabetes. Only 1 of the 68 patients in this group had minimal tuberculosis whereas 51 (75%) had far advanced disease. The diabetes was mild in 11%, moderate in 28% and severe in 61%. It was diagnosed before tuberculosis in 69%, simultaneously in 24% and after in 7%. No significant relation was noted between the degree of control of the diabetes and the course of the tuberculosis. Over two thirds of the patients were over 44 years old.

Of the 68 patients, 53 were discharged and 15 were still hospitalized. Of the 53 discharged, 35 were known to be dead, the disease had been arrested in 11 for periods ranging from six months to nine years, 2 were living with active tuberculosis and 5 were untraceable. Of the patients still hospitalized, the disease was active and unimproved in 7 and active and improved in 8. The prognosis is graver for the patients who have diabetes than for those who do not. All diabetics should have a chest x-ray examination at least every six months, or more often if signs or symptoms warrant.

[Various studies have resulted in contradictory reports on whether diabetes predisposes to pulmonary tuberculosis. More rigorous control of each disease is required when the two conditions coexist than when they occur singly, for aggravation of one may result in exacerbation of the other.—Ed.]

Effect of Repeated Phlebotomies in Hemochromatosis is reported by W. D. Davis, Jr., and W. R. Arrowsmith[3] (Tulane Univ.). Previous evidence indicates that normally iron is excreted only through passive loss as in hemorrhage and ex-

(2) New England J. Med. 246:55-56, Jan. 10, 1952.
(3) J. Lab. & Clin. Med. 39:526-532, April, 1952.

foliation, and that an intestinal barrier prevents absorption of unneeded iron. It seems likely that hemochromatosis results from a breakdown in this barrier. The authors tried to mobilize large iron stores in three patients with hemochromatosis by forcing use of tissue iron for production of hemoglobin. Blood was removed in 500 ml. aliquots and the plasma reinfused after separation from the cells. Bleeding was done daily until the red blood cell count reached 3,000,000-3,500,000/cu. mm. and hemoglobin content was 10-11 Gm. The procedure was periodically repeated to maintain this level; 25-45 L. blood was withdrawn annually from each patient. They were placed on a high carbohydrate, high protein, low fat diet with vitamins supplemented because of cirrhosis. The patients had striking regenerative ability as evidenced by return to normal of red blood cell values every three weeks after as long as two years of phlebotomy. Liver function test results returned to normal, the size of the liver decreased and, in all three, serial liver biopsies showed decreased amounts of iron; two of the three patients had a rise in serum protein. The two diabetics showed increased utilization of carbohydrates and decreasing fasting blood sugar level.

Cardiac Complications of Hemochromatosis: Report of Case Including Radioiron Studies and Note on Etiology is presented by T. H. Bothwell, B. van Lingen, T. Alper and M. L. du Preez[4] (Univ. of Witwatersrand).

Young woman had hemochromatosis, established by liver biopsy, manifested in chronologic order over 20 months by secondary amenorrhea, generalized slate-gray skin pigmentation, scanty pubic and axillary hair, hepatomegaly, cardiac arrhythmias and cardiac failure. The cardiac manifestations were controlled by quinidine and digitalis.

For radioiron absorption studies, 20 mg. of a mixture of Fe^{55} and Fe^{59}, as ferrous sulfate, with an activity of approximately 20 μc. measured as Fe^{59}, was given four hours after breakfast. Subsequent assays of radioiron were made of (1) total feces for 7 days, (2) blood samples at intervals for 50 days, and (3) serial in vivo measurements over midheart and midliver positions for 100 days. As a control, an adult menopausal woman with mild diabetes mellitus was similarly studied. To establish whether counts over the midheart position were due to a real deposition of radioiron or to

(4) Am. Heart J. 43:333-340, March, 1952.

scatter from the liver, measurements were made over a cadaver in which a model liver made of printer's roller composition was placed.

The patient excreted 28% of the administered dose of radioiron in the first seven days, while the control excreted 74%. Blood uptake studies revealed an initial peak in the first 24 hours, probably representing the plasma uptake, followed by a fall, probably due to storage, then a gradual rise due to liberation of stored iron for hemoglobin formation. After 30 days, blood measurements reached a peak of 3.5% in the patient as compared to 1.1% in the control. In vivo measurements of the patient revealed a very high uptake of radioiron in the liver, and readings over the midheart region were greater than could be accounted for by radiation scatter. No readings were obtained over any organ of the control.

The authors postulate, on the basis of these studies and those previously reported in a young man with hemochromatosis, that the higher incidence of cardiac failure in younger than in older patients with hemochromatosis may be related to a more acute form of the disease in which iron is absorbed and deposited at an accelerated rate. On this basis, the damage to the myocardium would be related not so much to the degree as to the rate of iron deposition.

[As pointed out by Althausen and others (A.M.A. Arch. Int. Med. 88:553-570, November, 1951), it has been thought that the rarity of hemochromatosis in women is due to the normal loss of iron through menstrual bleeding. The use of this hypothesis as a basis for the practical treatment of this condition, while radical, seems completely justified, in view of the progressive invalidism typical of women with untreated hemochromatosis. —Ed.]

Insulin

Present Status of New Insulin Modifications is discussed by Franklin B. Peck, W. R. Kirtley and F. C. Ottai[6] (Indianapolis) on the basis of an expanded clinical trial of NPH insulin in 1,281 patients. Diabetes was classified as severe, brittle or juvenile in 522, moderate in 562 and mild in 197. One third of the group was under age 30. Previous diabetic control was known to have been optimal for the type of therapy used. Before NPH insulin was utilized, 89.5% of all patients were taking protamine zinc insulin; insulin mixtures had been utilized in almost half the entire group.

In all three groups classified as having mild, moderate or severe diabetes, there was a significant shift toward better management when NPH insulin was used. Contrary to anticipation, improvement was most pronounced in the mild group,

(6) Diabetes 1:290-296, July-Aug., 1952.

in which the more efficient timing of insulin effect possible with NPH insulin is usually considered least critical. In the group with mild diabetes, patients previously classified as having "poor" control (13%) diminished to 1.7%, and those having "excellent" control (39%) increased to 65.5%; in the group with moderate diabetes, the corresponding shift was 11% to 2.1% for poor control and 15% to 44% for excellent control. In the group with severe diabetes, the corresponding figures were 31.4% to 10.2% for poor control and 6.9% to 27.6% for excellent control. After changing to NPH insulin, more insulin reactions were reported by 2.6%, no change in frequency by 22.7%, fewer reactions by 51.3% and no reactions by 23.4%. Of those patients who had reactions while using NPH insulin, 34.5% had them in the morning, 37.7% in the afternoon and 27.8% in the evening. These figures suggest that hypoglycemic reactions with NPH insulin follow individual variations in the patient's response to insulin, modified by diet and exercise.

Although NPH insulin exhibits the most generally useful time action now available, it is not a panacea, it does not change the severe unstable case to a stable one, and such cases remain difficult individual problems.

[As indicated by the authors, it is important to realize that no one of the insulin preparations now available is *the* ideal agent. Regular insulin is useful for short action, protamine zinc insulin for long action and NPH insulin for intermediate action and as a base for mixtures of long-acting and short-acting preparations.—Ed.]

Duration of Action of Different Insulins. F. Gerritzen[5] (Univ. Hosp., Leiden) compared the duration and character of action of ten different insulins, using 20 units subcutaneously, under standardized conditions. Normal subjects received 50 Gm. mashed potatoes and 30 cc. water every hour to avoid the variable effects of fasting or eating a full meal.

Figure 103 presents the average results. Regular insulin caused the blood sugar to fall to its lowest point after one hour. Contrary to other reports, protamine zinc insulin had a duration of action of only 18 hours with a low point in 5-8 hours. The action of globin insulin lasted 16 hours, with a low point in 3. The effect of NPH insulin lasted 11 hours, with a low point in 4.

(5) Brit. M. J. 1:249-250, Feb. 2, 1952.

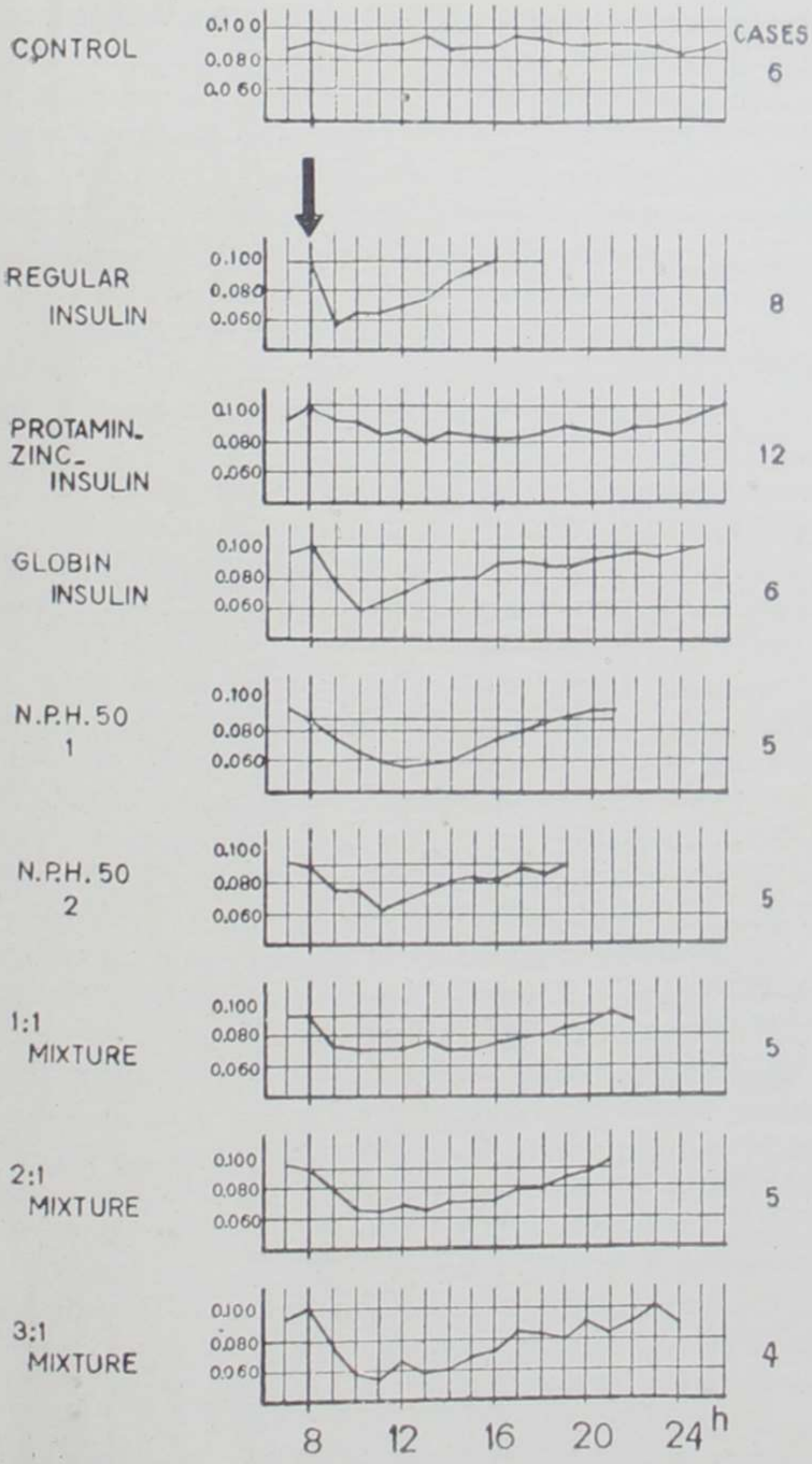

Fig. 103.—Duration of action of eight insulins. (Courtesy of Gerritzen, F.: Brit. M. J. 1:249-250, Feb. 2, 1952.)

Management of Insulin Allergy and Insulin Resistance in Diabetes Mellitus. Henry Dolger[7] (Mount Sinai Hosp., New York City) states that impurities and traces of secondary protein present in all commercially available insulin are responsible for the frequent appearance of local cutaneous allergic reactions at the site of injection, soon after insulin treatment is begun. Since such reactions are usually mild and always subside spontaneously in a few weeks, no specific treatment is necessary. Reassurance, changing the brand of insulin and administering antihistamines by ointment over the site before injection or orally two hours before injection are usually sufficient.

Severe reactions can be dealt with by desensitization to insulin which can be accomplished within 24 hours. Three dilutions of crystalline zinc insulin are made, 1:1,000, 1:100 and 1:10. Beginning with the weakest dilution, 0.1 cc. is administered initially, followed by an increase of 0.1 cc. every half-hour thereafter until 1 cc. of the dilution is being given. At this point the same progressive dosage scale, beginning with 0.1 cc., is initiated with the next dilution (1:100). In like manner the final (1:10) dilution is approached, progressing through to the final dose of 1 cc. Undiluted crystalline zinc insulin is administered in the same fashion, beginning with 0.1 cc. (4 units) and increasing the dose by 0.1 cc. every hour until the physiologic effect or optimal dose of insulin is attained. When fully desensitized, the patient can tolerate any slow-acting insulin without allergic reactions.

Another simple way of managing this problem is to denature the insulin by immersing the vial of crystalline zinc insulin in boiling water for 30 minutes. Boiling for 15 minutes results in a loss of only 10-20% of the insulin activity. After two to three weeks, ordinary insulins may be used again without difficulty. Rarely, a specific sensitization to one of the animal proteins used as the source of insulin may be known from the allergic history, and in such instances relief can be obtained by changing to a nonantigenic animal source. Severe generalized allergic manifestations may represent a true allergy to the insulin protein itself. This need not be a deterrent to the use of insulin when necessary, since denatur-

(7) M. Clin. North America 36:783-790, May, 1952.

ing by heat can yield a physiologically potent insulin without sensitizing properties.

Insulin resistance may be due to (1) insufficient insulin because of a damaged pancreas, (2) increased need due to obesity or hyperthyroidism, (3) increased insulin destruction, (4) increased antagonism from hormones such as cortisone or (5) insulin-neutralizing agents. Although the cause in an individual case is usually unknown, treatment consists solely of administering without timidity as much insulin as necessary until the transitory period of resistance comes to an end.

[Various commercial insulins are derived from different species of animal—Sharp & Dohme from sheep; Lilly, Burroughs Wellcome, and Squibb from beef and hog mixtures—and Lilly also prepares special beef and special hog preparations. Some sensitivity reactions to insulin preparations are species-specific and can be avoided by changing to an insulin from another animal source.—Ed.]

Temporary Insulin Resistance: Report of Case Requiring 5,490 Units of Insulin in 24 Hours is presented by Joseph H. Crampton and Clarence D. Davis[8] (Seattle).

Man, 51, was hospitalized in March 1947 after four months of rapid weight loss, polyuria and polydypsia. Crystalline insulin, 12 units daily, relieved symptoms and caused weight gain for two months. When weight loss recurred, studies revealed blood sugar 406 mg./100 ml. albumin and globulin normal, thymol flocculation 3 units, bromsulfalein and other values normal. Daily insulin dosage was increased to 96 units without controlling glycosuria or weight loss. Joint pains, enlarging lymph nodes and liver were noted. Gradually, over three months insulin dosage was increased to 880 units/day. Liver function revealed 28% bromsulfalein retention. Despite 440 units of insulin before breakfast on July 2, he progressed toward diabetic coma, requiring 5,490 units in 24 hours. The next three days only 50-350 units were necessary, but subsequently the requirement rose to 680 units and, two weeks later, fell to 140 units/day. He returned to work until May 1950, when a tuberculous draining sinus appeared from the fourth rib. Diabetes was controlled with 56 units/day and after 4¾ years showed no evidence of increasing again. The episode is attributed to an infectious process accompanied by liver cell damage.

Study of 14 Cases of Insulinlipodystrophy. The dystrophic lesions sometimes induced by injected insulin may be either hypertrophic or atrophic; they begin insidiously and may pass unnoticed until well established. R. Boulin, H. Chimènes and R. Tourneur[9] (Paris) studied 14 diabetics with enormous dys-

(8) Diabetes 1:201-204, May-June, 1952.
(9) Presse méd. 60:1024-1027, July 9, 1952.

trophic lesions; their conclusions differ notably from some current views. Insulinlipodystrophy is found almost exclusively in women; discounting minor swellings or small depressions, the incidence may be set at 2-6%. Hypertrophic lesions resemble solid lipomas, covered with thick "orange-peel" skin with dilated and separated pores, and are found chiefly on the anterior surface of the thighs, usually extending below the zone where insulin is injected. Atrophy apparently begins in the center and extends outward; in recovery, the process is reversed. The lesions are characteristically painless and the tissues often hyposensitive, so that many diabetics deliberately inject into the atrophic areas to avoid the pain of a slight prick in sound tissues. This practice leads to loss of insulin, which may be one source of difficulty in control of diabetes in insulinlipodystrophy. In many insulin-resistant or -unstable patients, control was easily attained when lipodystrophy was recognized and treated.

The lesions rarely appear when injection site is varied and regress when injections are made elsewhere. The determining influence of sex in producing the lesions, however, is clear. It is believed that insulin itself is responsible, being able to produce them only in terrain not impregnated with androgens. Apparently its action is indirect, affecting the nerve endings and thus leading first to excessive cellular function and later to cessation of function and atrophy. Biopsy in four instances showed that the only significant lesions involved the hypodermis and consisted of simple atrophic regression of the adipose tissue and a more or less intense mutilating sclerosis. Evidence of an inflammatory tissue reaction to insulin was also seen in two specimens.

Prevention is the best treatment, but when there are lesions, therapy is essential to cure. Patients should be advised not to inject insulin in the same spot oftener than once a month. Observance of this rule, combined with 40-100 mg. testosterone propionate weekly given in one or two injections, has resulted in regression of the lesions and better control of diabetes with doses of insulin smaller than those previously used. Patients' reports that they feel better than they have for years have been fully substantiated by laboratory tests, and

improvement in the lesions has often been both rapid and extensive.

Encephalopathy of Hyperinsulinism may be temporary or permanent. S. K. Fineberg and Alexander Altschul[1] (Harlem Hosp., New York City) define hyperinsulinism as that state produced by excessive insulin, whether exogenous or endogenous in origin. They prefer this term to "insulin shock," which is inaccurate and misleading. With hyperinsulinism, brain function may be profoundly disturbed and may mimic psychosis, as in the case reported here.

Woman, 31, with known diabetes mellitus for 10 years, was found in coma. Muscle twitches were found in the arms and legs. After administration of 50% (and later, 5%) glucose she gradually revived after somewhat more than 24 hours of coma. When conscious, she was lethargic, irrational and completely disoriented. She was totally incontinent of urine and feces. This state persisted for 10 days. Even a month after hospitalization she appeared withdrawn, melancholic and became enraged without provocation.

Another patient was in coma for 19 days, with severe and variable neurologic signs. A year after hospitalization, she was totally dependent on others; understanding was adequate, but orientation was poor. She had aphasia, right monoparesis and bilateral Babinski signs.

Two patients died of brain damage caused by hyperinsulinism. Autopsy on one showed diffuse cellular changes throughout the brain. In a fifth patient, 15, diabetes mellitus (since age 7) had never been well controlled. In one episode, she was comatose for 72 hours; in the posthypoglycemic phase, she had Babinski and other signs of neurologic involvement. These had cleared by the time she left the hospital. An EEG a year later was normal. In the three years after that hospitalization she was rehospitalized 12 times, yet never showed deficient or impaired mentality.

Encephalopathy from hyperinsulinism depends on insufficiency of glucose in the brain. There may also be some direct toxic effect of insulin in the brain when the blood sugar is low. It appears worth while to consider use of the insulin-antagonistic pituitary adrenocorticotrophic hormone (ACTH) and adrenocortical hormones in the treatment of hyperinsulinism if

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(1) Ann. Int. Med. 36:536-550, February, 1952.

encephalopathy and coma do not respond to glucose therapy.

[Hypoglycemia may result from excess of insulin (endogenous or exogenous) or from lack of insulin antagonists (as occurs in hypopituitarism and hypocorticism). In either instance it is often difficult to predict whether the encephalopathy resulting from hypoglycemia is reversible. Prolonged hypoglycemia may produce irreversible brain damage such as occurs in prolonged myxedema or hypocalcemia. It may be that abolition of the EEG abnormalities by intravenous infusion of glucose could be used as a prognostic index in hypoglycemia, just as the response to calcium can be used in hypocalcemia.—Ed.]

Insulin Tumors of Pancreas. John Morley[2] (Manchester) presents five cases of benign insulin adenoma of the pancreas in which the tumor was successfully removed by operation, one case of suspected insulin adenoma treated by subtotal resection of the pancreas and one fatal case of insulin carcinoma of the pancreas. Symptoms which may be due to an islet cell tumor are nervousness, confusion, convulsion, coma, meaningless laughter, epileptic seizures, hysteria and psychoneurosis. The fasting blood sugar is usually 50 mg./100 cc. or lower. Immediate relief from symptoms almost always follows ingestion of glucose. Of the five patients with proved insulin adenoma, two had been regarded as suffering from epilepsy, one for nine years and the other for three. The diagnosis for one patient was first cerebral tumor, then hysteria and then cerebral tumor. One was considered to have a subdural hematoma. Three had on occasions been suspected of alcoholic intoxication. The ages of the patients with proved adenoma ranged from 28 to 57. In all but one the tumor was in the tail of the pancreas. These five patients and the one suspected of having an adenoma were cured of symptoms after surgery. The one with malignant tumor died after surgery.

Diagnosis can be made by the glucose tolerance test. It should be done on the ambulant patient and prolonged for 5 hours instead of the usual 2½.

[Islet cell tumors bear out the general rule that the function of an endocrine organ is not proportional to its size. Some of the most severe cases of hypoglycemia are caused by the smallest islet cell tumors. In addition, the minuteness of such tumors makes their detection, and hence their removal, most difficult. It will be noted that in one of the patients reported on here, no adenoma could be found, but the patient was cured by subtotal resection of the pancreas. It is worth noting, too, that the portion of pancreas removed showed no hyperplasia of the islets of Langerhans and that no tumor was found. Perhaps a tiny adenoma was buried so deeply in pancreatic tissue that it could not be identified.—Ed.]

(2) Brit. J. Surg. 40:97-103, September, 1952.

Islet Cell Tumor of Pancreas. A. N. Smith and J. B. Cochran[3] report a case which illustrates the difficulties in management, yet the reward of a dramatic cure.

Man, 40, had had "blackouts" for 2½ years. His illness began with an attack of sudden blindness in November 1948, when his routine mealtimes were altered. A cup of sweet tea revived him, and sight returned. Several weeks later he was missing for two weeks and, when eventually found by the police, had lost his memory. From this time on he had periodic emotional outbursts, for which he sought psychiatric treatment, without effect, and further blackouts, which he learned to forestall or minimize by taking bread and jam every two hours. Toward the end of 1950, he had an epileptiform seizure accompanied by a wild staring expression, slow sighing breathing, deterioration of memory, profuse perspiration and twitch-

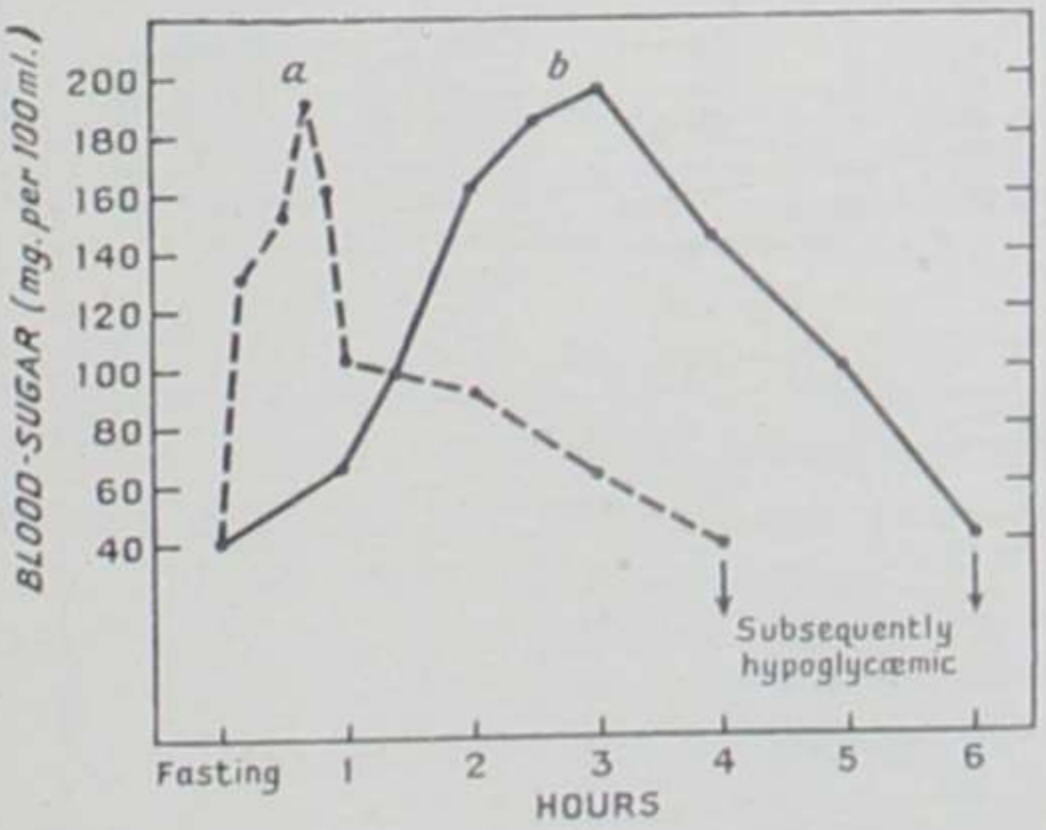

Fig. 104.—Glucose tolerance: *a*, on admission; *b*, after standardization on high protein diet and before operation. (Courtesy of Smith, A. N., and Cochran, J. B.: Lancet 1:289-293, Feb. 9, 1952.)

ing. He was then hospitalized. The blood sugar level in an attack was 32 mg./100 ml. A glucose tolerance test done before standardization of the diet showed a rapid initial hyperglycemia, followed by a fall to hypoglycemic levels in the fourth hour. This contrasts strongly with a glucose tolerance test done after one week on the standard high protein diet recommended by Conn (Fig. 104).

Electroencephalography in the hypoglycemic phase showed a well marked dysrhythmia, consisting of irregular slow activity, sometimes paroxysmal. This was thought to be typical of grand mal epilepsy, but after administration of glucose the abnormality disappeared.

The patient was kept on a standard diet containing 300 Gm. carbohydrate, 100 Gm. protein and 80 Gm. fat and was given such quantities of glucose in measured amounts as were necessary to

(3) Lancet 1:289-293, Feb. 9, 1952.

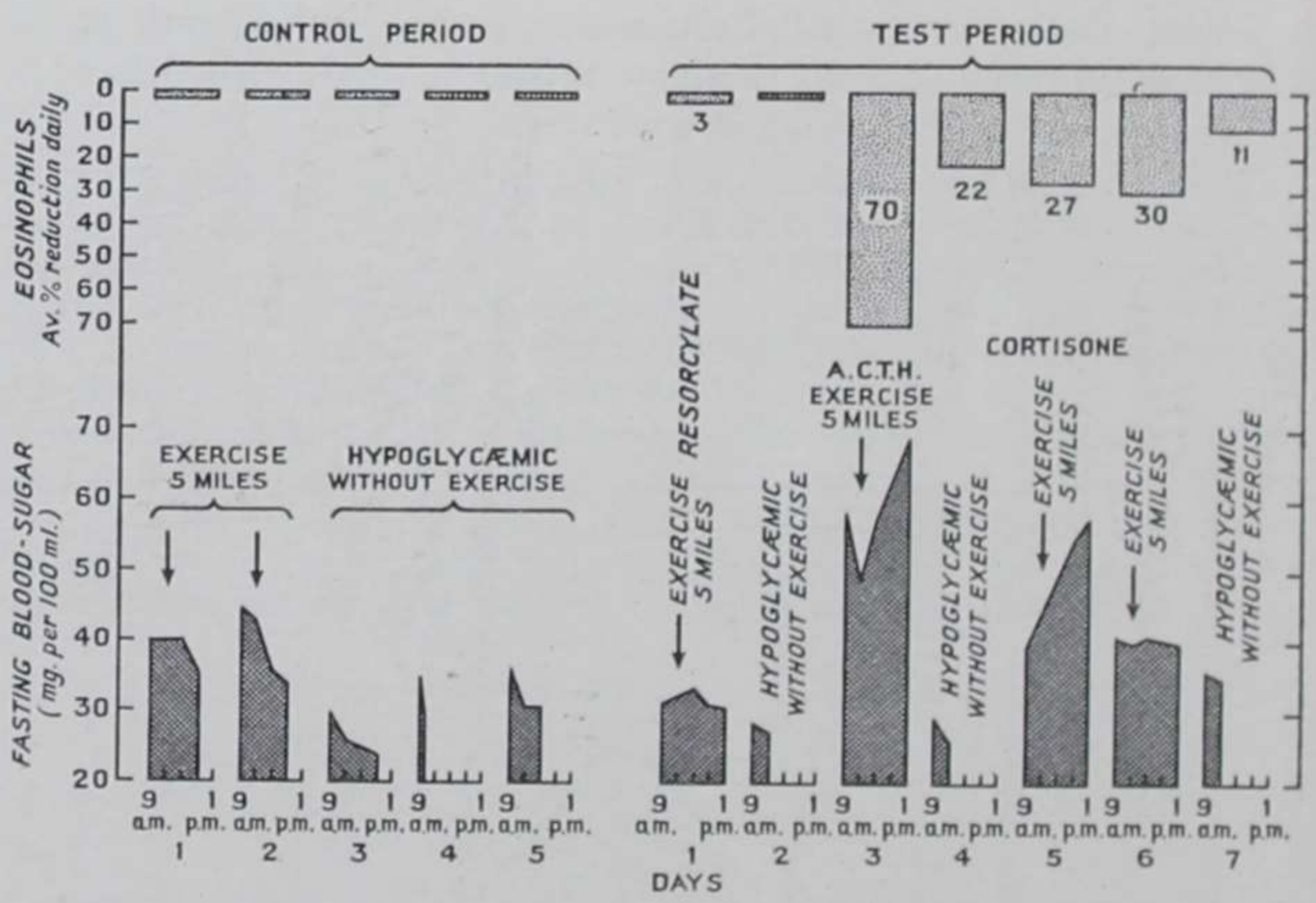

Fig. 105.—Fasting blood sugar and average eosinophil levels in control period and after administration of sodium gamma-resorcylate, ACTH and cortisone. (Courtesy of Smith, A. N., and Cochran, J. B.: Lancet 1:289-293, Feb. 9, 1952.)

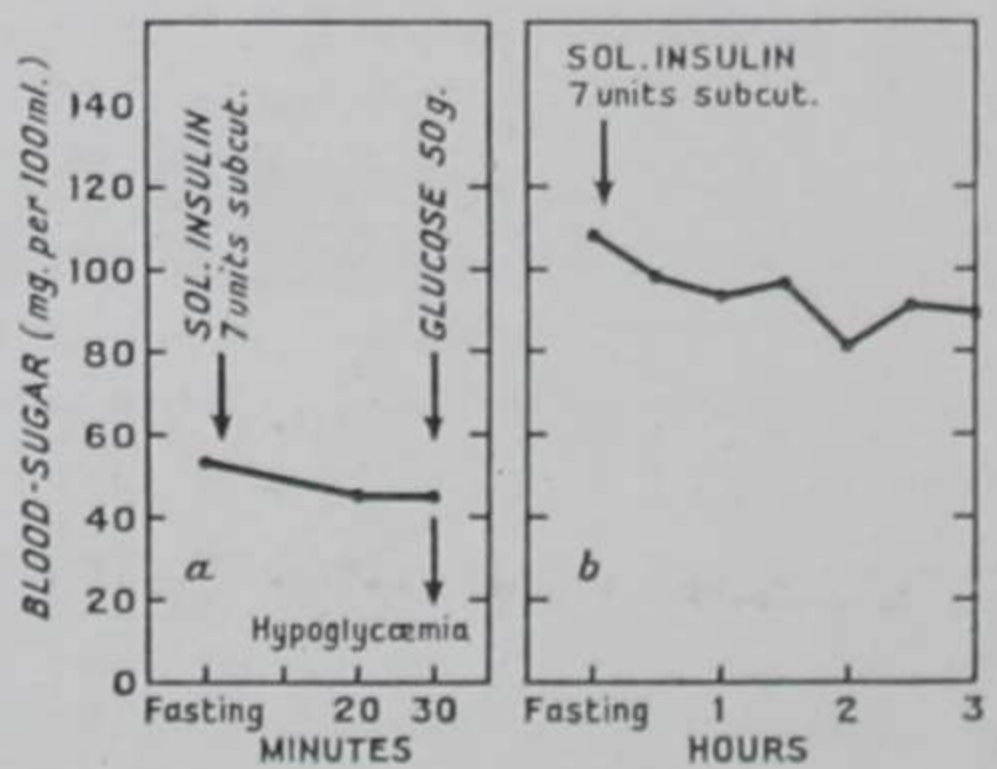

Fig. 106.—Insulin tolerance: *a*, before operation; *b*, after operation. (Courtesy of Smith, A. N., and Cochran, J. B.: Lancet 1:289-293, Feb. 9, 1952.)

rescue him from hypoglycemia. He exercised for 5 miles on a static training bicycle and was observed from 9 a.m. to 1 p.m. after an overnight fast. Fasting alone precipitated hypoglycemia. At 6 p.m., 100 mg. sodium γ-resorcylate was given, at midnight 200 mg. and at 7 a.m., immediately preceding the test, 300 mg. The patient did 5 miles on the bicycle, but the fasting blood sugar level was not significantly raised and the eosinophils remained at a high level (Fig. 105). Next day he readily became hypoglycemic without exercise. At 6 p.m., 25 mg. ACTH was given, at midnight 50 mg. and

at 7 a.m., immediately preceding the second test, 50 mg. He did 5 miles on the bicycle and remained symptom free. Glycosuria was evident in the 24 hour specimen, and the eosinophil counts showed a significant reduction. Next day an overnight fast without exercise produced hypoglycemia. At 6 p.m., 100 mg. cortisone acetate was given, at midnight 100 mg. and at 6:30 a.m., immediately preceding the third test, 100 mg. The patient did 5 miles on the bicycle and remained symptom free. Next day he was again symptom free before and after exercise.

Laparotomy was performed. The pancreas appeared normal, but a lump 1 in. in diameter was palpated in the tail and resected. Histologically, it was "borderline malignant." Assay revealed 14 units of insulin/Gm. (about five times normal pancreatic tissue). After operation there was a two day period of hyperglycemia, glycosuria and ketonuria. Two weeks later the insulin tolerance was considerably increased (Fig. 106), and the patient was discharged with demonstrable improvement in his memory and ability to calculate.

Islet Cell Adenoma of Pancreas: Metabolic Studies on Patient Treated with Corticotrophin and Cortisone are reported by Harold Brown, Harold P. Hargreaves and Frank H. Tyler[4] (V.A. Hosp., Salt Lake City).

Man, 58, had hypoglycemic attacks for seven years, interpreted as psychogenic. After correct diagnosis, 30 mg. corticotrophin every six hours produced a remission, as did 200 mg. cortisone a day. There were normal blood sugar values and normal insulin tolerance during hormone treatment, which was used over two months. Removal of a 6 Gm. insuloma led to complete recovery.

Since tests of adrenal and pituitary function gave normal results, it is curious that the pituitary-adrenal system did not respond to the hypoglycemic stress and thereby abort attacks as well as exogenous corticotrophin or cortisone did. Apparently self-regulating mechanisms prevent this to avoid other physiologic aberrations which hyperadrenocorticism would produce. The mechanism by which cortisone relieved this patient is unknown. Nitrogen excretion rose from 14.5 to 18.6 Gm./day—only enough to explain the production of an equivalent of 15 Gm. carbohydrate by gluconeogenesis—clearly not enough to raise the blood sugar level to normal. Insulin sensitivity may have been reduced; however, insulin tolerance was normal during cortisone therapy. Noteworthy was the promptness of the return of hypoglycemic attacks within 24 hours after stopping cortisone or several days after stopping corticotrophin. Although these hormones had a remarkable ability

(4) A.M.A. Arch. Int. Med. 89:951-960, June, 1952.

to relieve this patient's hypoglycemia, such treatment is advocated only until cure can be effected surgically.

[These two reports show that corticotrophin can mask the symptoms produced by an islet cell tumor. This phenomenon is extremely important, since the amelioration of symptoms by medical treatment is often used as an index of whether hypoglycemia results from tumor or from a "functional" cause. Apparently response to administration of cortisone or corticotrophin may not be used for this purpose; in fact, it may delay proper therapy of a malignant tumor.—Ed.]

Fatal Hypoglycemia with Multiple Pancreatic Islet Adenomas is reported by Antonio Luisi[5] (Univ. of Rio de Janiero).

Middle aged woman for 10 years had convulsive seizures and atypical psychotic manifestations. She was hospitalized in confused and agitated state, had several convulsions, lapsed into coma two nights later and died. Autopsy revealed four pancreatic adenomas composed almost entirely of cells similar to beta cells of normal pancreatic islets. The brain was congested and showed rarefaction of cells, especially in the cerebellum. Lungs, spleen and lymph nodes contained granulomas resembling those in sarcoidosis. Blood glucose content on hospitalization had been 61 mg./100 ml.

Some Observations Based on Six Cases of Hyperinsulinism Treated Operatively. John Hellström[6] (Karolinska Inst.) states that hypoglycemic attacks may occur in unstable individuals following a high carbohydrate meal, in liver insufficiency, after physical exertion, starvation, vomiting, renal glycosuria accompanying lactation, or dyscrasia of the adrenal, pituitary or thyroid glands. When these causes are ruled out, pancreatic hyperfunction may be diagnosed and surgery performed. Delay with medical management adds to the risk because of brain damage following repeated hypoglycemic insults and because obesity often ensues, adding to the operative mortality of 16%.

The author's six patients all presented Whipple's triad of (1) crisis after fasting, (2) low blood sugar during crisis and (3) prompt recovery after receiving glucose. Results of glucose tolerance and epinephrine tests were often similar to those in diabetics and served no useful purpose in the diagnosis of insuloma. The test results varied from day to day in the same patient. Diabetes may coexist with insuloma. Operation showed five patients to have tumors; the sixth had resection of both head and tail of the pancreas but no tumor

(5) Presse méd. 60:51-54, Jan. 10, 1952.
(6) Acta chir. scandinav. 53:120-130, 1952.

was found. There was one death and one large postoperative pancreatic pseudocyst, which was dealt with surgically. Four patients were completely well.

ENDOCRINE TREATMENT OF NEOPLASTIC DISEASES

Advanced Mammary Cancer

Reports of the efficacy of hormonal therapy on neoplasms have been sufficiently numerous for evaluation only in cases of malignancies which arise in tissues naturally sensitive to the sex hormones. Practically speaking, hormonal therapy has proved useful in neoplasms of the prostate and the breast and possibly in some chorioepitheliomas. Even in these conditions, the mechanisms by which amelioration is produced are not completely understood. The effect of the hormones is limited to palliation and cannot be looked on as curative. For this reason, these agents should be used only after the proved methods of surgery and roentgen therapy are no longer effective. Probably hormones should be given only when symptoms demand treatment, since their benefits are inevitably transient.

In carcinoma of the prostate, the rationale of endocrine therapy is based on the fact that the cancerous tissue is dependent on androgenic secretion, just as is normal prostatic epithelium. It is largely due to the epoch-making work of Huggins of Chicago that "anti-androgenic" therapy has been used for patients with advanced carcinoma of the prostate who no longer respond to surgical treatment. Castration or the administration of estrogen, or a combination of both, may add greatly to the comfort, productivity and longevity of these patients. When relapse occurs, it has been suggested, again by Huggins, that the resumed growth of the neoplasm may be the result of androgenic stimulus from the patient's adrenals. Accordingly, adrenalectomy has been tried in such patients, apparently with some transient benefit. It is, of course, too soon to prove that removal of all the known sources of androgens (gonads and adrenals) will result in permanent remission of the disease. Indeed, I think this is too much to hope, since in general the hormones are capable only of modifying existing processes and not of initiating new processes. Only time will tell, however, whether anti-androgenic therapy will totally abolish carcinoma of the prostate or whether the malignant cells, having lost their "androgen dependence," will continue to grow in the absence of androgen.

The rationale of hormonal therapy for advanced carcinoma of the breast is completely unknown. Since breasts are a feminine characteristic, it was hoped at first that administration of "the male hormone" would prove beneficial in some patients with advanced mammary carcinomatosis, and this has indeed proved to be the case. However, the mechanism of action may not be related to the androgenic properties of testosterone at all. Androgens may be estrogen-neutralizing or pituitary depressing, may stimulate growth of fibrous tissue surrounding the carcinoma or may, by reason of their anabolic activity, aid the general resistance of the patient. It is by no means established that carcinoma of the breast is

induced or fostered by the presence of estrogen. Indeed, the best results I have seen in the treatment of far-advanced carcinoma of the breast have been in elderly women treated with large doses of estrogens. About all that can truly be said of endocrine therapy in carcinoma of the breast is that production of hormonal imbalance by castration, by administration of androgen or of estrogen or by the sudden withdrawal of these agents after a period of treatment may be beneficial. In general, estrogens should not be given to women until five years after onset of the menopause, since there is a 1:5 chance of acceleration of the rate of growth of the tumor in younger women. Androgens may be given at any age; they seem to be more effective in controlling osseous metastases than soft tissue lesions, while estrogens, in general, are more effective when soft tissue is involved.

There are now quite a few strings to our bow in the treatment of advanced mammary carcinomatosis. When the cancer no longer responds to radical mastectomy or x-ray therapy, it still may be treated with androgen (e.g., 40 mg. methyltestosterone a day sublingually), or estrogen (e.g., 2 mg. ethinyl estradiol a day swallowed) or methylandrostenediol (40 mg. a day buccally). When the patient ceases to benefit from one of these agents, she may respond to another. By stretching out one form of therapy after another, it is often possible to make the patient comfortable for a long period. Hormonal therapy, when effective, gives greater relief from pain than opiates or other analgesic agents. It has been reported that adrenalectomy may be used as the last resort. Again the underlying reason is not established, although Huggins suggests abolition of the last source of estrogen. The method is still under investigation, and the results are conflicting and controversial.

The effects of hypophysectomy in melanosarcomatosis are discussed in the section on the Pituitary Gland, as are reports of pheochromocytomas in patients with acromegaly. Spread of carcinoma in experimental animals treated with cortisone and corticotrophin is discussed in the section on Cortisone, Hydrocortisone and Corticotrophin.—Ed.

Sex Hormones in Advanced Breast Cancer were evaluated by Edward F. Lewison and Robert G. Chambers[7] (Baltimore). All of the patients were beyond help by ordinary methods; diagnoses had been confirmed by biopsy. None had had artificial menopause or radiation therapy within six months of treatment. Response was evaluated by a panel of consultants. Testosterone propionate was given intramuscularly three times a week in 75, 150, 300 or 600 mg. doses weekly to all patients, regardless of age, who had bone or soft tissue lesions. Estrogens were given to postmenopausal women, regardless of age, in one of three dose schedules: 3 mg. ethinyl estradiol, 15 mg. diethylstilbestrol or 24 mg. tri-para-anisyl-chloroethylene (tace®) daily.

Subjective response was favorable in 46 of 57 patients receiving testosterone and in 21 of 40 receiving estrogens. Op-

(7) New England J. Med. 256:1-8, Jan. 3, 1952.

timal testosterone dosage appeared to be 2 Gm. over a period of three months. With estrogen, prolonged therapy improved the subjective responses. Regression of bone metastases was seen in 8 of 32 patients given testosterone and in 3 of 11 given estrogens. Regression of primary tumor and soft tissue metastases (lung, skin, lymph nodes) was noted in 17 of 48 patients treated with estrogens. Testosterone appeared least effective in primary tumor and estrogens least effective in pulmonary metastases. During the three year study, 48 of the 80 patients died—usually of progressive cancer. Those with a favorable response survived longer. The usual side effects incident to treatment with these agents were encountered, but of special interest was a high incidence of edema, easily controlled with diuretic measures, and hypercalcemia, which is difficult to treat and a grave prognostic sign.

[Whether estrogen should be administered cyclically or continuously in the treatment of advanced mammary carcinoma has not been established. I have given it only in cycles of 40 days on and 10 days off, which, if the patient's uterus is still present, permits withdrawal bleeding. Theoretically, more prolonged suppression might result from continuous administration of the agent. Data on this point would be most welcome. See the adverse effects of prolonged, uninterrupted estrogen therapy on the male breast (pp. 381-382).—Ed.]

Effect of Testosterone on Patients with Bone Metastases: Metabolic Study, Particularly of Breast Carcinoma. Daniel Laszlo, Albert Schilling, Judith Bellin, Estelle D. Gottesman and Cyril A. Schulman[8] (Montefiore Hosp., New York City) placed six patients with osteolytic metastases secondary to breast carcinoma on a mineral balance study before, during and after testosterone treatment and compared the data with those of three patients having similar bone metastases from other types of malignancy.

Active osteolysis due to malignancy is characterized by a high urinary excretion of calcium and phosphorus; if the loss is great enough it may exceed the excretory capacity of the kidneys, resulting in increased blood serum calcium content. These changes may occur in any type of malignant osteolysis and are characterized by periods of spontaneous increase or remission. Osteoporosis from bed rest disuse may exaggerate the negative mineral balance. Hormones affect bone metabolism in several ways, androgens producing protein (matrix)

(8) J.A.M.A. 148:1502-1507, Apr. 26, 1952.

anabolism, and estrogens producing predominantly mineral anabolism. These hormones also influence the growth of metastatic breast carcinoma, usually favorably, but occasionally accelerating tumor growth.

In none of the six patients with breast cancer was testosterone beneficial. It accelerated osteolysis and induced hypercalcemia in three, with pain, tendency to fracture and a downhill course attributed to acceleration of tumor growth. Since patients with unfavorable response cannot be selected by any known criteria, hormone therapy should be given with close clinical and laboratory follow-up. Two patients had temporary improvement in mineral and nitrogen balance with testosterone and one with radiation castration. If a positive mineral balance is obtained, oral supplements of calcium are well utilized. However, in one patient, mineral loss was made worse by testosterone, with hypercalcuria, nephrocalcinosis, uremia and death.

[These studies, which are based on valuable but relatively complex balance methods, indicate that hypercalcuria can be used as an index of bony breakdown. A simpler yet adequate and more readily available method can be used by practicing physicians—the urinary Sulkowitch reaction. Ordinarily, a 3-4 plus Sulkowitch reaction indicates hypercalcuria; when estrogens or androgens are effective, the Sulkowitch reaction usually is zero; i.e., no turbidity results when the Sulkowitch reagent is added to the urine.—Ed.]

Methylandrostenediol in Palliative Treatment of Breast Cancer. S. C. Kasdon, W. H. Fishman, R. M. Dart, C. D. Bonner and F. Homburger[9] (Boston) evaluate methylandrostenediol therapy in 44 patients with advanced inoperable cancer of the breast. Dosage schedules were 25 mg. in oil suspension six times a week, 100 mg. three times a week for the 20 ambulatory patients receiving aqueous suspensions, and 100 mg. daily for hospitalized patients. Pellets (150-300 mg.) were implanted at one, two and four week intervals. Oral medication was given in 100-300 mg. daily doses.

Nine patients, aged 43-74, had a demonstrable remission lasting 3 weeks to 19 months (average 8 months). In only one case was a remission obtained a second time after relapse. Three remissions were induced by pellets alone, and one by oral medication alone. In 21 patients, subjective improvement ranged from increased feeling of well-being to euphoria, last-

(9) J.A.M.A. 14:1212-1216, Apr. 5, 1952.

ing up to six months, despite progressive tumor growth. The other 14 showed no change.

Undesirable side effects, noted in 13, were hypercalcemia (3 patients; fatal in 2), hirsutism (3), increased libido (2) and acne (3). There were no signs of congestion or edema.

Spinster, 51, seven years after the menopause had a left radical mastectomy for carcinoma with node involvement. High voltage x-ray therapy and a short course of diethylstilbestrol caused fair

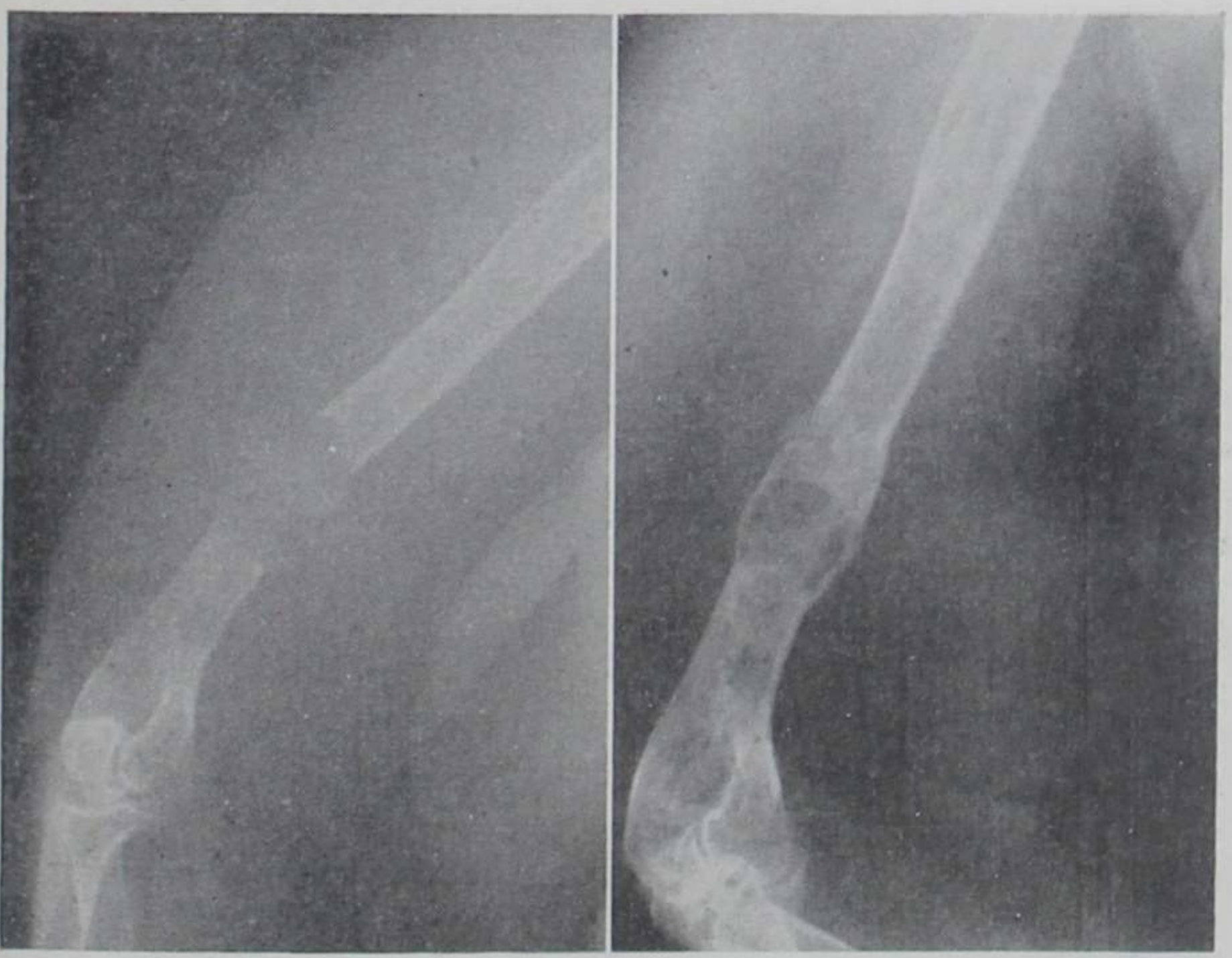

Fig. 107.—Pathologic fracture of humerus before and after methylandrostenediol therapy. (Courtesy of Kasdon, S. C., *et al.*: J.A.M.A. 14:1212-1216, Apr. 5, 1952.)

response at first; then she deteriorated rapidly and became bedridden, requiring narcotics several times daily for pain. She was hospitalized, and after a week of 90 mg. aqueous suspension of methylandrostenediol intramuscularly daily, she was free from pain, and there was x-ray evidence of improvement of a pathologic fracture of the humerus (Fig. 107). She became able to walk with some assistance and showed pronounced euphoria. After more than 200 days of treatment, hypercalcemia developed, the disease progressed rapidly and she died.

Methylandrostenediol appears to act as an anabolic agent in the same way that testosterone does. Neither has any car-

cinolytic or carcinostatic properties. It is thought that the amount of testosterone necessary to produce similar beneficial effects would certainly produce more severe virilizing effects than result from methylandrostenediol.

Hormonal Therapy in Cancer of Breast: II. Effect of Methylandrostenediol on Clinical Course and Hormonal Excretion. In a recent study on patients with advanced carcinoma of the breast receiving testosterone propionate, Segaloff and his co-workers showed that there was an apparent correlation between creatinuria and clinical course. In general, patients who improved with therapy exhibited a decrease in creatinuria, whereas those who failed to improve showed an increase. Albert Segaloff, Douglas Gordon, Benjamin N. Horwitt, Joseph V. Schlosser and Paul J. Murison[1] (New Orleans) therefore decided to treat such patients with a male sex hormone with a pronounced protein anabolic action which would affect creatinuria yet have little undesirable androgenic effect. Methylandrostenediol was selected for trial. Of 24 patients with advanced mammary cancer treated with 100 mg. intramuscularly three times weekly or once daily, only two showed objective regression of lesions, a much lower incidence than would be expected from testosterone therapy. The poor therapeutic effect was accompanied by no evidence of edema, virilism, improved strength, increased appetite or change in urinary hormone excretion. Local reactions were sometimes severe, and creatinuria progressively increased in all cases. At the dosage used, methylandrostenediol was definitely inferior to testosterone propionate.

[The different opinions expressed in this and the preceding article are difficult to reconcile. I, too, have used methylandrostenediol in the treatment of advanced cancer of the breast but have administered it only in doses of 40 mg. a day by the buccal route. Any statistics presented at this point would be misleading since the patients have been followed for only three years. We have seen a higher incidence of remissions than reported by Segaloff *et al.* This agent in doses of 40 mg. daily produces only mild virilization, i.e., acne and slight hirsutism. It seems to work more effectively on soft tissue lesions than on osseous lesions, and occasionally it has benefited patients who had previously responded to methyltestosterone but had subsequently become refractory to it.—Ed.]

Adrenalectomy for Mammary Cancer: Surgical Technic of Bilateral One Stage Adrenalectomy in Man. Charles Huggins and Thomas Ling-Yuan Dao[2] (Univ. of Chicago) have per-

(1) Cancer 5:271-274, March, 1952.
(2) Ann. Surg. 136:595-603, October, 1952.

formed bilateral simultaneous adrenalectomy on 42 patients, with two deaths; no operative deaths occurred in the last 38 consecutive patients. The operation was done under general anesthesia and each adrenal removed through a posterolateral approach with resection of the 12th rib. An adequate hormone substitution regimen exists whereby adrenalectomized patients can be maintained in good health, presumably indefinitely.

Among the eight patients (seven women) with far advanced mammary cancer, there was one postoperative death. In this group the gonads were also removed or the patients were already postmenopausal. They were followed for 7-11 months. Three patients responded poorly or showed no change, and four had a satisfying remission.

Adrenalectomy can induce remission in patients otherwise not amenable to treatment by present methods. Bilateral simultaneous adrenalectomy is a practical therapeutic method for selected cases.

It is not possible to determine before operation which mammary cancers are "adrenal-dependent." The most favorable prognostic signs are large adrenal cortices with hypertrophy of the zona glomerulosa and rather well differentiated mammary neoplasms. The cytologic appearance of the tumor, however, is not a valid indicator. Hormone dependence of tumors is a function of physiology rather than of morphology.

[Since this report was submitted, bilateral adrenalectomy has been performed on a great many more patients with cancer of the breast. Time alone will tell whether this radical procedure results in sufficient palliation to justify its use.—Ed.]

Advanced Prostatic Cancer

Carcinoma of Prostate: With Particular Reference to Hormonal Treatment. Seymour F. Wilhelm[3] (New York City) reviews the present status of this subject. According to several published reports, prostatic cancer has been discovered clinically in as high as 20% of all males seen for prostatic obstruction. A three year clinical survey by the author at Beth Israel Hospital revealed 860 cases of benign prostatic hypertrophy and only 45 (5%) cases of cancer. These figures confirm, perhaps, a lower incidence of prostatic carcinoma among

(3) M. Clin. North America 36:689-704, May, 1952.

Jews. A pathologic report based on serial sections of the prostate obtained at 50 consecutive unselected autopsies on men over age 50 revealed cancer in 46%.

These investigations reaffirm the fact that the incidence of carcinoma is always higher for the pathologist than for the clinician. This applies particularly to prostatic carcinoma since the tumors are often occult. Wilhelm believes that the miniature occult tumors often found by the pathologist do not always represent an early stage of a biologically malignant neoplasm.

The regional lymph nodes and bones are most frequently involved by metastases, followed, in order of frequency, by the lungs, liver, pleura and adrenals.

Prostatic carcinoma usually grows insidiously for a considerable period without causing symptoms. By the time attention is called to the prostate, the growth has usually infiltrated beyond the capsule by direct and lymphatic invasion as well as by metastases. As the neoplasm enlarges, the clinical picture is almost identical with that of benign hypertrophy. The early symptoms, frequency, nocturia and dysuria, are later followed by hematuria, sciatic and lower back pains, and urinary retention. For cancer to be detected before it causes symptoms, all men over age 50 should have semiannual rectal examinations. Discovery of a painless hard nodule or induration is an indication for further urologic study, including biopsy.

Biopsy is best carried out through a perineal incision, since aspiration and punch biopsy are unreliable. Papanicolaou's technic is not sufficiently reliable to warrant prostatectomy without corroborating clinical and histologic evidence. Contemporary clinical experience indicates that a decided increase in serum acid phosphatase activity is specific enough to be helpful in diagnosis if skeletal metastases are present. However, it is of little or no value in early diagnosis. Although tumor growth often seems to be dependent on androgens, the urinary 17-ketosteroid excretion of patients with prostatic carcinoma does not differ from that of controls of a similar age group.

Prostatic carcinoma almost always ends fatally. A follow-up study in the literature on 795 patients, treated from 1925 to 1940, before the endocrine era, showed that the average in-

terval between onset of symptoms and death was 52 months. For patients with metastases, the average interval between diagnosis and death was 16.9 months.

Treatment was virtually at a standstill until in 1941, when Huggins and his associates reported spectacular remissions in 15 patients after bilateral orchiectomy. A review of numerous reports from various centers indicates that both castration and estrogen therapy are immediately beneficial in about 75% of patients, but that benefits are often temporary. In one reported series, the average interval from diagnosis to death after castration was 30.3 months and from diagnosis to death after stilbestrol therapy, 20.5 months; average survival in a control series was 21.2 months. Others report better results with combined estrogen therapy and castration. This form of therapy appears to offer the best chance for longer survival. Wilhelm prefers to use oral estrogen therapy at first, thus avoiding the shock of castration for as long as possible. In advanced cases with metastases, it is generally agreed that primary orchiectomy should be done first and promptly supplemented with estrogens. The remarkable regression of prostatic cancer after castration and estrogen therapy has suggested that certain lesions, previously considered inoperable, might be made suitable for radical surgery. The rarity of authenticated cures and the frequent severe postirradiation reactions have discouraged the use of radon and x-ray therapy. X-ray castration has never found general acceptance. Since the advent of cortisone, Huggins and Bergenstal have reported impressive clinical remissions in two patients after total adrenalectomy.

Carcinoma of Male Breast with Axillary Metastasis Following Stilbestrol Therapy: Report of Case Treated by Radical Mastectomy. G. Y. Graves and H. S. Harris[4] (Bowling Green, Ky.) review five cases from the literature in which cancer of the male breast followed estrogen therapy for prostatic cancer. To these they add a case of their own, which they believe is the first to be discovered before bone metastases developed and which was seen early enough for radical mastectomy to be done.

Man, 78, was hospitalized in November 1948 with acute urinary

(4) Ann. Surg. 135:411-414, March, 1952.

retention. Diagnosis of cancer of the prostate was confirmed by transurethral resection biopsy. He was discharged on 6 mg. stilbestrol daily and seen at three month intervals. He gained weight and strength for six months, when he complained of nausea, anorexia and painfully enlarging breasts. Estrogen therapy was stopped in August 1950, after a total of 4,400 mg. had been taken. The swelling and tenderness of the breasts subsided, exposing a hard, nontender nodule, 4 cm. in diameter, in the left breast, associated with hard axillary nodes. On October 25, radical mastectomy and bilateral orchiectomy were done. Histologic study revealed adenocarcinoma of the breast with metastases. One year later there was no evidence of recurrence of breast cancer.

Bilateral Mammary Carcinoma in Male Following Stilbestrol Therapy. Aage H. I. Jakobsen[5] (Bergen, Norway) reports a case in which this condition developed during estrogen therapy for cancer of the prostate.

Man, 70, was hospitalized because of slow, frequent micturition over a year. On rectal examination the prostate was hard, nodular and enlarged, with extensive infiltration. X-rays failed to reveal metastases. Inoperable carcinoma was diagnosed, and he was placed on 15 mg. stilbestrol daily. Marked symptomatic improvement followed. He worked for one year, became irregular in his medication and relapsed after 18 months. Autopsy revealed a small prostate with two pea-sized nodules, atrophic testes and carcinomatous nodules in the center of each breast, just under the nipple, which was infiltrated. Prostatic cancer was found in the spine, liver and lungs. Although the histologic structure of the breast cancer did not exclude the possibility of metastases from the prostate, the appearance was more like that of primary breast cancer.

[The evidence at hand now justifies the belief that mammary carcinoma in men which follows the administration of large amounts of estrogen is actually induced by the prolonged, unremitting estrogenic influence. Accordingly, whenever I find it necessary to give estrogen to men, I prefer to give it cyclically and to adjust the intervals on and off therapy so that no tenderness, induration or swelling of the nipples occurs. Cycles of three weeks on and one week off therapy may be tried, but the exact time intervals must be determined for each patient individually.—Ed.]

MISCELLANEOUS

Hormonal Studies in Patients with Chronic Liver Disease. In studies of the urinary excretion of various hormones in 36 patients with liver disease I. J. Pincus, A. E. Rakoff, E. M. Cohn and Henry J. Tumen[6] (Jefferson Med. College) found

(5) Acta path. et microbiol. scandinav. 31:61-66, 1952.
(6) Gastroenterology 19:735-754, December, 1951.

low or low normal values of 17-ketosteroids, low values of gonadotrophins, elevated estrogen levels in about one third of the cases and low or normal estrogen values in the remainder. In only a few instances could the depression of the gonadotrophin excretion be attributed to hyperestrogenism with resultant inhibition of pituitary activity. The more normal values of 17-ketosteroid excretion were noted in the better nourished patients and tended to occur in patients whose liver function tests yielded normal or nearly normal values. No such correlation was present between estrogen levels and liver tests. The estrogen clearance test gave abnormal results in at least one third of the instances in which it was tried, most frequently when results of liver tests were also abnormal.

The authors found no consistent correlation between estrogen studies and occurrence of palmar erythema, spider telangiectasia or gynecomastia. They did not ascribe the instances of testicular atrophy to elevated estrogen levels but felt that pituitary gonadotrophin depression (independent of hyperestrogenism) accounted for at least part of these changes. The frequent association of low gonadotrophins, diminished estrogens and low 17-ketosteroids is suggestive of primary depression of pituitary function.

Reflections on the Nature of Obesity. A. Schüpbach[7] (Bern) opens his discussion with a reference to the American literature which views the problem of obesity as a very simple one: people get fat by eating too much or by physical laziness —usually both. The European schools of medicine have tried to find other explanations, often presuming a lowered BMR. Once obesity is established, however, the fat person has a greater surface than one of the same height and of ideal weight and correspondingly a higher BMR.

Endocrine disturbances have also frequently been blamed, although such things as pituitary, gonadal and thyrogenous obesity do not exist. Hypothyroid children with lowered BMR are rarely obese; they are overweight because of water retention. Obesity caused by endocrine disturbances is found only in Cushing's disease and hyperinsulinism both of which result from an overproduction of hormones.

The American "balance" theory has, however, been carried

(7) Schweiz. med. Wchnschr. 82:441-443, Apr. 19, 1952.

too far, for example, by Newburgh, who claims that the obese person needs more calories than the healthy one in order not to lose any weight. This belief departs from fact, for no reducing program can be carried out with a normal calorie allowance, since many obese people eat only moderately and are physically active and since every obese person has his own maximal weight to which he returns after a loss during illness or reducing programs and starts to eat excessively again. That "normal" weight is not exceeded even if he continues to eat the same amount he did during the increase.

Sometimes certainly the balance theory (too much food and too little physical activity) explains the obesity. Such exogenous obesity is relatively rare and most often endocrine causes undoubtedly play the major role.

The main objection against the balance theory is its complete disregard for the periphery, namely, the fatty tissue itself. Much of the glucose is transformed into fat in the fat cell itself. Clinical observations have indicated that the obese cannot mobilize their fat reserves as easily as persons of normal weight. This is only relative, for in extreme hunger the obese will also lose their fat reserves. However, they tolerate the loss much more poorly than people who are slender to begin with; they feel extremely weakened and are greatly bothered by the feeling of hunger. Patients have been observed whose fat tissue remains relatively intact, whereas muscle tissue decreases. In such instances one can speak of a lack of fat in the obese organism since the stored fat is so difficult to mobilize. The good appetite of the obese may be a result rather than a cause of the obesity. The complexity of the problem of obesity is evident in the lipodystrophies and lipomatoses in which tissue rich in fat is in close contact with tissue that contains almost no fat.

Diet restriction will always result in slenderness. The disease itself, however, is not cured any more than edema is cured by restricting salt and water intake. Salt and water are not the causes of edema, nor do foodstuffs cause the obesity. The only way to treat either condition is to eliminate whatever builds up pathologic changes in the abnormally functioning organism. There are no fast cures for obesity. Rapid weight reduction will cause discomfort and will most likely lead to a

return to the original condition shortly after therapy ends. The treatment must aim at reduction over a long period to a weight which is the obese person's optimal weight and not to the ideal weight of normal persons of the same height. Since all obese people retain more or less salt and water, this should be considered in their treatment. Also, weakened obese patients lose weight faster if they stay in bed than if they are exercising. Treatment of obesity must be adjusted to the individual patient and general schedules should be avoided.

[Here is a welcome dissertation on the age-old subject of obesity. I do not believe that obesity is an exception to the laws of thermodynamics or that obese persons can fix atmospheric carbon dioxide; but I also do not believe that all people use calories in exactly the same way. It will be recalled that Evans and Strang showed that some obese patients did not lose weight when restricted to a measured intake of 550 Calories a day. (Their studies were carried out over long enough periods to exclude a masking water retention.) It is certainly true that the person who gets fat is eating too much, but what is too much for him may well be too little for most of us. Many obese patients can be kept at normal weights only when limited to subnormal caloric intakes. Many more, of course, are just gluttons.—Ed.]

Local Action of Steroids on Senile Human Skin. Joseph W. Goldzieher, Irene S. Roberts, William B. Rawls and Max A. Goldzieher[8] (New York City) applied estrone, alpha-estradiol, beta-estradiol, testosterone, pregnenolone, methyl-androstenediol and calciferol to the skin in 27 elderly patients, mean age 77, and obtained skin biopsies every 15 days for 45 days. The crystalline steroids were applied to the skin in an ether-alcohol solution. A trace of light liquid petrolatum was sometimes added to prevent mechanical loss of crystals from the skin surface. The reflectance spectra of the intact skin were also analyzed.

Application of estrone, alpha-estradiol and testosterone elicited epidermal proliferation, progressive development of the rete pegs and papillae and increased production of keratohyalin granules. New formation of elastic fibrils and increased vascularization of the cutis were also noted, especially after application of estrogens. Spectrophotometry showed changes in absorption bands at 275 and 290 mμ which correlated well with histologic changes in keratohyalin formation. Pregnenolone and calciferol caused no changes. The estrogenically inactive beta-estradiol and the androgenically weak 17-

(8) A.M.A. Arch. Dermat. & Syph. 66:304-315, September, 1952.

methylandrostenediol had the same effect as estrone and testosterone.

Epidermal proliferation and thickening were not as pronounced as expected, probably because highly volatile solvents, like ether and alcohol, were used to apply the steroids to the skin, causing poor contact between skin and steroids. Application of steroids at high dosage level did not increase proliferation; actually, effectiveness was lower, and often skin atrophy was produced by prolonged estrogen application. The inhibitory effect of high doses does not appear to result from a systemic reaction after percutaneous absorption of the steroids. Sometimes, the steroids produced a change in the dermis.

The study shows that inadequate hormone secretion is important in the pathogenesis of senility of the skin.

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