GENERAL PATHOLOGY

Infectious Diseases

Special Article

EPIDEMIC HEMORRHAGIC FEVER

By **Arthur Steer** *and* **R. L. Hullinghorst***

When it became evident that this disease is present among troops of the United Nations in Korea, the editor suggested to Brig. Gen. Elbert DeCoursey, M.C., U.S.A., that he request an article on the pathology. This special article is published with the authorization of the Surgeon General of the Army. The Army as a routine does not accept responsibility for the statements contained in it. This is in essence an abstract of some of the material presented at a Symposium on Epidemic Hemorrhagic Fever held in Tokyo. It therefore represents the work of numerous medical officers. We are deeply grateful to Lieutenant Colonels Steer and Hullinghorst for preparing this article on short notice.—Ed.

An epidemic disease characterized by high fever and hemorrhagic manifestations has appeared among the United Nations forces in Korea during the past year. This condition apparently can be identified with the disease called epidemic hemorrhagic fever described within the last decade by the Japanese[1] and the Russians.[2]

Epidemic hemorrhagic fever is a disease of specific seasonal and geographic distribution with an incubation period known to vary from 14 to 30 days, a febrile period of about 5 days, a reaction period varying in duration and severity, and a recovery period which may be prolonged up to several months. The *febrile period* is characterized by acute onset with fever, nausea, vomiting, malaise, severe paravertebral pain, transitory and inconstant thrombocytopenia and mild leukopenia, and a hemorrhagic tendency varying considerably in intensity and affecting multiple tissues and organs. Subconjunctival congestion and hemorrhage and oropharyngeal and cutaneous petechiae are frequent. The face and neck show an intense flush. Hematemesis, melena, epistaxis, hematuria and leukocytosis with a leukemoid reaction usually appear in the more severe cases toward the end of this stage and become progressively prominent. During the *reaction period* there may be oliguria, anuria, unstable blood pressure with recurrent and

*Lt. Colonels, Medical Corps, U.S. Army.
From Department of Pathology, 406th Medical General Laboratory, APO 500, c/o Postmaster, San Francisco, Calif.

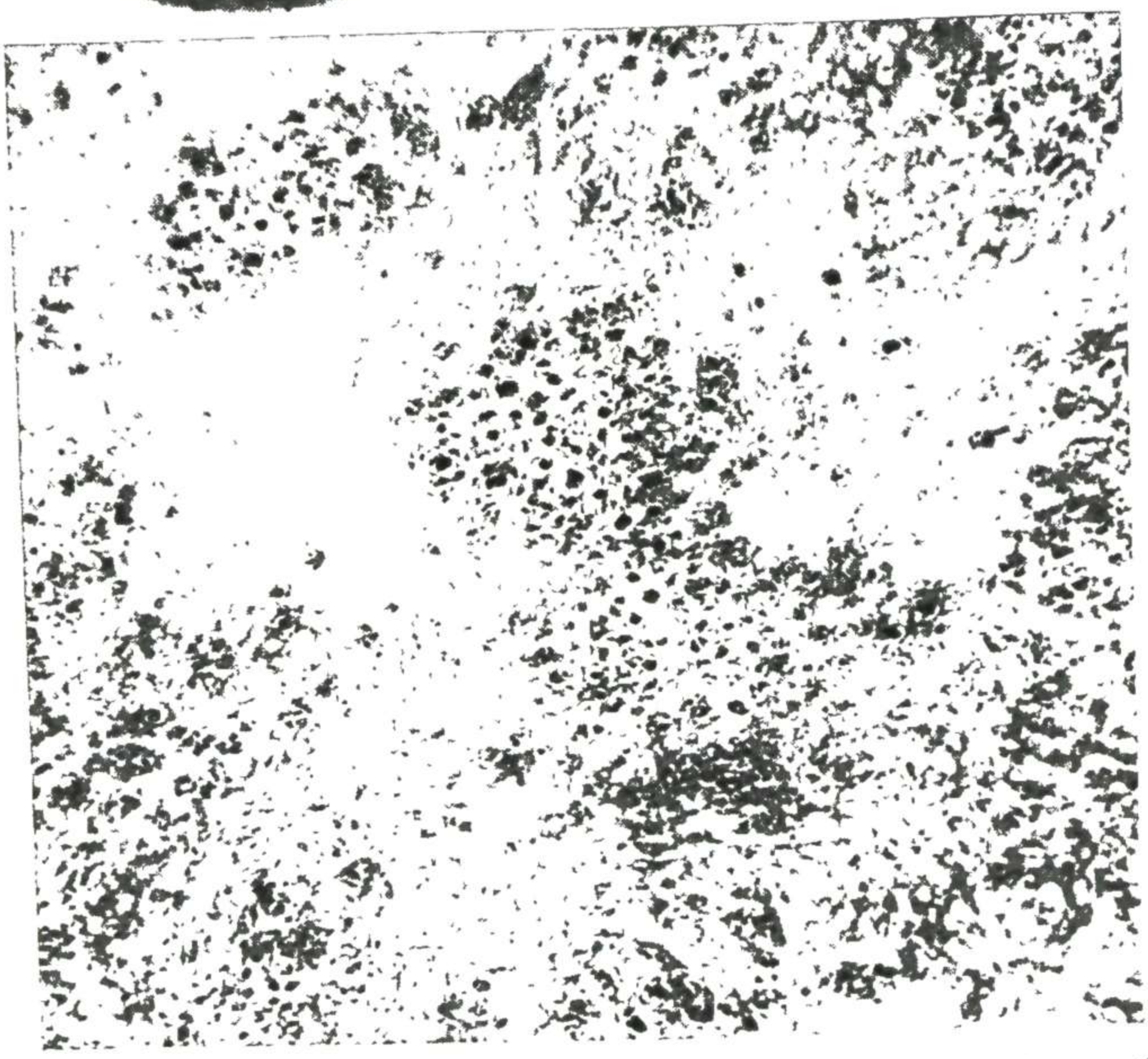


Fig. 1 (top).—Kidney of epidemic hemorrhagic fever: sharp demarcation of cortex and medulla, medullary hemorrhage, pale and necrotic areas in pyramids and submucosal pelvic and ureteral hemorrhage.

Fig. 2 (bottom).—Medulla of kidney: foci of necrosis, hemorrhage, casts and absence of inflammatory reaction.

prolonged episodes of shock, continued severe vomiting and hemorrhage.

Epidemic hemorrhagic fever has been reported in eastern and northern Manchuria and in Siberia. The Japanese believed that it was due to a virus, although the infectious agent has never been adequately characterized. According to Japanese reports, the disease was transmitted to man by a mite (Laelaps jettmari) found on the common field mouse (Apodemus agrarius) which they regarded as the reservoir of the disease. No specific laboratory test is available for diagnosis.

In United Nations troops in Korea in 1951 the mortality rate was approximately 8 per cent. The important immediate cause of death in approximate percentages were: renal failure 55, shock 25 and pulmonary edema 15.

Sixty-one fatal cases of epidemic hemorrhagic fever have been studied pathologically. The kidneys showed the most consistent changes. Combined weight was above normal, averaging 521 Gm. The bulging cortex was pale in comparison with the intensely hyperemic and hemorrhagic medulla (Fig. 1). Generally there was intense subepithelial pelvic hemorrhage. Microscopically glomeruli showed little change except in cases of long duration, when there was slight proliferation of endothelial elements. In some cases glomeruli were bloodless, in others hyperemic. Both distal and proximal convoluted tubules were dilated and contained numerous casts. In all cases there were intense hyperemia and interstitial hemorrhage extending from the corticomedullary junction into the medulla. In 73 per cent there were poorly demarcated central areas of necrosis in the pyramids which resembled areas of infarction and varied from small foci (Fig. 2) to large conglomerate areas (Fig. 3) recognizable grossly. No evidence of vascular occlusion could be found, and in only a few cases was there any cellular reaction to either the hemorrhage or the necrosis. Pigmented casts were observed in the loops of Henle, but the renal lesions were obviously something more than lower nephron nephrosis. The peripelvic fat frequently showed diffuse hemorrhage which often excited an inflammatory reaction.

In 30 of the 38 available pituitary glands there were foci of coagulation necrosis resembling infarcts in the anterior lobe (Fig. 4). In 12 of these, almost the entire anterior lobe was involved. There was no evidence of vascular occlusion. In

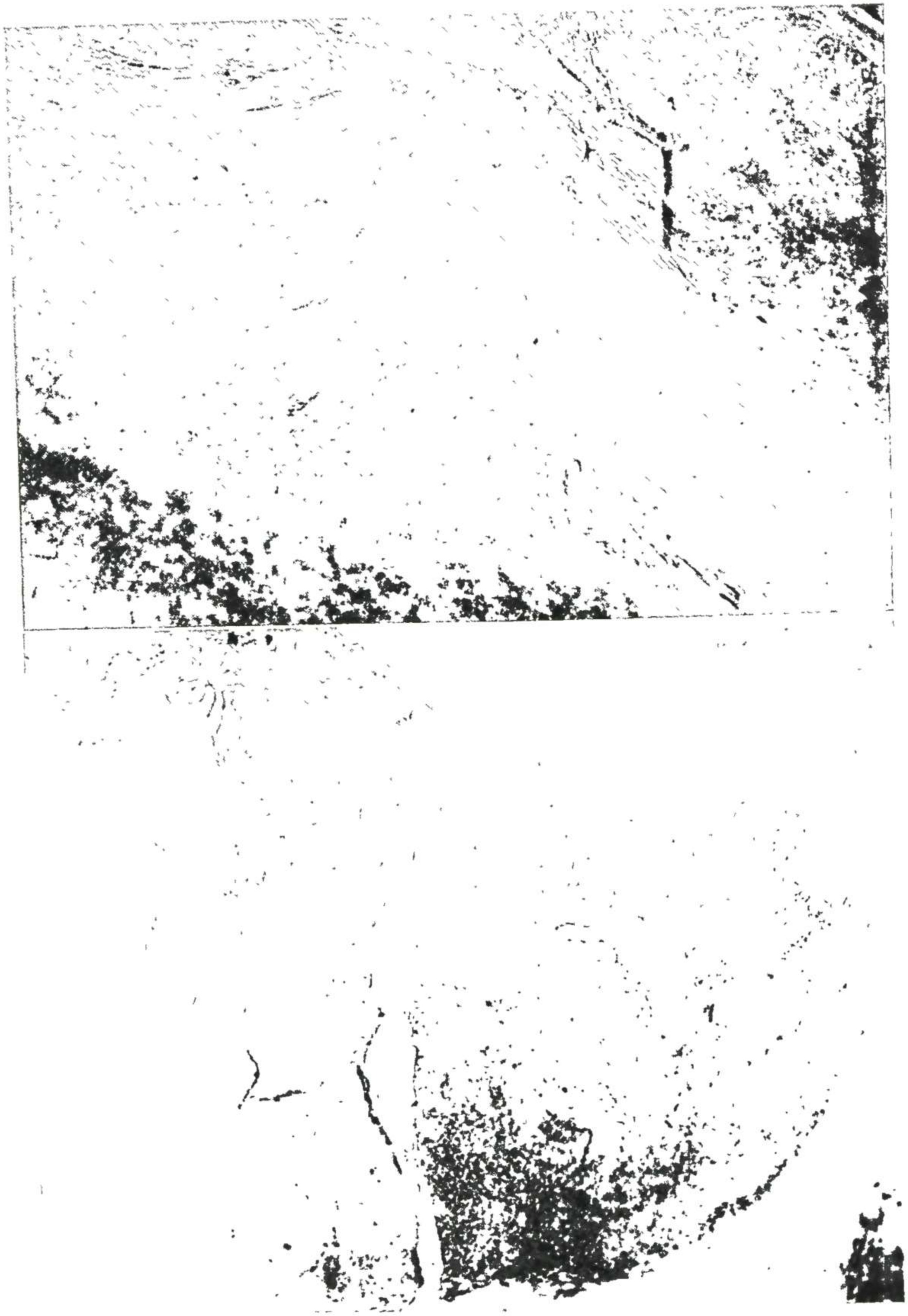


Fig. 3 (top).—Kidney of epidemic hemorrhagic fever: diffuse necrosis of pyramid.

Fig. 4 (bottom).—Pituitary: focal necrosis in anterior lobe; focal hemorrhages in infundibulum and posterior lobe.

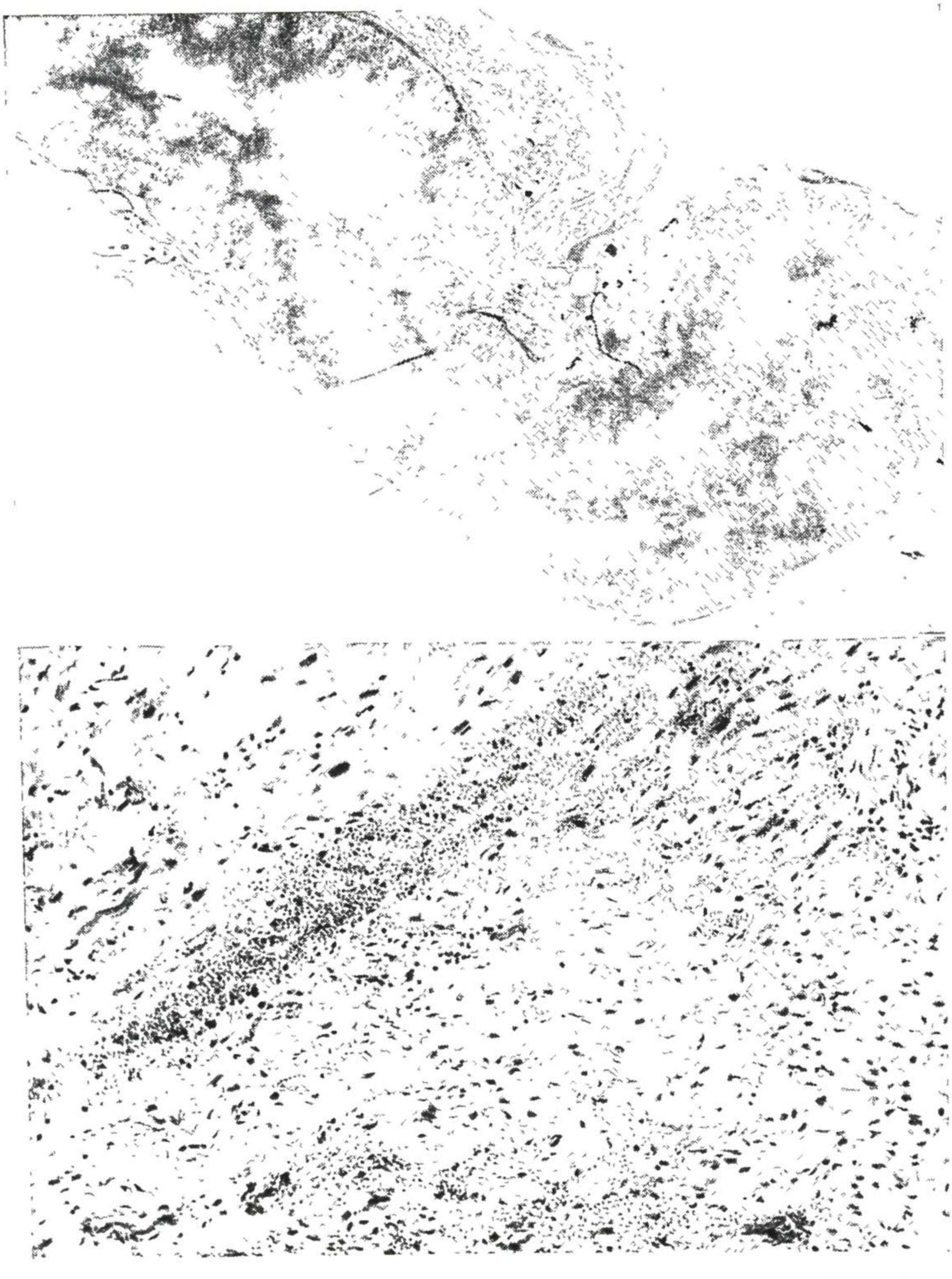


Fig. 5 (top).—Adrenal gland: conglomerate areas of necrosis and hemorrhage.
Fig. 6 (bottom).—Right atrium: hemorrhage and mild diffuse mononuclear cell infiltration.

27 of 59 cases there were focal hemorrhages in the adrenal glands involving principally the fasicular layer, and in 11 of these, large areas of coagulation necrosis were present (Fig. 5). In no case was the entire gland involved.

In 11 of 46 cases the heart weighed over 400 Gm. The

right atrium was sometimes dilated and contained diffuse, intense myocardial hemorrhage. Microscopically, there was hemorrhage in the right atrium (Fig. 6), varying from mild to severe, in some cases accompanied by a mild mononuclear cell infiltrate. In addition, considerable separation of myocardial fibers suggested interstitial edema. In the left atrium the cellular infiltrate usually was more intense and hemorrhage was much less frequent. The infiltrate extended into

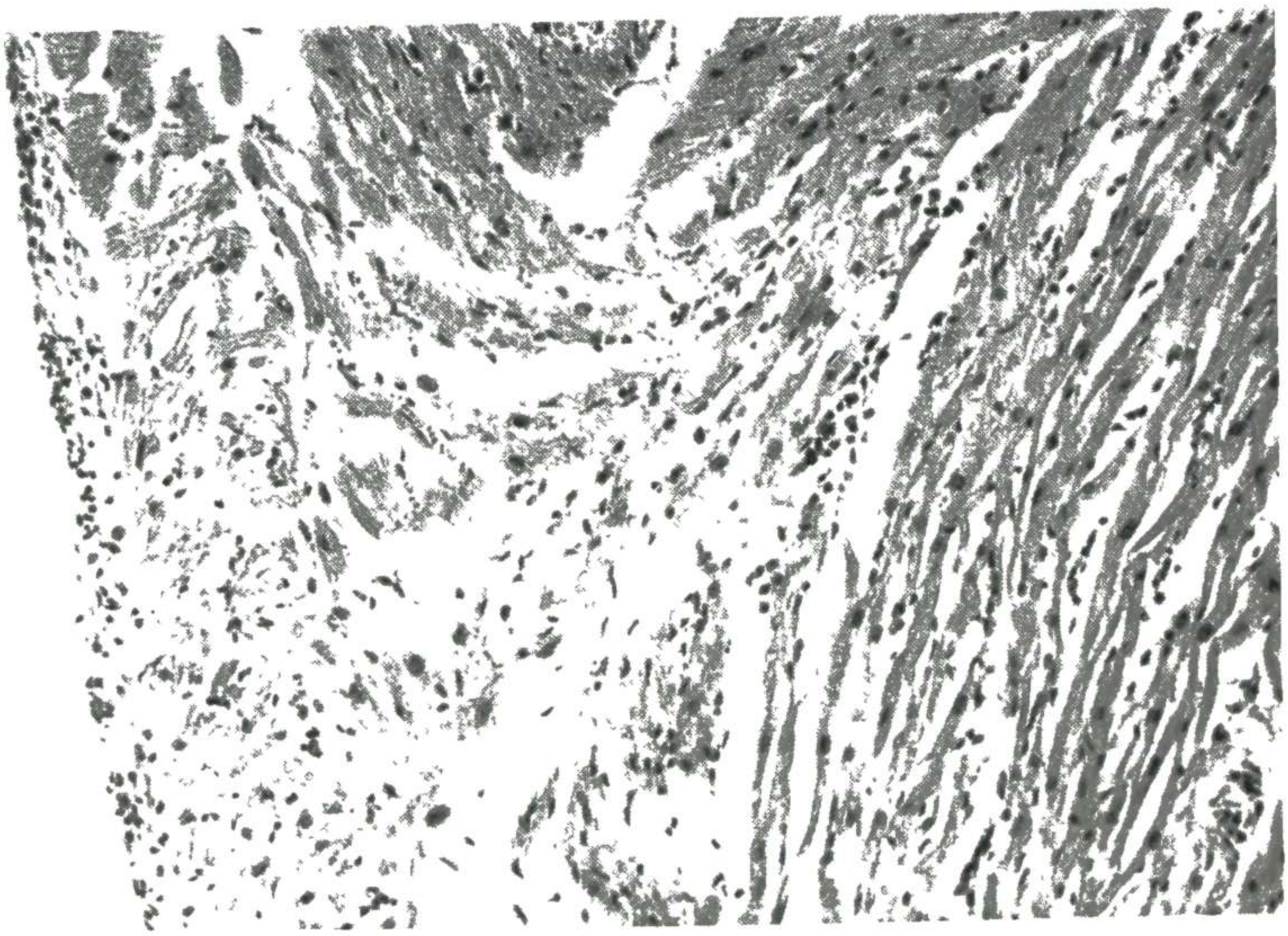


Fig. 7.—Left ventricle near auriculoventricular junction; endocardial and myocardial infiltration by mononuclear cells.

adjacent portions of the ventricles. Often a diffuse subendocardial infiltrate caused the endothelium to appear three or four cells thick (Fig. 7). There were no overlying thrombi or vegetations.

The cellular infiltrate seen in the heart and other tissues consisted of poorly defined focal accumulations of medium and large mononuclear cells resembling tissue phagocytes. Some of the larger cells resembled immature granulocytes and were indistinguishable from cells found in vascular channels, particularly the sinusoids of the liver and spleen, where, in a few cases, they were so numerous as to suggest extramedullary myelopoiesis.

The lungs were increased in weight, averaging 1,270 Gm. The changes observed were principally pulmonary edema and hyperemia and an occasional focus of bronchopneumonia. There appeared to be no characteristic pulmonary lesions.

The pancreas was not remarkable grossly. Microscopically a mild to moderate, diffuse interstitial cellular infiltrate and focal areas of hemorrhage were observed in 40 per cent. In a few cases pronounced hyperemia and necrosis were present, limited to occasional islands of Langerhans.

Although the liver was sometimes enlarged, no consistent change was recognized. In some cases there was mild focal hepatitis and in two cases midzonal necrosis.

Mild superficial, but sometimes severe, esophagitis was frequently observed. The stomach and small intestine often were the sites of severe diffuse mucosal hyperemia and hemorrhage.

The spleen was generally hyperemic and enlarged, averaging 357 Gm. Follicles were not prominent and active germinal centers were not evident. Similarly, lymph nodes appeared edematous but showed no evidence of germinal center activity. Bone marrow showed both hyperplasia and intense hyperemia. Megakaryocytes appeared normal in size and number. Plasma cells were present but not numerous.

Microscopically, the epidermis showed little change other than prominence of pigment. The subpapillary portion of the corium contained engorged vessels, frequently accompanied by a perivascular mononuclear and mast cell infiltrate.

In 54 cases the brain was examined. Gross cerebral hemorrhages were observed in two brains and subdural hematoma in one. No other significant lesions were found.

The etiologic agent of epidemic hemorrhagic fever has not been identified during this epidemic. Neither poisons, bacteria, leptospira nor fungi have been demonstrated. Search for inclusion bodies and rickettsia has been unsuccessful. Although it is believed that some viral or rickettsial agent may be the cause, no such agent has been isolated despite intensive experimentation with a wide range of animals, including monkeys, horses, guinea pigs, rabbits, hamsters, mice and rats and also embryonated eggs.

The pathologic physiology involved is not entirely clear. It is evident that the disease produces a widespread effect suggesting the presence of a potent circulating toxic agent.

The necrosis in the kidney medulla, anterior lobe of the pituitary and fascicular layer of the adrenal cortex suggests a tissue specificity. However, the portals of entry of a living agent and the site of multiplication of that agent have not been recognized. The possibility of persisting renal and pituitary malfunction must be considered.

Further study may clarify many of the still unanswered questions pertaining to this disease.

REFERENCES

1. Takami, R. M.: "Epidemic Hemorrhagic Fever," Report of Medical Section Far East Command, U.S. Army.
2. Mayer, C. F.: "Epidemic Hemorrhagic Fever, A Collective Study of the Literature (Preliminary Draft)," Army Medical Library, Washington, D. C., December, 1951.

Fatal Acute Chagas' Disease in a North American in the Canal Zone is reported by William F. Enos and Norman W. Elton[1] (Gorgas Hosp.).

Youth, 18, had a sore foot for three days. The next day he noted headache, chills and fever. The dorsum of the left foot was swollen, red and painful, and the left inguinal nodes were enlarged and ten-

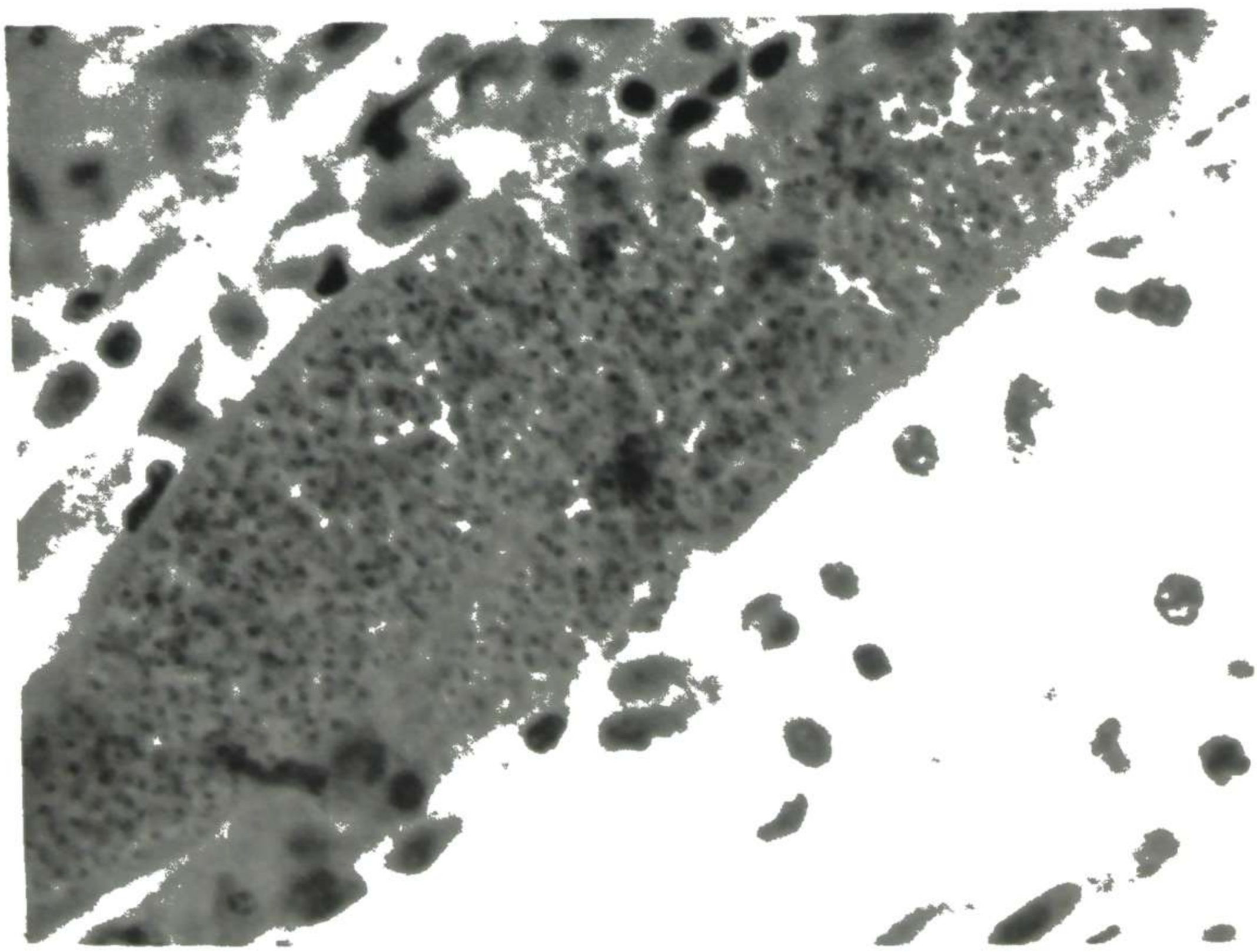


Fig. 8. Aggregation of T. cruzi in myocardial fiber. This is not a true cyst as no capsule is formed. Organisms are merely confined in the limits of the sarcolemma. × 980. (Courtesy of Enos, W. F., and Elton, N. W., Am. J. Trop. Med. 30:829-833, November, 1950.)

(1) Am. J. Trop. Med. 30:829-833, November, 1950.

der. Laboratory studies were unrevealing except that heterophil agglutination was positive to a 1:1,024 dilution. Antibiotic agents were ineffective. Despite intensive therapy a shocklike state developed and he died about six weeks after hospitalization. Immediate cause of death was congestive heart failure in acute Chagas' disease.

Autopsy disclosed an enlarged heart (500 Gm.), with striking dilatation of both ventricles. The myocardium presented no gross evidence of inflammation, necrosis, infarction, hemorrhage or fibrosis. Microscopic examination of the heart revealed extensive myocarditis, with lymphocytes and plasma cells between the muscle fibers and about the blood vessels. The fibers were swollen and contained masses of parasites, identified as the leishmanial forms of Trypanosoma cruzi (Fig. 8). Individual parasites measured about 2 μ in diameter, exhibiting a dark-staining, rodlike kinetoplast and an oval, basophilic nucleus. Intensive search failed to reveal areas of parasitic infection in any other organ. The liver and lungs were greatly congested.

[Dr. Elton has drawn our attention to a series of papers by J. Muniz and M. C. Felippe dos Santos of O Hospital, Rio de Janeiro (February, October and November, 1950), concerning heterophile antibodies in American trypanosomiasis (Chagas' disease). In addition to agglutinins, there are "conditioned hemolysins." Muniz claims that "red cells when adsorbed with the polysaccharide fraction of S. cruzi" are subject to hemolysis, provided they are "placed in contact with a specific serum and with the complement." The agglutinins reach a higher titer in the acute than in the chronic cases, but the hemolytic titers run higher in both. Dr. Elton writes that he does not find the high rate of positive reactions in chronic cases as reported by Muniz. These tests are apparently of value but not strictly specific for Chagas' disease.—Ed.]

Inflammation and Healing

Studies on Cellular Immunology and Acute Bacteremia: Intravascular Leukocytic Reaction and Surface Phagocytosis. W. Barry Wood, Jr., Mary Ruth Smith, William D. Perry and John W. Berry[2] (Washington Univ.) report investigation of intravascular phagocytosis of virulent pneumococci and Friedländer's bacilli. When the organisms were injected directly into the veins of nonimmune animals, there was prompt phagocytosis in the sinusoids of the liver, spleen and capillaries of the lungs. Fatal pneumonia with terminal bacteremia was produced in rats by intrabronchial inoculation. Specific antibody is rarely demonstrated in bacteremia. Death occurred before homologous opsonins appeared in detectable quantities in the serum. Phagocyted pneumococci were found in the macrophages and polymorphonuclear leukocytes in the hepatic and splenic sinusoids and in the polymorphonuclears in the lung capillaries. Bacteria were often visible in the interstices of fibrinoid deposits which appeared to be minute thrombi

(2) J. Exper. Med. 94:521-534, December, 1951.

present in pulmonary capillaries and sinusoids of liver and spleen.

In the vessels of the ear chamber in normal rabbits, the circulating leukocytes rolled freely along the walls of patent arterioles, capillaries and venules. A few minutes after intravascular injection of organisms into the opposite ear, the leukocytes began to adhere to the vascular endothelium. After 15-30 minutes, many leukocytes had accumulated on the endothelium where they became motile and migrated on the endothelial surface. Phagocytosis of blood-borne bacteria rarely occurred in small vessels where blood flow was rapid. In capillaries where blood flow was sluggish, phagocytosis was found 15-30 minutes after inoculation. Phagocytosis invariably resulted from one of three mechanisms: (1) surface phagocytosis in which bacteria were entrapped against the vessel wall by the leukocytes, enabling the pseudopods of the leukocytes to surround the organism; (2) intercellular surface phagocytosis, in which bacteria in stagnant capillaries were sometimes caught between two adjacent leukocytes, and (3) phagocytosis of bacteria caught in the interstices of the reticular deposits of what appeared to be fibrin within the capillary lumen. The circulating leukocytic response to intravascular introduction of large numbers of bacteria is a mobilization of active phagocytes within the blood stream occurring without aid of antibody or opsonins and serving as an important defense of the host.

[Dr. Wood prepared a special article on the general phases of this topic which appeared in the 1950 YEAR BOOK, page 15. The current article reports further studies based in considerable measure on observations in vivo.—Ed.]

Role of Some Higher Peptides in Inflammation. W. G. Spector[3] (London) investigated the properties of certain enzymic digests of proteins which reproduce some features of acute inflammation. Three biologic effects were studied: (1) capillary permeability response; (2) ability to induce leukocytic emigration, and (3) swelling of the capillary endothelium. Rats were used for most experiments; rabbits were used for comparison with previous work. Permeability response of capillaries was determined by gross discoloration at the site of intradermal injection of test substance after previous intravenous administration of trypan blue. Leukocytic emigration and capillary endothelium swelling were determined micro-

(3) J. Path. & Bact. 63:93-110, January, 1951.

scopically in sections taken from animals killed 30 minutes after intradermal injection.

A peptic digest of fibrin showed all three effects. An attempt to purify the crude digest by charcoal adsorption and elution was unsuccessful. With fuller's earth the active material was almost quantitatively adsorbed but elution with the same material yielded only a small quantity of partially insoluble material. Purification was not accomplished by exposure of the substance to cation and anion exchanges. No consistent result was obtained by exposure of the crude digest to paper partition chromatography. Both water and alcohol soluble fractions of crude digest showed activity by producing all three biologic effects. The active principle of the crude digest was precipitated by ammonium sulfate, the precipitated material having several times the potency of the original solution. The supernatant portion caused no increased capillary permeability but was of the same potency as the precipitate in producing polymorphonuclear emigration and endothelial swelling. The same effect existed after the supernatant fluid was separated from all free amino acids by prolonged electrodialysis at an acid pH. When a solution of the ammonium sulfate precipitate at pH 3 was placed in an electrodialysis apparatus, the active principle of the capillary permeability test appeared to migrate quantitatively to the cathode side, yet the peptides recovered from the cathode cell had the same potency as the starting material although comprising only 20-35 per cent by dry weight of the total recovery. The material remaining, first thought to be inert, was found to exert some action in high concentration.

There were 5 amino acids in the average peptide chain of the ammonium sulfate supernatant fluid and 10 in the average peptide chain of the ammonium sulfate precipitates. Acid hydrolysates of all fractions were devoid of the three biologic effects. Ammonium sulfate precipitate when digested with commercial trypsin lost the power to produce capillary permeability but retained the other two biologic effects. The same change was caused by digestion of the supernatant fluid. Both precipitate and supernatant factors were able to lower surface tension; this ability is common to higher peptides. The acid hydrolysates, when all peptide bonds had been destroyed, had no power to lower surface tension. Intramuscular injection of an antihistamine delayed but did not prevent increased capil-

lary permeability caused by the precipitate. In rabbits this effect was completely inhibited.

Pepsin digestion of blood albumin gave a mixture with a less active capillary permeability effect than the fibrin material. Peptic digestion of gelatin followed by ammonium sulfate precipitate yielded an active capillary permeability agent. Blood fibrin and albumin digested with commercial trypsin resulted in a factor having both capillary permeability and leukocyte-attracting activity. Crystalline beef pancreas trypsin inhibitor, a peptide with a molecular weight of about 6,000, produced increased capillary permeability, leukocytic emigration and endothelial swelling in the rat. An inflammatory exudate produced by turpentine injection contained a variety of amino acids and peptides. The active biologic principle concentrated by precipitation with ammonium sulfate induced all three effects in rats.

The biologic properties studied in the experiment and manifested in inflammation can be caused by a variety of peptides. The basic activity seems to depend on length of the peptide chain and is possessed by many peptides within certain limits of molecular size.

[The value of this study seems to lie in the exact chemical determination of the substances concerned. It appears to throw some doubt on the specific agents described in this country by Menkin and his associates. —Ed.]

Chorionic Gonadotrophin, ACTH and Adrenal-Hyaluronidase Relationship. Jeanette C. Opsahl, C. N. H. Long and Edith G. Fry[4] report that systemic administration of ACTH, chorionic gonadotrophin or heat-inactivated chorionic gonadotrophin in doses of 1-5 mg. caused striking inhibition of dermal spreading of India ink with hyaluronidase in normal animals. It is of importance that heat-inactivated chorionic gonadotrophin gave entirely similar results because heat inactivation destroys essentially all gonadotrophic activity without affecting the activity of adrenocorticotrophic hormone.

Numerous experiments showed that all of the substances are completely without effect in the adrenalectomized animal. This suggests that their inhibitory action on hyaluronidase is mediated through the adrenal glands.

Striking inhibitory effects were produced by administration of chorionic gonadotrophin or heat-inactivated chorionic gonadotrophin to castrated animals of both sexes. Potency

(4) Yale J. Biol. & Med. 23:399-406, April, 1951.

of enzyme or time interval of spreading was not a limiting factor in the inhibitory capacity of chorionic gonadotrophin. Presence or absence of the gonads seemed of little significance. Experiments with hypophysectomized mice showed that both inhibit the hyaluronidase-enhanced spreading phenomenon even in the absence of the pituitary.

Two possibilities as to the source of the ACTH-like activity found in these preparations derived from human pregnancy urine are: (1) the process of extraction includes such quantities of pituitary adrenocorticotrophic hormone as may have been excreted; (2) the placenta may normally form an agent similar to adrenocorticotrophic hormone, a portion of which is also excreted in the urine. These experiments provided no means of discriminating between the two possibilities. The work of Jailer and Knowlton, however, indicates that adrenocorticotrophic hormone-like activity can be demonstrated in placental tissue. Therefore the urinary factor demonstrated by these experiments may have a similar origin. It is thus possible that adrenocorticotrophic hormone or adrenocorticotrophic hormone-like material may be obtained from man for clinical use, which would provide another source to supplement the limited quantities now available only from animals.

Adrenal-Hyaluronidase Relationship in Infection. George H. Smith and Jeanette C. Opsahl[5] administered intradermal injections of a hyaluronidase-containing bacterium, Staphylococcus aureus, to normal mice, and found that the inoculum was not lethal but that severe lesions appeared two to four days later. When normal animals were given aqueous adrenal cortical extract intraperitoneally before administration of the infectious agent, there was pronounced resistance to the development of lesions. In adrenalectomized mice severe lesions appeared to develop more rapidly than in normal animals; there was a high mortality as early as one day after injection and all died within seven days. Replacement therapy with adrenocortical extract in the adrenalectomized animals increased their resistance to infection, as evidenced by lowered mortality and development of less severe lesions. Replacement therapy, however, was not complete. To test the concept that inhibition of spreading was due to cortical steroids, a mixture of adrenal extract and bacteria was injected. In both

(5) Yale J. Biol. & Med. 23:361-369, April, 1951.

types of animal the adrenocortical extract provided considerable protection, as indicated by smaller and less severe lesions than those produced in control groups.

Suspensions of Salmonella aertrycke, an organism which does not contain hyaluronidase, were injected into normal and adrenalectomized mice. Within 10 days, all died. Administration of adrenal cortical extract did not appear to affect the course of infection in normal animals significantly, but adrenalectomized animals were somewhat protected by it. Replacement therapy was not complete since treated animals did not survive as long as controls.

The adrenal-hyaluronidase relationship may be one of the factors involved in the lowered resistance of adrenalectomized animals to infection, but lack of inhibition of hyaluronidase can be only one component of this complicated deficiency condition.

Selective Damage to Fibroblasts by Desoxycorticosterone in Cultures of Mixed Tissues is described by Ivor Cornman[6] (George Washington Univ.). In cultures fragments of hearts taken from newborn line C white mice showed outgrowths of fibroblasts and endothelial cells (Fig. 9). When the original nutrient medium was replaced by balanced saline solution containing 0.02 mg. desoxycorticosterone (Delta)/ml., cytologic changes became visible in 16 hours. Fibroblast cell membranes lost their smooth contours and became angular; cytoplasm became granular, and cells narrowed to half or a third of their usual width although the filamentous processes remained extended. Endothelium similarly became granular, and the cells sometimes shrank, separating the membrane into isolated or grouped cells.

With this dosage the original outgrowth usually never recovered. In one experiment, however, exposure to 0.1 mg. desoxycorticosterone (Ciba)/ml. for 25 hours did not damage the endothelium. Fibroblasts never recovered but the endothelium resumed normal morphology and growth when returned to the nutrient medium (Fig. 10). Before treatment, only 2 per cent of the explants were pure endothelial growth; after treatment, regenerated tissue was composed of endothelium alone in 57 per cent. In untreated cultures distribution of endothelium and fibroblasts did not change.

(6) Science 113:37-39, Jan. 12, 1951.

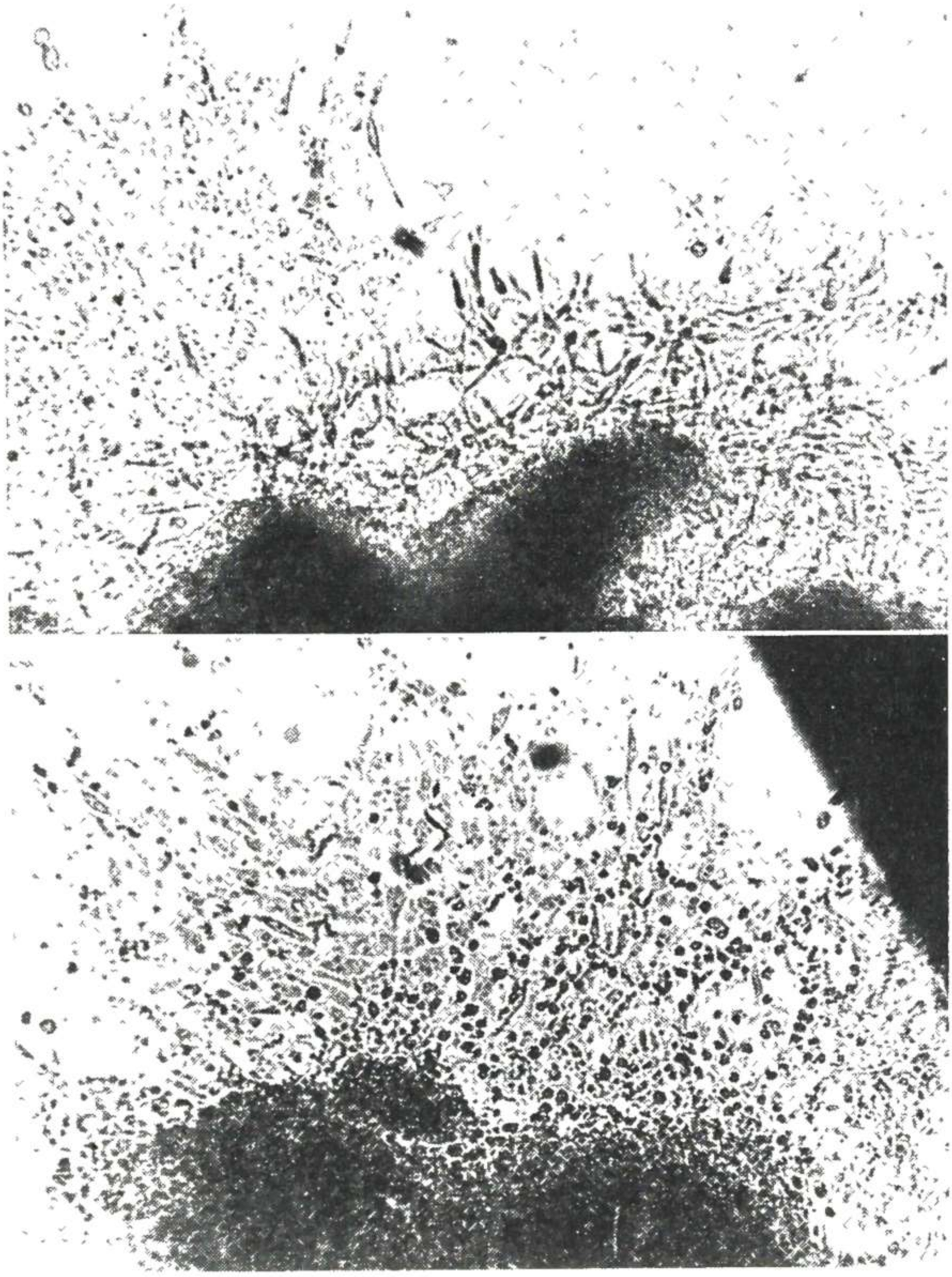


Fig. 9 (top).—Two day growth from heart fragment. Endothelium on left, fibroblasts on right; about × 100.

Fig. 10 (bottom).—Two days after return to nutrient solution. Endothelial cells expanded and transparent; fibroblasts rounded or shriveled and densely granular. Endothelium is growing, but fibroblasts have remained unchanged for the two days; about × 100.

(Courtesy of Cornman, I.: Science 113:37-39, Jan. 12, 1951.)

Cortisone, 0.05-0.15 mg./ml. added to desoxycorticosterone, accelerated and increased the visible cytologic alterations but did not interfere with the favoring of endothelium in explants which survived.

In Vivo Observations of Effects of Cortisone on Vascular Reaction to Large Doses of Horse Serum Using Rabbit Ear Chamber Technic. Robert H. Ebert and Robert W. Wissler[7]

(7) J. Lab. & Clin. Med. 38:497-510, October, 1951.

(Univ. of Chicago) report the effect of cortisone on the vascular and intravascular changes which accompany serum sickness in rabbits. Seven cortisone-treated rabbits were given two injections of normal horse serum 18 days apart, and four of the seven were given a third injection after cortisone therapy had been stopped. Since in untreated rabbits the most intense and consistent change produced by horse serum occurred in the first four days after the second injection, in five of the rabbits, 25 mg. cortisone daily was started five days before the second injection and in two, 5 mg. daily was started at

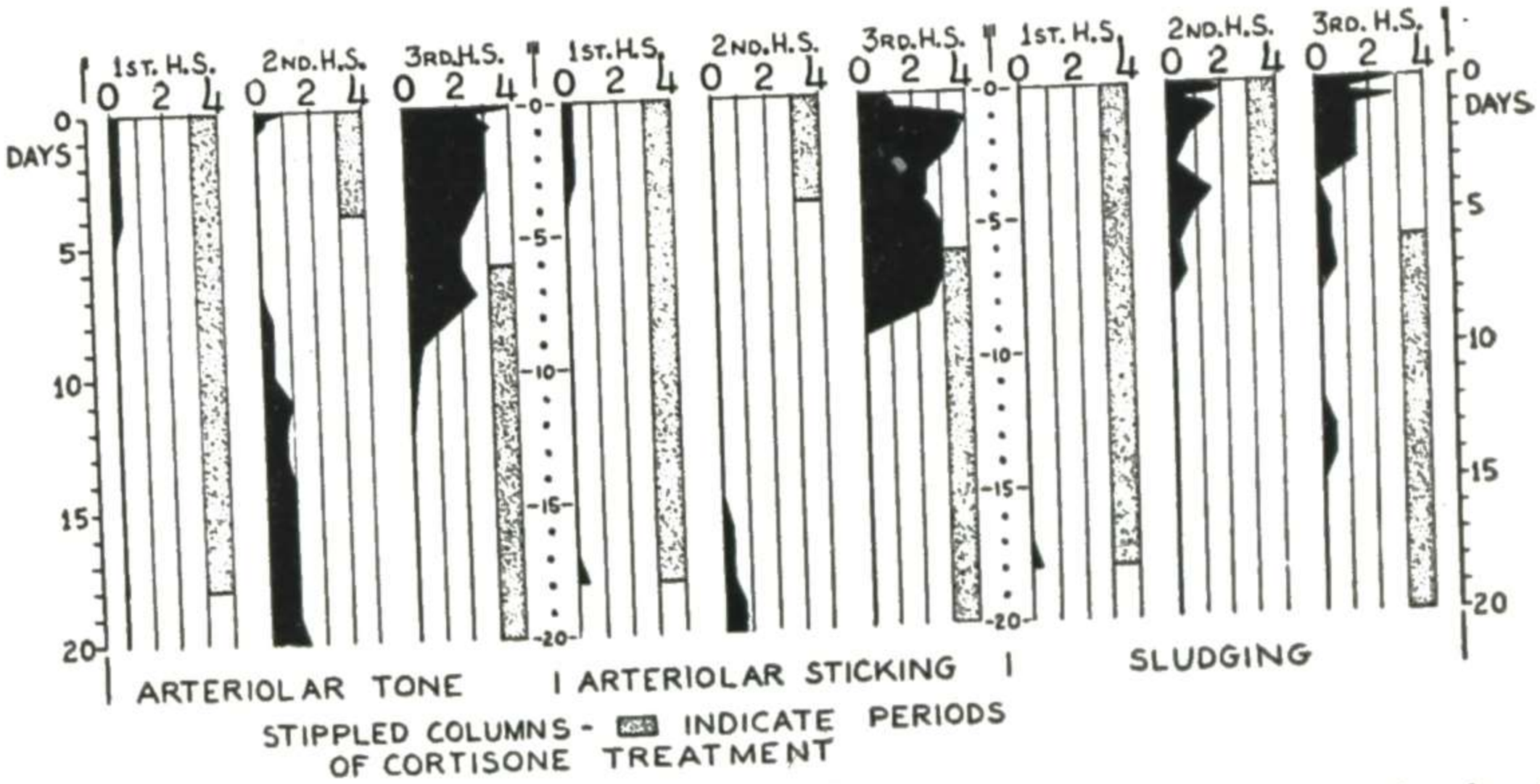


Fig. 11.—Serum sickness. Average of reactions in two animals (three chambers) with and without cortisone treatment after first, second and third horse serum injections. Stippled columns indicate periods of cortisone therapy. (Courtesy of Ebert, R. H., and Wissler, R. W.: J. Lab. & Clin. Med. 38:497-510, October, 1951.)

the time of the first injection. Quantitative estimations of changes were made for arteriolar tone, sticking of leukocytes to arteriolar endothelium and sludging (Figs. 11 and 12). The number of platelet and white blood cell thrombi and emboli was also studied.

The most striking effect of cortisone was on arteriolar tone. In apparently normal animals there was a gradual increase of tone during cortisone therapy, and changes in tone usually associated with serum sickness were suppressed or abolished. In two animals receiving cortisone from the time of first injection, no abnormalities occurred. In other rabbits, localized vascular constriction and dilatation which followed the first serum injection disappeared three to four days after cortisone treatment was begun. In only one rabbit receiving cortisone was cessation of blood flow observed during the second serum

injection. Dilatation of arterioles following the second injection and subsequent localized constrictions and dilatations were quantitatively reduced by cortisone therapy. Arterioles of treated animals tended to maintain a more normal tone after the second injection. After cortisone therapy was stopped, tone was gradually lost and significant abnormalities developed. In three animals observed during a third serum injection after cortisone had been stopped, cessation of blood flow occurred. Sticking of leukocytes to arteriolar endothelium did not

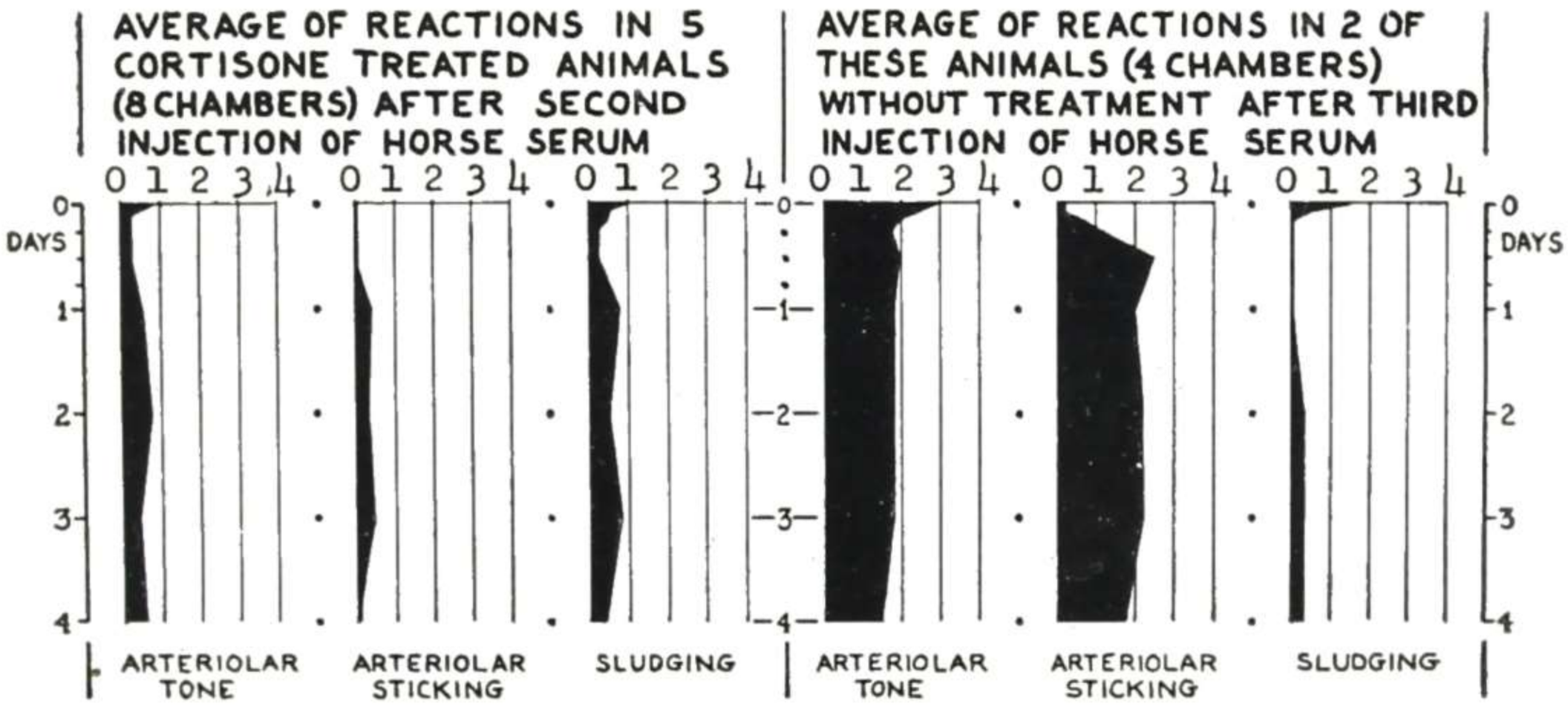


Fig. 12.—Serum sickness. Comparison of reactions in same animals with and without cortisone treatment. (Courtesy of Ebert, R. H., and Wissler, R. W.: J. Lab. & Clin. Med. 38:497-510, October, 1951.)

develop during the first serum injection in the two animals treated with cortisone from the first day of the experiment. The phenomenon was present in two of the other five but disappeared the third day of cortisone therapy. Little arteriolar sticking developed in treated animals after the second serum injection, but sticking was present when cortisone was stopped and a third dose of serum administered. Endothelial swelling was not found in treated animals but appeared following cessation of cortisone.

In general, venule and capillary changes followed the same pattern as those for arterioles. There was a reduction in degree of sludging in cortisone-treated animals, but the suppression was less dramatic than that of vascular change. Few platelet and leukocytic thrombi and emboli were seen in treated, compared with untreated, animals after the second serum injection. The severe systemic symptoms seen in untreated animals during or after the second injection were al-

most completely suppressed in animals receiving cortisone before the second injection. These effects of cortisone are reversible and exacerbations occur after cessation of treatment.

The suppression of in vivo manifestations of serum sickness is believed due to the effect of cortisone on the integrity and reactivity of small vessels rather than to a suppression of antibody formation or antibody-antigen union.

Effect of Cortisone on Mast Cells of Rat is reported by Cesare Cavallero and Carlo Braccini[8] (Univ. of Milan). Three groups of six male rats were given cortisone subcutaneously, 10, 5 and 1 mg./day for 3, 20 and 70 days respectively; 18 control rats were given similar doses of physiologic saline. The number of mast cells in the skin, skeletal muscle and myocardium were investigated. Mast cells were counted in a measured area of the section and tabulated as cells/millimeter of tissue examined. Hyaluronic acid in the tissue was identified by use of bull testis hyaluronidase and subsequent staining with periodic acid leukofuchsin.

Cortisone-treated rats had skin atrophy and a decrease in dermal hyaluronic acid. Fibroblasts were scanty and fibrils reduced in number. In all experimental animals, mast cells and granules were reduced in number and size. Many cells were disintegrated and the granules dispersed in the ground substance. As in normal animals, these cells showed mainly a perivascular distribution. The metachromatic material of the granules was refractory to the action of hyaluronidase in contrast to the ground substance of the connective tissue. Similar results were obtained from examination of the myocardium and skeletal muscle.

The inhibitory effect of cortisone was well marked on all the cellular constituents of the connective tissue: fibroblasts, reticuloendothelial system and plasma cells. Reduction in number of mast cells may be regarded as a partial manifestation of this general inhibitory effect of the hormone. It has been shown that cortisone applied locally decreases the mast cells as well as other cellular constituents in the dermal tissue. The action of cortisone is probably more pharmacologic than hormonal in nature.

[The subject of mast cells continues to attract attention. Two articles on this same subject appeared in the 1949 YEAR BOOK (pp. 24-26). At that time it appeared that these cells can form heparin. Whether this has importance in relation to the effects of cortisone is still uncertain.—Ed.]

(8) Proc. Soc. Exper. Biol. & Med. 78:141-143, October, 1951.

Desoxycorticosterone Acetate and Wound Healing. Conrad L. Pirani, Robert C. Stepto and Kenneth Sutherland[9] (Univ. of Illinois) studied the effects of desoxycorticosterone (DCA) on granulation tissue of healing and healed linear laparotomy wounds in young adult male guinea pigs maintained on a complete diet and on a known intake of ascorbic acid. DCA induces production of an excessive amount of granulation tissue, as evidenced by a relatively great number of fibroblasts and a larger amount of ground substance. This effect was accompanied by slight to moderate lag in the maturation process of both cellular and intercellular elements. These changes were observed when DCA administration was begun 5 days before operation but were less obvious or absent if DCA injection began 5 or 10 days postoperatively. Results indicate that the action of DCA on immature, proliferating connective tissue is striking and is considerably less or absent when connective tissue elements have reached partial or almost complete maturity. The effect of DCA on connective tissue does not appear to rest on altered nutritional status. Chemical and histochemical studies of the adrenals suggest that the action of DCA on connective tissue is probably mediated through disturbance of adrenocortical function: namely, imbalance between hormones of the zona glomerulosa (excess of DCA) and those of the zona fasciculata (deficiency of glucocorticoids). Presence of changes in granulation tissue and lack of them in mature resting connective tissue of DCA-treated animals demonstrate the profound difference in the response of resting and active connective tissue.

[It is interesting that DCA has somewhat the influence exhibited by cortisone. The following articles elaborate on the effects of cortisone in repair and healing.—Ed.]

Influence of Cortisone on Skin and Wound Healing in Experimental Animals. Hamilton Baxter, Carl Schiller, John Whiteside and Richard E. Straith[1] (McGill Univ.) examined wounds in rabbits at intervals before and after cortisone injections. All cortisone-treated animals showed a tendency to hemorrhage at the site of incision. This treatment retarded epithelial union, granulation tissue formation, fibroblastic and capillary proliferation in wounds. After cortisone, epithelial growth was slow and did not become firmly united until 10 days in contrast to firm epithelial union in 4-7 days in the

(9) J. Exper. Med. 93:217-228, March, 1951.
(1) Plast. & Reconstruct. Surg. 7:24-31, January, 1951.

controls. A quantitative decrease in proliferating fibroblasts and capillaries was noted. Collagen formation was inhibited. These factors influenced the delayed filling of the wound and firm union of the edges in treated animals.

In all animals receiving cortisone, atrophic changes developed in the skin distant from the wound. Appearing earlier in animals given heavy doses was a gross "crinkling" of the skin, produced by condensation of dermal collagen, with diminution of the subcutaneous adipose layer. Later, epidermal thinning developed, with loss of polarity in the basal layer as well as disappearance of the granular layer. Hair follicles became smaller and more superficial. These changes occurred after 17 days of treatment. No difference in number of capillaries or of mitosis in the epithelial cells could be distinguished.

Cortisone inhibits the inflammatory reaction and reduces fibroblastic proliferation. This prolongs healing of experimental wounds.

Histologic Study of Effect of Cortisone on Wounds Healing per Primam: Experimental Study is reported by Jack W. Cole, J. Lowell Orbison, William D. Holden, Thomas J. Hancock and John F. Lindsay[2] (Western Reserve Univ.). Four dogs were given cortisone, 2 mg./kg. body weight daily for 20 days; three dogs served as controls. Linear aseptic wounds of skin and soft tissue were made one day after the first cortisone injection. Wounds were closed with sutures, which were removed on the seventh day in both experimental and control animals. Biopsies of wounds were done 3, 7, 10 and 20 days postoperatively.

In biopsies taken the third postoperative day there was a mass of amorphous material overlying the epithelium at the wound site. Fibrin and a few leukocytes could be identified in this surface accumulation. The epithelium had not regenerated. In the corium, subcutaneous tissue and muscle the wound contained small amounts of fibrin and amorphous material. No cellular proliferation could be demonstrated. New connective tissue or reticulum was not present.

On the seventh day the crust remained on the surface but the underlying epithelium had regenerated. Epithelium was thickened at the wound site. The prickle cell layer contained large amounts of glycogen. The basement membrane was re-

(2) Surg., Gynec. & Obst. 93:321-326, September, 1951.

ormed but thinner than normal. In deeper levels fibroblastic roliferation, collagen and reticulum formation were evident. y the tenth day reticulum and collagen were increased. Bipsy on the twentieth day revealed an increase in collagen associated with a diminution of reticulum. The epithelium at the ound site was thinner than normal. Elastic tissue had not egenerated by then.

In biopsies from cortisone-treated and control dogs no difference could be found in the rate or quality of healing of pithelium, corium, subcutaneous tissue, fascia or muscle.

Observations in Experimental Animal on Nature of Metachromatic Ground Substance in Granulation Tissue are presented by M. Campani and O. Reggianini[3] (Univ. of Bologna). In sections of tissue taken 48 and 96 hours after wounding and stained with toluidine blue, metachromatic substance is not uniformly diffused, but is especially abundant in regions rich in newly formed vessels and scarce or absent in areas not yet invaded by granulation tissue cells. With high magnification, this substance looks almost like an amorphous mass of metachromatically stained tiny granules or very thin fibrils closely connected with each other. The cytoplasm of the fibroblasts, endothelial cells of newly formed vessels and cell nuclei exhibit metachromasia of a different character than that of the extracellular metachromatic substance. These formations show a purple instead of a red tint.

In fragments excised 6-10 days after wounding the metachromatic substance is gradually disappearing, to be replaced by numerous connective fibrils which develop a purple coloration. At this stage the tissue looks more compact and more abundant in both cells and fibers.

After treatment of sections with purified ribonuclease the ground substance still exhibits metachromasia. Treatment of sections of tissue with hyaluronidase from various sources 48-96 hours after operation causes disappearance of metachromatic staining in the ground substance, but that in the cytoplasm of fibroblasts and endothelial cells of newly formed vessels is not altered. In sections taken 6-10 days after wounding, treatment with hyaluronidase does not alter the staining reactions.

The results suggest that the active substance in the repair connective tissue of skin wounds is hyaluronic acid.

---

(3) J. Path. & Bact. 62:563-568, October, 1950.

Effect of Cortisone on Survival of Skin Homografts in Rabbits. Using rabbits of different breeds, R. E. Billingham, P. L. Krohn and P. B. Medawar[4] (Univ. of Birmingham) studied pinch grafts comprising epidermis and full thickness corium by serial sampling technic. Multiple homografts from a common donor were transplanted to animals receiving cortisone and to controls. Autografts were done simultaneously on the recipients.

Cortisone-treated animals exhibited subdued initial inflammation in both autografts and homografts. The dermal vascular supply was poor and the graft unfixed after six days. Epithelial proliferation in autografts appeared later but continued for a longer period than in the untreated animals.

In the control groups, homografts produced violent inflammation, became temporarily united, underwent necrosis and mummification and were replaced by an undergrowth of native epithelium in less than 10 days. Cortisone delayed the onset and progress of the reaction, so that homografts survived three or four times the usual period. The native epithelium of the treated animals grew centrally, passing over the homograft dermal fibers. This observation suggests that cortisone permits survival of homograft dermal fibers. It retarded but did not lessen scarring.

[It will be recalled that cortisone has been suggested for treatment of burns, but it seems that the side effects interpose difficulty and the general physiologic effects are open to various interpretations. This article and the one which follows indicate that the inhibition of granulation and the hyperplasia of collagenous tissue offer contraindications.—Ed.]

Effect of ACTH on Survival of Homografts in Man. Hamilton Baxter, Carl Schiller, John H. Whiteside, Herbert Lipshutz and R. E. Straith[5] (Royal Victoria Hosp., Montreal) define homograft as a graft of any tissue transplanted from one individual to another of the same species. The effect of ACTH, started at various time intervals after the application of skin homografts in three patients, was studied. One patient received two homografts. Two patients received autografts also at the time of operation. ACTH was started 6 days before application of the homograft in one instance, at the time of operation in two and 15 days afterward in another. The two autografts showed no deviation from the ordinary course of healing. Grossly the homografts appeared to take and live for

---

(4) Brit. M. J. 1:1157-1163, May 26, 1951.
(5) Plast. & Reconstruct. Surg. 7:492-504, June, 1951.

more than two weeks. Changes usually developed around the 19th day after application, and sloughing rapidly terminated the graft.

Biopsy of a homograft seven days after application and start of ACTH therapy showed slight epithelial degeneration and proliferation of the rete pegs and diffuse inflammatory cell infiltration, chiefly by polymorphonuclear leukocytes and eosinophils. The graft was still vascularized. Granulation tissue, formed at the junction, was irregular and meager. Biopsy on the 15th day showed more prominent degenerative cellular changes of the epithelium. Capillaries were scarce in the graft. There was an irregular fibroblastic ingrowth from the graft bed. The inflammatory infiltration had increased and now consisted largely of lymphocytes and eosinophils. Biopsy 23 days after application showed striking degenerative changes throughout the homograft with almost complete loss of epithelium. The surface was covered by necrotic and purulent exudate. Extensive polymorphonuclear leukocytic and eosinophilic infiltration was apparent. Capillary walls were necrotic, and small hemorrhages had occurred. In one homograft, biopsy 15 days after application and 21 days after ACTH was started revealed early degeneration of the epithelial cells. The collagen fibers of the dermis had lost the normal fibrillary character. The graft was united by a broad zone of proliferating fibrous tissue. Biopsy of this graft on the 23d day showed only remnants of collagen fibers covered by necrotic tissue and fibrin. Proliferating granulation tissue was invading the graft. Inflammatory cells were numerous. The original junction of the graft with the underlying bed was occupied by well formed fibrous tissue.

When both homografts and autografts were applied at the beginning of ACTH therapy, they took completely and appeared quite normal. The gross appearance of the grafts was similar 15 days after application, but biopsies showed considerable variation. The autograft was united to its bed with granulation tissue. Only slight edema of the epithelium and dermis was present. In the homograft there was moderate inflammation of the epithelium and dermis. The inflammatory cell infiltrate consisted of mononuclear and eosinophilic leukocytes. Only a small amount of granulation tissue was present at the junction of the graft and its bed. The epithelium of the homograft began to separate on the 20th day. At this time

the autograft was well united to its bed with collagen tissue and the epithelium was assuming its normal appearance. On the 23d day there was conspicuous degeneration and inflammation in the homograft dermis. The epidermis had been separated from the dermis in numerous areas by an accumulation of fluid. The inflammatory reaction was entirely mononuclear. Capillary proliferation was seen in the graft dermis although little granulation tissue was formed at the junction of the graft and its bed.

[In one case in which major blood groups and Rh status of donor and recipient were compatible, the homograft sloughed in the usual fashion. The theory of "active immunity" is not supported, and it may well be that new theories must be proposed.—Ed.]

Thermal Injury

Pathogenesis of Muscle Necrosis Due to Experimental Local Cold Injury. R. B. Lewis[6] (M.C., U.S.A.F.) produced muscular necrosis without sloughing of the skin in the extremities of rabbits. Limbs of animals were exposed to an alcohol bath of —12 C. for 30 minutes. This procedure did not produce ulceration, thereby eliminating changes due to secondary infection. The frozen limbs were thawed at room temperature and the animals killed at various intervals. Control material included changes from nonthermal ischemia produced by tourniquet compression.

In all animals, up to 72 hours after exposure the muscles of the frozen limbs were a diffuse dull red, in contrast to the bright red of muscles after ischemia. Edema appeared early and reached a maximum of approximately 40 per cent increase in weight 72 hours after freezing. Muscle fibers were wavy and swollen, with loss of cross striations 15 minutes after removal from the alcohol bath. Vacuoles and amorphous eosinophilic debris appeared within the substance of muscle fibers. Nuclei were often absent and occasionally the sarcolemma had degenerated. Fibrin and eosinophilic granules were deposited in the intercellular and interfascicular spaces. Blood vessels were dilated and blood cells extravasated.

All initial changes had progressed 30 minutes after exposure. More muscle fibers were involved. Complete degeneration of many muscle fibers appeared one hour after freezing. Sarcolemma sometimes remained surrounding empty spaces. Eosinophilic granular debris and scattered hemorrhages were common.

(6) Am. J. M. Sc. 222:300-307, September, 1951.

In animals killed two, four and six hours after exposure, degenerative changes were more severe. Large areas of unrecognizable muscle tissue replaced living cells. Polymorphonuclear leukocytic exudation was noted as early as four hours after freezing. No thrombi were demonstrated in the vessels of damaged muscles up to 14 hours after exposure. Necrosis continued to progress for 24 hours after injury. Complete necrosis of individual muscles sometimes developed, and in the same limb other muscles had degenerated cells adjacent to normal fibers. Connective tissue was increased in regions of early muscle destruction. An occasional thrombus was observed in the small veins. Thrombosis of vessels was frequently noted in sections taken 48 hours after injury. Fibrosis, phagocytosis and mononuclear infiltration were present to a variable degree. Healing in the form of marginal fibrous tissue replacement of the necrosis was apparent in muscles 72 hours after damage. Fibroblastic proliferation was still limited to the margin of the affected areas eight days after freezing. Incompletely degenerated muscle fibers were represented by amorphous shreds and eosinophilic remnants. Vascular thrombi were numerous. Alterations in the muscles shortly after frostbite could not be attributed to ischemia. Vascular changes during freezing and thawing are not considered the primary cause of tissue damage although they may influence the outcome of the injury.

Morphologic Changes of Adrenal Cortex in Frostbitten Rabbits with and without Heparin Treatment. Bernhard Hoelscher[7] (Randolph Field, Tex.) exposed the hindlimbs of rabbits to low temperatures in an alcohol bath. One group of exposed animals and one group of controls received 3 cc. heparin sodium solution intravenously every six hours for six days.

Heparin did not benefit the local or systemic effect of frostbite. The death rate of heparin-treated animals, greater than that of all other groups, was commoner in winter than in summer. After exposure to cold, body weight decreased and adrenal gland weight increased, being even greater when heparin was injected into frostbitten animals but only slight in heparin-treated rabbits unexposed to cold.

There was a distinct seasonal difference in histologic changes caused by heparin. In summer, only mild swelling of

(7) A.M.A. Arch. Path. 52:378-383, October, 1951.

the cortical cells with vaguely outlined cell borders was observed. When heparin was administered during the winter, changes in the adrenal cortex were more severe. The cells of the zona fasciculata became enlarged, with coagulation of the cytoplasm and nuclear swelling. The adrenal glands of frostbitten untreated animals showed a disorderly arrangement of cortical cells with obscure borders in the zona fasciculata. There was cloudy swelling of the cytoplasm and nuclear pyknosis. All alterations of the zona fasciculata in frostbitten rabbits were increased by heparin treatment. Animals given heparin after freezing of the leg did not have the typical arrangement of cortical cells. Congestion and dilatation of the sinusoids was associated with all stages of cortical necrosis. Cells of the fascicular layer were foamy and granular, with cytoplasmic vacuoles which appeared empty on frozen sections. The nuclei were pyknotic. No connective tissue reaction was observed. The entire cortex was largely devoid of fat.

It appears that heparin treatment may augment the degenerative changes of the cortical tissue observed in frostbite.

Pathologicoanatomic Changes Following Rapid and Slow Thawing of Frozen Skin in Man. J. Adams-Ray and B. Falconer[8] (Stockholm) report changes produced experimentally by freezing skin of lower extremities in 20 patients whose limbs were about to be amputated because of obliterative processes of arteries and in 1 because of tumor. Areas on the medial and lateral aspect of the extremity in regions of visibly normal skin were simultaneously frozen with ethyl chloride. One area was immediately warmed in water at 37 C. and the limb then placed under the bedclothes. Amputation 24 hours later was followed by histologic examination of the tissue.

Degenerative and inflammatory alterations were found in the skin and supporting tissues of both rapidly and slowly warmed areas. Notable decrease in affinity for staining in tissue was taken to indicate necrosis or necrobiosis. Blisters formed in severely damaged areas. Cells of the adnexa, especially the epithelium of the sudoriparous glands, showed shriveling in all cases. Fibrinoid degeneration of elastic tissue and arrectores pilorum was sometimes evident. Edema, hyperemia and cellular infiltration varied in degree. Vessels were dilated and engorged but did not show endothelial lesions or thrombosis.

---

(8) Acta chir. scandinav. 101:269-278, 1951.

In 15 patients the slowly thawed lesion was more damaged than that rapidly warmed. Degenerative changes were especially prominent in the gradually warmed lesion. Of the others, three had more damage in the rapidly warmed area and three showed equal damage in the two lesions.

[This and the preceding two articles are further evidence that war accelerates research. Cold injury is being studied by teams of military medical officers in the hope that the results may contribute to the treatment of local cold injury and preservation of frostbitten and frozen members.—Ed.]

Eosinophil and Other Leukocyte Changes in Burned Patients: With Special Reference to Adrenocortical Activity. S. Sevitt[9] (Birmingham Accident Hosp.) studied quantitative changes in eosinophil counts of 35 patients with burns of various degrees of severity; lymphocyte and neutrophil counts were also made in 18. At the initial dressing, 1 per cent cetrimide was used to clean the skin and then penicillin cream, often supplemented by polymyxin cream, was applied. In patients not in shock skin grafting of deep burns was generally done the first or second day. Patients in shock were treated with plasma or 6 per cent dextran in saline, or both. Blood transfusions were sometimes given, and skin grafting was delayed a week or longer.

The eosinophil count followed a constant pattern. Within a few hours of burning the number of circulating eosinophils, determined by the "wet-field" method of Dunger, was either falling or had fallen to a low or zero value. Eosinopenia was maintained for a variable number of days and then the count began to rise. After a peak value was reached the count declined. Lymphocytopenia and a neutrophilic leukocytosis accompanied the initial fall of eosinophils. Eosinopenia lasted longer in the more extensively burned patients, and the height of the primary neutrophilic leukocytosis increased with the percentage area burned. A secondary wave of neutrophilic leukocytosis developed 5-10 days after burning.

Since the blood changes after ACTH therapy, i.e., fall in eosinophil count, lymphocytopenia and neutrophilic leukocytosis, are the same as those that follow burning, it appears that adrenocortical hyperactivity occurs in the burned patient and is more prolonged in those with prolonged eosinopenia. Sodium and chloride retention, increased potassium loss, hyperglycemia, increased nitrogen excretion, degenerative

(9) Brit. M. J. 1:976-983, May 5, 1951.

changes in lymphoid tissue and increase in urinary excretion of 17-ketosteroids are seen in patients with burns and in those given ACTH.

It is suggested that eosinopenia is a sensitive index of adrenal cortex activity in burns and that a "premature" rise in eosinophil count in relation to percentage area burned may help in diagnosis of adrenal cortex failure. Eosinophil changes in five of eight fatally burned patients suggested that hyperactivity of the adrenal cortex was present before death. In another there was some evidence of adrenal cortex failure, and in two the evidence was inconclusive. Cortisone and desoxycortone acetate have been reported to give beneficial results in patients with burns.

Immunity and Hypepsensitivity

Zone of Localization of Antibodies: Use of Radioactive Sulfur^{35} as Label for Antikidney Serum. David Pressman, Herman N. Eisen, Malcolm Siegel, Patrick J. Fitzgerald, Beila Sherman and Arthur Silverstein[1] (Sloan-Kettering Inst. for Cancer Research) found that antibody specificity was not destroyed when antibodies were labeled with S^{35}. This was accomplished by coupling the antiserum with diazotized aminobenzenesulfonic acid containing S^{35}. Labeled anti-mouse-kidney serum localized specifically in the glomeruli of mouse kidneys. In kidney tissue a high level of radioactivity was maintained for 41 days with S^{35}-labeled antikidney serum. Similar duration was obtained with I^{131}-labeled antibodies but there was no such retention of activity with antiovalbumin serum labeled with S^{35}. The I/S ratios in kidney and liver indicated that more sulfur-labeled protein accumulates non-specifically in these organs than does iodinated protein, or that the iodine-labeled protein is metabolized with more rapid removal of the label.

Effect of Cortisone and Adrenocorticotrophic Hormone on Concentration of Circulating Antibody. Mogens Bjørneboe, Edward E. Fischel and Herbert C. Stoerk[2] immunized rabbits with polyvalent pneumococcic vaccine. Serum antibody nitrogen concentration after 14 and 28 days of immunization was less in animals treated with ACTH or cortisone than in controls. Immunization was continued in three animals after cortisone was stopped on the 14th day; two showed appreci-

(1) J. Immunol. 65:559-569, November, 1950.
(2) J. Exper. Med. 93:37-48, January, 1951.

able increases in antibody content. When cortisone was administered two weeks after onset of immunization, there was absolute decrease in the antibodies as compared with levels in control animals.

All rabbits immunized but not treated with ACTH or cortisone showed splenomegaly, lymphadenopathy and slight reduction in thymic weight. Microscopic examination showed enlarged malpighian bodies which contained numerous mitotic figures. Large mononuclear cells were increased throughout the pulp. Lymph nodes showed prominent germinal centers, with increased numbers of large mononuclear cells in the medullary tissue. Immunized animals treated with ACTH and cortisone showed moderate to striking atrophy of malpighian bodies and fragmentation of lymphocytes. Cortisone appeared to inhibit or reverse most of the alterations associated with immunization. There was striking absence of hyperplasia of the germinal centers in the follicles.

The relation of lymphoid tissue to immunization is emphasized by the coincidence of atrophy of lymphoid tissue and depression of antibody formation. The diminished antibody content of the serum observed in hormone-treated animals may result from the negative nitrogen equilibrium which is due to administration of these substances.

[Clinical studies of the use of ACTH and cortisone have shown numerous peculiarities. It is therefore of interest to have experimental studies on the effects of these hormones on antibody production.—Ed.]

Mechanism of Action of 17-Hydroxy-11-Dehydrocorticosterone (Compound E) and of Adrenocorticotrophic Hormone in Experimental Hypersensitivity in Rabbits. Frederick G. Germuth, Jr., Jiro Oyama and Barbara Ottinger[3] (Bethesda, Md.) studied the effect of ACTH and compound E on active and passive immunization.

Animals were sensitized by daily intracutaneous injections of crystalline egg albumin. Skin reactions, usually produced in 8-12 days, were graded according to size and severity. One group of animals was treated with ACTH, another with compound E and a control group with injections of a cholesterol suspension. Quantitative precipitin determinations of antibody were made on the blood serum.

ACTH caused only slight reduction in the local hypersensitive skin reaction. Compound E definitely inhibited the re-

(3) J. Exper. Med. 94:139-170, August, 1951.

action. After two weeks the serum antibody concentration in the ACTH-treated animals was about one-third that of the controls, whereas the concentration in animals given compound E was less than 5 per cent of the controls. When the antigen injections were discontinued from the 23d to 26th day of the experiment there was rapid rise in antibody titer followed by decrease when injections were resumed. When compound E was started after two weeks of egg albumin injections and after the skin reaction had developed, there was no significant change in the skin lesions even though a striking reduction of antibody in the blood could be demonstrated. Compound E had no effect on the circulating antibody levels of animals passively immunized. It did not prevent development of the Arthus reaction in animals sensitized by intravenous antibody administration before the challenging dose.

The results suggest that the inhibitory effect of compound E and ACTH on development of experimental hypersensitivity is due to hormonal reduction of circulating antibody. The hormones act by inhibiting antibody formation rather than promoting antibody destruction.

Cutaneous Hypersensitivity Due to Beryllium: Study of 13 Cases was made by George H. Curtis[4] (Cleveland Clinic) among workers in beryllium extraction plants. Dermatitis was caused by beryllium fluoride in 10, ground metallic beryllium in 2 and water drippings from overhead pipes coated with dust of various beryllium compounds in 1. Clinical, histologic and experimental criteria for establishing the dermatitis as an allergic-eczematous type were fulfilled.

Patch tests with beryllium fluoride, nitrate, chloride and sulfate gave positive results. Anions, acidity and primary irritancy of the soluble beryllium compounds were eliminated as direct causative factors. Control metallic salts containing the anions fluoride, sulfate, chloride and nitrate produced no patch test reactions in patients or controls. This and negative reactions to the acids HF, H_2SO_4 and HCl indicate that the anions did not have positive allergenic properties.

Of 16 controls who had never been exposed to beryllium or its compounds, hypersensitivity developed in 8 after patch testing. Incubation period was 6-16 days, which corresponds to 7-14 days in clinical dermatitis. Subsequently, 48 hour ec-

(4) A.M.A. Arch. Dermat. & Syph. 64:470-482, October, 1951.

zematous reactions were produced by dilutions higher than the sensitizing concentrations.

It is believed that the antigenic capacity of beryllium is due to the beryllium ion, whereas the acidity and anions of the beryllium compounds serve merely to maintain beryllium in solution and ionic state, thus permitting conjugation with protein and then the hapten-protein antibody reaction. Beryllium fluoride can sensitize the skin to a high degree; this accounts for the high incidence of dermatitis among workers in the fluoride process of beryllium extraction. Beryllium sulfate and chloride had less capacity than beryllium fluoride to sensitize the skin, and beryllium nitrate had little or no such capacity under the conditions of the experiments. Mucous membrane manifestations and possibly acute pneumonitis may be allergic reactions to beryllium compounds, though experimental proof has not been obtained.

Allergic Granulomatosis, Allergic Angiitis and Periarteritis Nodosa. Jacob Churg and Lotte Strauss[5] (Mount Sinai Hosp., New York City) review the findings in nine females and four males with severe asthma, fever, hypereosinophilia and symptoms of vascular embarrassment in various organ systems. In most, gross observations were those of periarteritis nodosa; they included nodular swellings along the course of the small arteries in many organs, accompanied by infarcts, hemorrhage or scars. In one patient nodules were widespread and similar to those of miliary tuberculosis. The spleen was considerably enlarged and showed innumerable nodules up to 1 cm. in diameter (Fig. 13).

Except for minor variations, histologic changes were essentially similar in all cases. Lesions of extravascular connective tissues were an important feature. The most characteristic extravascular lesion was a granulomatous nodule associated with, or replacing, inflammatory exudate and often located near a small vein. The nodules varied in size from about 50 μ to 1 mm. or more. They showed a central eosinophilic core surrounded by radially arranged macrophages and giant cells. This core consisted of necrotic cells and severely altered collagen fibers. Eosinophilic leukocytes were prominent throughout the lesions and comprised a portion of the necrotic core. The collagen change resembled so-called fibrinoid swelling.

(5) Am. J. Path. 27:277-301, Mar.-Apr., 1951.

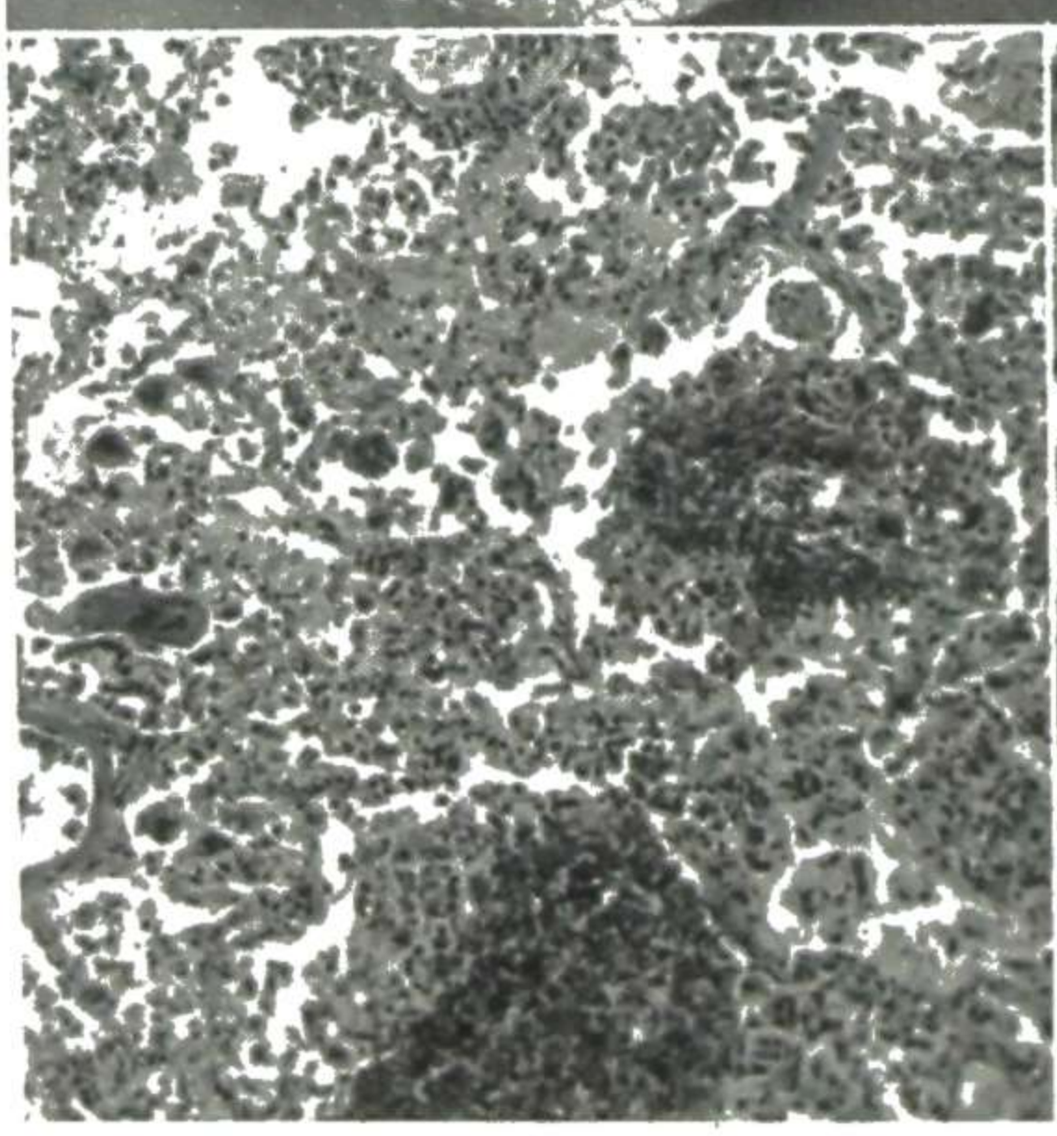
At autopsy, lesions of blood vessels were observed in 9 of 10 patients. The arterial alterations were essentially similar to those usually seen in periarteritis nodosa, with the addition that they were related to the changes described in the extravascular connective tissue. An important feature in many arterial lesions was presence of macrophages and giant cells around necrotic areas. Alterations of the veins were less fre-

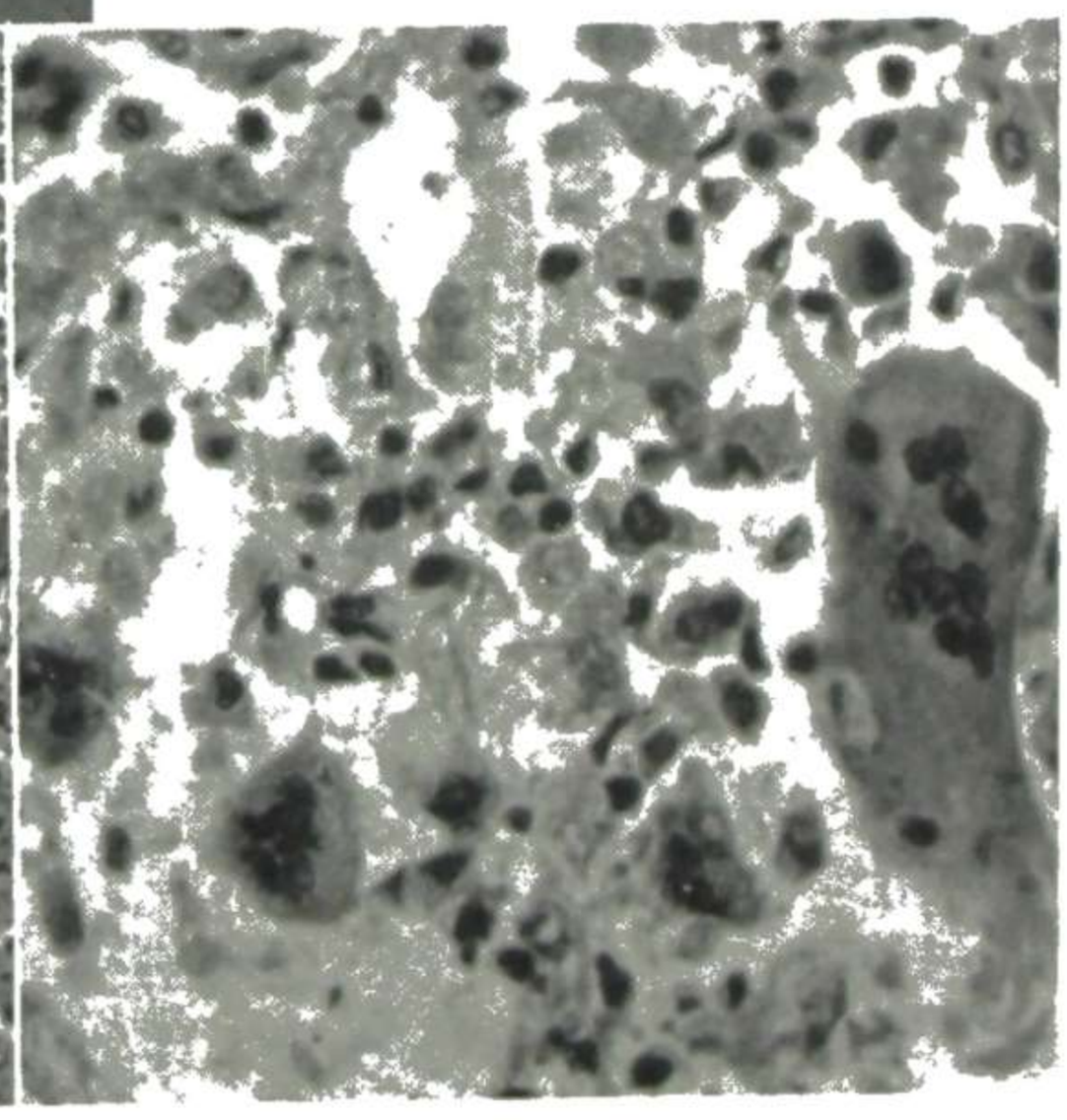
Fig. 13 (left).—Gross appearance of spleen. Note subcapsular and parenchymal nodules.

Fig. 14 (below left).—Eosinophilic pneumonia with necrosis of exudate, and giant cells; reduced from × 100.

Fig. 15 (below).—Same as Figure 14, at higher magnification. Giant cells, edema and infiltration of alveolar septa by eosinophils; reduced from × 375.

(Courtesy of Churg, J., and Strauss, L.: Am. J. Path. 27:277-301, Mar.-Apr., 1951.)





quent and less prominent than those of the arteries. Location of the granulomatous lesions in both vessel walls and connective tissue throughout the body suggests that this syndrome is an entity distinct from classic periarteritis nodosa. No extragranulomatous or granulomatous vascular changes were found in a review of 15 cases of periarteritis nodosa not associated with asthma.

In about half of the patients there were pulmonary parenchymatous lesions in the form of a more or less extensive pneumonic process which involved septa and alveoli (Figs. 14 and 15). In the acute stage the exudate was characterized

by a predominance of eosinophils, mixed with giant cells. Healing often terminated in fibrosis. Histologic evidence of bronchial asthma was present in most patients but was never striking. Acute or chronic renal vascular lesions and their sequelae were prominent. Lesions of the liver were usually confined to the blood vessels, with resultant damage to the parenchyma. There were no specific lesions in the spleen. Generalized lymphadenopathy was common, but examination showed only nonspecific inflammatory changes, except in one patient in whom a single node showed diffuse granulomatous inflammation.

It is suggested that other allergic syndromes (Loeffler, Zuelzer, Šikl) may represent the more benign forms of allergic granulomatosis, whereas angiitis is its most malignant expression.

Allergic Granuloma of Lung: Clinical and Anatomic Findings in Patient with Bronchial Asthma and Eosinophilia are described by Joseph C. Ehrlich and Alfred Romanoff[6] (New York City). The patient, a man, 49, died of asphyxia 10 days after his first attack of bronchial asthma.

Autopsy disclosed two tumor-like masses in the lungs. Histologically the essential components were necrosis, cellular infiltrates in which eosinophilic leukocytes predominated, edema and fibrinoid swelling of collagen, and vascular changes. Epithelioid and giant cells were present infrequently. There were no bacteria or Charcot-Leyden crystals. The necrosis of various tissue elements was probably primary, a direct allergic injury, rather than a secondary effect of vascular damage or toxic substances. In these necrotic areas examination with the oil immersion lens revealed the remains of eosinophilic leukocytes and masses of eosinophilic granules. Another lesion in the lungs consisted essentially of bulbous swelling of alveolar walls, which resulted from interfibrillar edema or increase of ground substance, swelling of collagen fiber, infiltration by eosinophils, occasional plasma cells and foam cells, and capillary engorgement. This may represent a form of pulmonary parenchymal lesion in allergic disease. These lesions occurred near areas of exudative pneumonitis only.

Microscopic examination disclosed eosinophilic infiltration in the epicardium, diaphragm, intestinal wall, hilar lymph

(6) A.M.A. Arch. Int. Med. 87:259-268, February, 1951.

nodes and stomach. The splenic pulp contained foci with increased numbers of eosinophils, and bone marrow showed hyperplasia with a striking predominance of eosinophilic granulocytes in varying stages of maturity.

The concept of Loeffler's disease may be redefined justifiably as a form of systemic allergic disease of mild character and good prognosis in which the chief manifestations are confined to the pulmonary system. However, more severe forms of allergic disease may develop, and involvement of extrapulmonary organs and the general vascular system may overshadow the pulmonary changes. Some of these patients may die, usually with the anatomic changes of periarteritis nodosa and allergic granulomatosis.

[This and the preceding article demonstrate the intimate relationships of several diseases presumably the result of hypersensitivity. It appears that the reaction is not necessarily confined to one type of tissue. Later in this YEAR BOOK Lowman describes bony and other changes associated with disseminated lupus erythematosus.—Ed.]

Effect of Cortisone on Allergy and Complement Titer. M. Simonsen[7] (Copenhagen) produced anaphylactic shock in guinea pigs which had been passively sensitized against horse serum. Ten animals were given 10 or 20 mg./kg. cortisone hypodermically six to eight hours before the shock dose. Only 1 of the 10 died, whereas 4 of 5 controls died. Although cortisone reduced mortality, the symptoms of shock were not prevented.

In the experimental animals there was a fall of complement content in the blood following cortisone administration. A significant fall of the complement was also found in 12 of 19 normal guinea pigs six to eight hours after injection of cortisone. In vitro experiments in which complement of known strength was titrated with or without cortisone in a concentration of 5 mg./100 ml. resulted in identical titer values; this indicated that the changes of the complement could not be explained by a chemical reaction directly between complement and cortisone. Control animals showed no significant changes of complement content in the blood.

It is suggested that the increased complement content plays an important role in the allergic condition of patients with rheumatic fever. If determinations of complement in patients with rheumatic fever treated with cortisone or ACTH show

(7) Scandinav. J. Clin. & Lab. Invest. 2:287-291, 1951.

a fall in complement content immediately before or simultaneously with an abatement of the rheumatic symptoms the rise in complement content may possibly be a primary factor in the allergic condition. Still more convincing evidence would be improvement of rheumatic fever symptoms following injection of large doses of the anticomplementary heparin.

[The background of these experiments rests on an article by J. Orskov entitled "A Little Experiment with ACTH and Anaphylactoid Shock" (Acta path. et microbiol. Scandinav. 26:917, 1949). He administered ACTH in a single dose of 0.8 mg. from one to five hours before the shock dose in actively sensitized guinea pigs. Five of 10 treated animals died, whereas all 6 controls which were not given any ACTH died. It seems to me that these results require confirmation with a larger number of animals.—Ed.]

Mechanism of Anaphylactoid Phenomenon. Intravenous injections of foreign material may produce a state of shock which, because of its resemblance to anaphylaxis, has been termed the anaphylactoid phenomenon. Paul Gross and Jack H. U. Brown[8] (Mellon Inst.) prepared a 20 per cent suspension of English china clay in water, using sodium pyrophosphate as a buffer and dispersing agent. It contained 30 mg. clay/ml. After pH was adjusted to 7, rabbits were given intravenous injections of 0.75 ml./kg. body weight. Animals exhibited 100 per cent mortality when the particle size was 0.2 μ, whereas those receiving particles of 0.6 μ showed no significant mortality. An intermediate size produced a mortality somewhat less than 100 per cent.

Histologic examination of the lungs of animals killed by intravenous injection of the smaller size suspension uniformly demonstrated blockage of the pulmonary vessels by emboli of aggregated particles. This observation suggested that aggregation of the material occurred and that death resulted from blocking of the pulmonary vessels by the aggregates. It was thought that the relatively large surface area of the very fine particulate matter caused adsorption of protein from the plasma and thereby made the particles adhesive.

To prove this concept, materials of varying particle size were suspended in plasma or saline solution and the centrifuged sediment analyzed for its nitrogen content. Results indicated that the amount of nitrogen adsorbed varied inversely with the particle size. The amount of adsorbed plasma protein was four to nine times the weight of adsorbent dust.

---

(8) Am. J. M. Sc. 221:46-50, January, 1951.

To demonstrate that protein particle aggregates can obstruct pulmonary vessels without participation of fibrin, platelets or blood cells, the lungs of anesthetized rabbits were perfused with saline solution to wash out the blood. When plasma was substituted for saline solution, effective perfusion pressure rose slightly. Pressure rose promptly to almost double the perfusion pressure obtained with plasma alone on addition of 15 mg./100 ml. plasma of finely divided particulate mate-

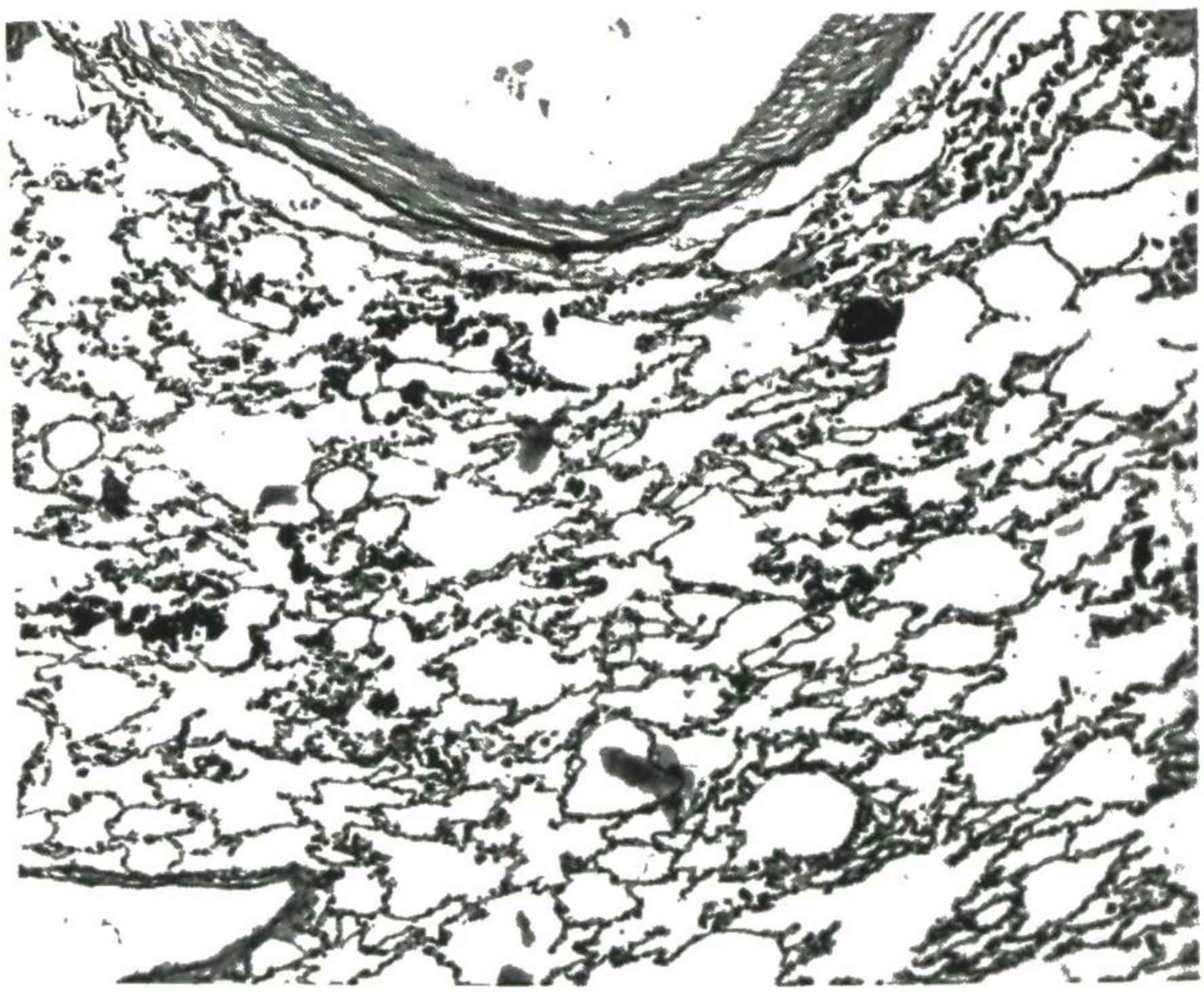


Fig. 16.—Rabbit lung perfused with blood plasma containing clay. Striking occlusion of alveolar vessels by dense, black pigment masses. (Courtesy of Gross, P., and Brown, J. H. U.: Am. J. M. Sc. 221:46-50, January, 1951.)

rial. This demonstrated the rapidity with which the particle-protein aggregates form and obstruct the pulmonary vessels. Histologic sections of the perfused lungs (Fig. 16) showed widespread vascular occlusions by aggregates of injected particles. These observations were similar to those made when the material was injected intravenously into living animals.

[The term "anaphylactoid phenomenon" has been used loosely in the literature to indicate reactions essentially the same as anaphylaxis. This article explains the mechanism of the phenomenon described earlier by Karsner and Hanzlik.—Ed.]

Studies on Mechanism of Shwartzman Phenomenon: Certain Factors Involved in Production of Local Hemorrhagic Necrosis. Chandler A. Stetson, Jr.[9] (Rockefeller Inst. for

(9) J. Exper. Med. 93:489-504, May, 1951.

Med. Research) injected meningococcic toxin intracutaneously into hybrid rabbits; 18-24 hours later, challenging material such as meningococcic toxin or glycogen was injected intravenously. In a few minutes there was profound leukopenia, which became fully developed within an hour. The first cells to disappear from the circulation were granulocytes, whereas fall in the lymphocyte count was less rapid and less pronounced. By the end of six hours, recovery was complete and there was a tendency for the total leukocyte count to rise above normal. Changes in the number of platelets paralleled those in the number of granulocytes. There was a rough correlation between the degree of leukopenia in the circulating blood and the numbers of leukocytes present in the capillaries of the lungs of each animal. The reason for the accumulation of cells in the lungs is not clear.

Glycogen, in the range of concentration necessary for elicitation in vivo of the Shwartzman phenomenon, produced in vitro a rapid and impressive clumping of platelets and leukocytes. Breakdown products of glycogen produced similar results. Bacterial toxins had no such effects in vitro on the cells, which suggested that their activity in vivo may be due to release in the circulation of some material that induces clumping of the cells. The longer time required for development of leukopenia and the Shwartzman phenomenon after intravenous injection of these materials may be a reflection of such an indirect mode of action.

Tissue sections taken before the intravenous challenge showed a more or less intense perivascular "cuffing" with polymorphonuclear leukocytes. Skin sections taken 15 minutes after the challenge showed that nearly all small veins and capillaries in the prepared sites had their lumens obliterated by cellular plugs which consisted mainly of platelets and varying numbers of polymorphonuclear leukocytes. No evidence of necrosis of the vessel wall could be seen at this stage. Skin sections obtained two hours after the challenge showed persistence of the cellular plugs in the vessels plus evident necrosis, not only in the cells but also in the vessel walls. Sections taken after four hours were characterized by pronounced dilatation of the arterioles and capillaries and hemorrhage into adjacent tissues. Serial sections showed that the hemorrhage was from small veins damaged during the preceding hours.

Reticuloendothelial Block and Effect of Antistine® on Sanarelli-Shwartzman Phenomenon. G. Filipp and M. Kelenhegyi[1] (Debrecen) used congo red to block the reticuloendothelial system in nine rabbits. In these and in 10 controls, Escherichia coli suspensions were utilized to elicit the Sanarelli-Shwartzman phenomenon, in which hemorrhagic-necrotic inflammation appears at the site of initial injection of a bacterial suspension, following intravenous injection, 24 hours later, of the same or another bacterial injection. Typical bloody inflammation was produced four hours after the second dose of organisms in the controls, three of which died. In the blocked animals, no secondary hemorrhagic lesions developed.

When antistine® was given intravenously with the bacterial injection, the anticipated hemorrhagic reaction was quite mild. It was not inhibited when the drug was given 30-60 minutes before intravenous injection of bacterial suspension. The larger the dose of antistine,® the more the inhibition of inflammation, when drug and organisms were given at the same time. With very large doses, however, the animals vomited and had convulsions. If the drug was given intravenously when the initial subcutaneous dose of bacteria was given, the antihistamine did not inhibit the secondary hemorrhagic reaction. When the drug was infiltrated into the site of the first injection 15-20 minutes before the second injection, the secondary reaction was very weak. These effects were not duplicated by similar administration of P vitamin.

The authors consider that the allergic mechanism (histamine) plays an important role in the Sanarelli-Shwartzman phenomenon, aside from the specific toxic action of the bacterial suspension. The secondary hemorrhagic inflammation can be inhibited by antistine® as well as by reticuloendothelial blocking.

[Studies of the Shwartzman phenomenon continue to provide information of scientific interest. Whether practical applications to human medicine will be forthcoming is still uncertain but, as more and more work is done, this becomes a probability. Of additional interest is the article by H. A. Schlang (The Shwartzman phenomenon. I. Inhibitory action of nitrogen mustard (HN_2). Proc. Soc. Exper. Biol. & Med. 74:749-751, 1950). The inhibition by nitrogen mustard and by protection of the lower limbs from the action of nitrogen mustard by aortic occlusion points strongly to the influence of the bone marrow.—Ed.]

(1) Schweiz. med. Wchsnchr. 81:920-921, Sept. 22, 1951.

Granulomatous Disorders

Contribution to Pathogenesis of Inclusion Bodies. H. U. Zollinger[2] (Univ. of Zurich) describes inclusion bodies found in the kidneys in experimental lead poisoning, in irradiated cells of pavement cell carcinoma, in alveolar epithelium in irradiation pneumonia and after experimental irradiation of rat kidneys. Such inclusions are also found in cells of spontaneous mammary cancer of C_3H mice, cells of the ascitic fluid in cystadenocarcinoma of the ovary, cytomegaly, yellow fever, rabies and varicella. These bodies are usually acidophilic. They give a negative Feulgen reaction, hence contain no desoxyribonucleoprotein. However, their reaction to distilled water and ribonuclease indicates considerable content of ribonucleoprotein; thus they resemble nucleoli.

Zollinger considers the formation of inclusion bodies indicative of disturbances of intracellular metabolism of albumin, possibly due to viruses or mitosis-inhibiting influences (lead, aluminum, ionizing rays), though they may also appear without recognizable cause or be demonstrated in tumors. Apparently, formation of inclusion bodies may be a reaction of the body to a variety of factors; hence such bodies cannot be considered specific for virus disease.

Mechanism of Liquefaction of Tubercles: Behavior of Endocellular Proteinases in Tubercles Developing in Lungs of Rabbits exposed to standardized aerosal suspensions of virulent bovine tubercle bacilli of the Ravenel strain has been studied by Charles Weiss and Marial L. Boyar-Manstein[3] (Jewish Hosp. of Philadelphia). By killing the animals at varying intervals after infection, observations could be made during successive stages in tubercle development. Rates of hydrolysis of benzoyl-l-arginine amidase and leucine-amino peptidase were studied on material removed from the interior of liquefied tubercles, from the centers of caseation and from the zones of inflammation which surround tubercles. These data on proteinase activity were correlated with histologic findings on comparable specimens.

There was greatly increased enzymatic activity of both substances in the inflammatory zones of the tubercles. The areas of lung intermediate between primary tubercles which

---

(2) Schweiz. Ztschr. allg. path. 14:446-455, 1951.
(3) Am. Rev. Tuberc. 63:694-705, June, 1951.

contained only microscopic areas of cellular infiltration showed only moderate increase in the rate of enzymatic hydrolysis. The rate of substrate cleavage was strikingly decreased in the zones of caseation, reaching zero for the amidase and becoming very low for the peptidase.

The findings suggest that the rate of proteinase action is proportional to the intensity of cellular infiltration. Wherever there are intact cells there is proteinase action and wherever the cells have undergone caseation or softening this action is decreased or absent. This decreased proteinase activity may be due to not only loss of certain enzymes and their activators but also to presence of inhibitors.

[For many years the liquefaction of tubercles has been studied with particular emphasis on the action of cells, such as lymphocytes. It now becomes possible to appreciate the importance of enzyme systems without reference to special cells.—Ed.]

Evolution of Tuberculous Lesions in Guinea Pig during Administration of Adrenocorticotrophic Hormone (ACTH) or Cortisone was studied by Charles LeMaistre and Ralph Tompsett[4] (New York Hosp.—Cornell Med. Center).

METHOD.—Guinea pigs were divided into three groups of 10 animals, one receiving injections of saline solution, the second 5 mg. cortisone every 12 hours and the third 8 mg. ACTH every 8 hours. After 48 hours of treatment, all animals were inoculated with Mycobacterium tuberculosis (H37Rv). Hormone and saline administration was continued for 14 days, at which time the animals were killed. A second experiment was similar except that the animals were not killed until the 28th day of infection, tuberculin tests were performed on half of each group and dosage of ACTH was reduced to 2.5 mg. every eight hours.

In all saline-treated animals killed after 14 days, nodules of caseation necrosis developed at the site of inoculation. All animals receiving ACTH also had such nodules, but they were not as extensive as in the saline-treated animals. Only half of the animals treated with cortisone had gross nodules at the site of injection. Tuberculous involvement of the axillary lymph nodes, lungs, liver and spleen was less frequent in the hormone-treated animals than in the controls. In the treated and control groups, acid-fast bacilli were demonstrated with equal frequency in the nodules and occasionally in the liver and lungs.

In the longer experiment a nodule containing caseation necrosis formed in all animals regardless of the substance ad-

(4) Am. Rev. Tuberc. 64:295-306, September, 1951.

ministered. Extent of the tuberculous process and number of acid-fast bacilli in the lesions were approximately the same in all groups. In the animals receiving saline solution the tuberculin reaction was strikingly positive on the 14th day. The hormone-treated animals had an equivocal reaction, characterized by slight erythema and a nodule less than 5 mm. in diameter.

Evidence of enhancement of the experimental tuberculous process induced by cortisone or ACTH was not obtained during the period when excessively large amounts of these agents were administered.

Influence of Cortisone on Experimental Tuberculosis of Guinea Pigs. Alfred G. Karlson and Joseph H. Gainer[5] (Mayo Found.) report that administration of cortisone was not beneficial and may even have been harmful. Guinea pigs were inoculated with virulent human type tubercle bacilli (H37Rv). One group, killed after 20 days, had grossly visible lesions of tuberculosis in the liver, spleen, site of inoculation and axillary lymph nodes as well as microscopic evidence of tuberculosis in the lungs. The remaining inoculated guinea pigs were separated into five groups on the 21st day of infection: (1) untreated controls, (2) treated with 6 mg. streptomycin daily, (3) treated with 2 mg. streptomycin daily, (4) treated with 2 mg. cortisone daily and (5) treated with 2 mg. cortisone and 2 mg. streptomycin daily. The surviving animals were killed after 62 days of therapy, the 83rd day of infection.

Tuberculous animals given cortisone or cortisone and streptomycin lost weight, whereas the others, including infected controls and uninfected animals given cortisone and streptomycin, gained. Animals given cortisone showed less severe reaction to the tuberculin test. When OT was injected on the 60th day of treatment, none of the animals given cortisone or cortisone and streptomycin combined showed necrosis of the skin reaction, and the size of the reaction was half that of the infected controls or the streptomycin-treated group.

When the animals were killed, those given 6 mg. streptomycin showed striking reversal of the progress of tuberculosis. There were residual foci of tuberculosis at the site of inoculation and in the axillary lymph nodes in a few of the animals treated with 6 mg. streptomycin. The 2 mg. dose

(5) Dis. Chest 20:469-481, November, 1951.

only partially inhibited the disease. Animals receiving cortisone alone or with streptomycin (with two exceptions) had lesions comparable to those in untreated guinea pigs.

Effect of Cortisone on Tuberculosis in Guinea Pig is reported by Robert G. Bloch, Kirsten Vennesland and Clifford Gurney[6] (Univ. of Chicago). Animals inoculated with cultured human strain of Mycobacterium tuberculosis (H37Rv) were separated into two groups, one receiving treatment from the time of inoculation and the other 24 days after inoculation. Untreated animals served as controls. Both the immediate and delayed treated groups were divided into three subgroups, animals receiving (1) cortisone, (2) streptomycin and (3) both cortisone and streptomycin.

Cortisone-treated animals showed the least resistance to disease, often dying of intercurrent nonspecific infection, frequently pneumonia. The tuberculin reaction was inhibited after cortisone, but sensitivity returned to normal after discontinuation of the drug. The same degree of sensitivity inhibition was observed in animals receiving both streptomycin and cortisone. Blood sedimentation rate rose for 10-12 days after inoculation in untreated controls but did not in the treated groups, probably owing to two different mechanisms, the bacteriostatic effect of streptomycin and the inhibitory effect of cortisone on body response. The sedimentation rate returned to normal 30 days after inoculation in the control and delayed treated animals. Eosinophil counts were lowered in all groups receiving cortisone.

Streptomycin temporarily inhibited the early development of tuberculosis when given at the time of inoculation, but the outcome was similar to that in the controls. When streptomycin was started 24 days after inoculation the tuberculosis was less extensive than in the controls. Mortality in animals given cortisone was greater than in the untreated guinea pigs. Animals treated from the beginning with streptomycin and cortisone had more tuberculosis than those given streptomycin alone, but when the combination was begun 24 days after inoculation, less tuberculosis occurred than in the corresponding group receiving streptomycin alone. In the early stage, cortisone promotes development of tuberculosis in guinea pigs and interferes with the therapeutic effect of streptomycin, but

(6) J. Lab. & Clin. Med. 38:133-147, July, 1951.

after hypersensitivity has been established in infected animals, cortisone does not impair the effect of streptomycin.

Acid-fast bacilli were hard to find in lesions of streptomycin-treated animals, particularly after early treatment. Bacilli were more numerous in lesions from animals treated from the beginning with cortisone than in the untreated group. When cortisone was started 24 days after inoculation the number of bacilli did not differ from that of the controls.

The adrenal glands were enlarged in the nontreated group, expressed histologically as loosening and widening of the fat-containing zona fasciculata. This was not present in cortisone-treated animals or, if present, as in the group given cortisone 24 days after inoculation, it disappeared during cortisone administration. When cortisone was discontinued it reappeared. Weight of the thyroid gland of cortisone-treated tuberculous guinea pigs was increased.

[This and the preceding two articles give evidence of the unfavorable effects of ACTH and cortisone on the progress of tuberculosis. This has definite clinical bearing and should indicate caution to those who treat the disease.—Ed.]

Experimental Studies on Etiology of Hodgkin's Disease. Warren L. Bostick and Lavelle Hanna[7] (Univ. of California) studied the cause by means of serial passage of Hodgkin's disease lymph node extracts in embryonated chicken eggs. A slight lethal effect was noted in the embryos. The harvested amniotic fluid was shown to possess virus growth interference activities against Lee influenza virus grown in chicken eggs. No hemagglutinative tendencies were encountered when it was tested against erythrocytes from many animals, and no sensitization effects on erythrocytes later exposed to known hemagglutinative viruses were noted. The amniotic fluid had no untoward effect on animal inoculation via many routes. Precipitin and flocculation tests were uninformative.

The amniotic fluid harvested after numerous serial passages from Hodgkin's disease-inoculated embryos seemed to possess certain filterable, transferable and virus-like properties. This material should make possible extensive serologic, chemical and physical studies.

[Although filtrable agents have been suspected as the exciting cause of Hodgkin's disease, no final proof has been forthcoming. This particular study gives promise of proving or disproving, by methods currently available, the theory of viral cause.—Ed.]

---

(7) Cancer Res. 11:505-510, July, 1951.

Studies in Pathology and Pathogenesis of Experimental Brucellosis: Formation of Hepatic Granuloma and Its Evolution. Abraham I. Braude[8] (Univ. of Minnesota) studied the morphologic reactions of mice and guinea pigs after inoculation with Brucella abortus. Varying amounts of the organism were injected into the peritoneal cavity and heart of animals killed at different intervals thereafter.

The size of the dose did not change the characteristics of the specific lesions. Brucellas appeared in smears of mouse blood 90 minutes after inoculation. Sometimes as many as six or eight organisms were found within a polymorphonuclear leukocyte. Extracellular organisms were scattered throughout the smears. In subsequent smears the organisms became concentrated in the polymorphonuclear leukocytes, and extracellular forms were rare. Brucellas were found in polymorphonuclear leukocytes and in large mononuclear cells circulating in the blood as long as five days after inoculation.

In the liver of mice killed after three hours, brucellas were within polymorphonuclear leukocytes in increased numbers in the sinusoids. Organisms were also found in Kupffer cells. By six hours all these sinusoids were filled with many cells containing brucellas. Both polymorphonuclear and Kupffer cells frequently formed solid focal aggregations. Reduction of circulating polymorphonuclear leukocytes was evident after 24 hours and the brucella organisms within Kupffer cells increased, filled the cytoplasm, produced swelling of the cells and obliterated the sinusoids. Aggregations of Kupffer cells filled with bacteria were noted 72 hours after inoculation. After 120 hours, these accumulations had grown larger and had assumed a typical granulomatous appearance. Two types of granuloma were evident, one composed largely of epithelioid cells and the other a mixture of epithelioid cells and polymorphonuclear leukocytes.

In guinea pigs, granulomas were present in the liver after five days. The characteristics were identical with those found in mice. In guinea pigs killed one month after inoculation, the lesions were larger, apparently formed by fusion of several small granulomas (Fig. 17). The small lesions forming the larger granuloma were still sharply delineated and equal in size and appearance to those described five days after inoculation. Hyaline necrosis began in the center of large granulomas

(8) J. Infect. Dis. 89:87-94, July-Aug., 1951.

and was most prominent after three months. No fibrosis was present at the periphery. Langhans giant cells could be recognized in the liver at this time. Granulomas with central hyaline necrosis were still present in livers after six months. By this time only a few polymorphonuclear leukocytes and epithelioid cells remained. Organisms could still be cultured. One

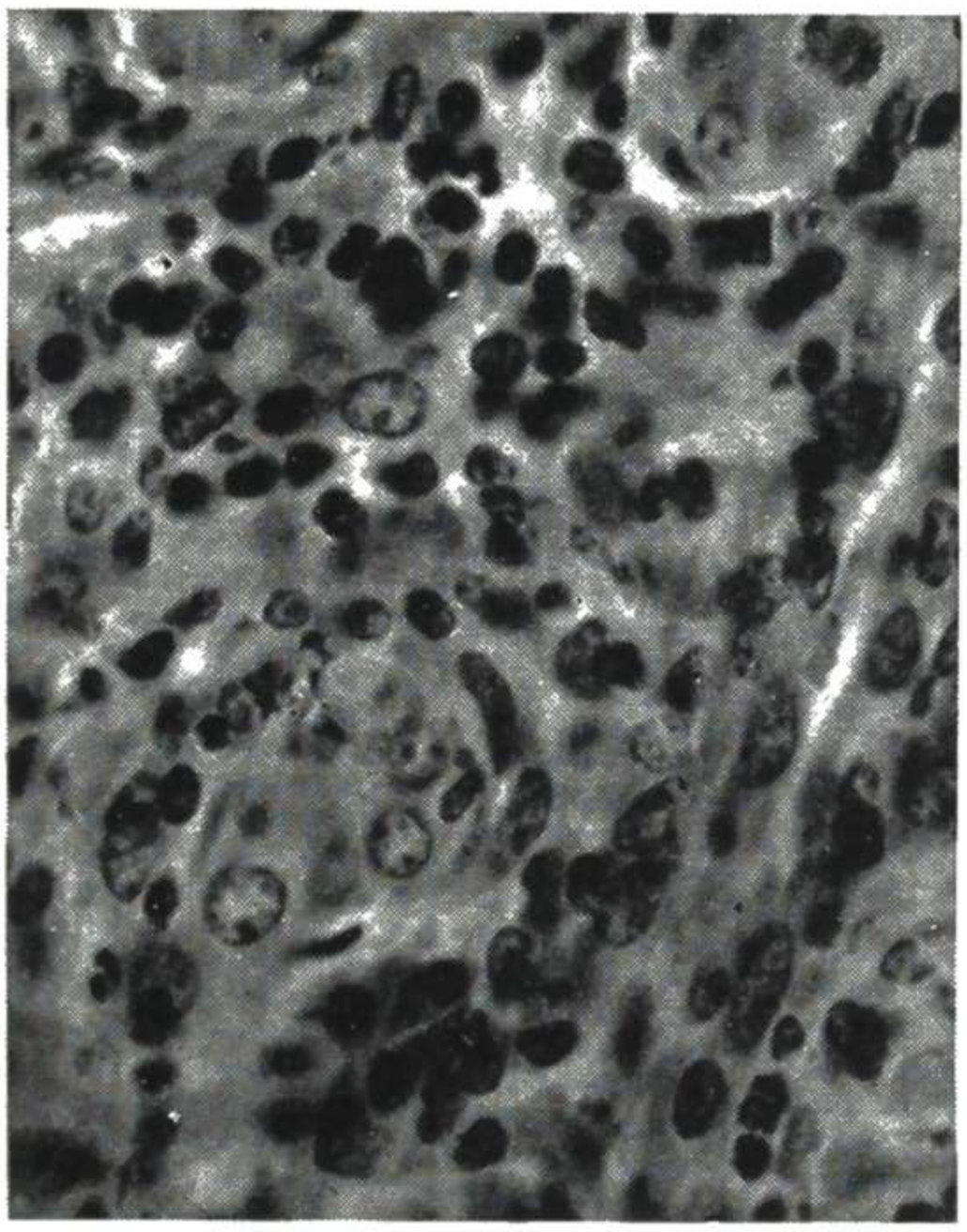


Fig. 17.—Liver of guinea pig one month after inoculation with Br. abortus. Hematoxylin-eosin; reduced from × 900. (Courtesy of Braude, A. I.: J. Infect. Dis. 89:87-94, July-Aug., 1951.)

year after injection of Br. abortus there was complete absence of specific histologic changes in serial sections of the liver as well as lack of positive culture results.

Several infected animals were made anergic by weekly subcutaneous injections of heat-killed Br. abortus. Granulomas were found in the tissues of most of the anergic animals. Development of the granuloma does not depend on the existence of hypersensitivity in experimental brucellosis. The nonsuppurative granuloma of experimental brucellosis closely resembles the tubercle of experimental tuberculosis.

Hepatic Manifestations of Sarcoidosis and Other Granulomatous Diseases: Study Based on Histologic Examination of Tissue Obtained by Needle Biopsy of Liver was conducted by Gerald Klatskin and Raymond Yesner.[9] A total of 650 biopsy specimens was taken. Diagnosis of sarcoidosis was

(9) Yale J. Biol. & Med. 23:207-248, December, 1950.

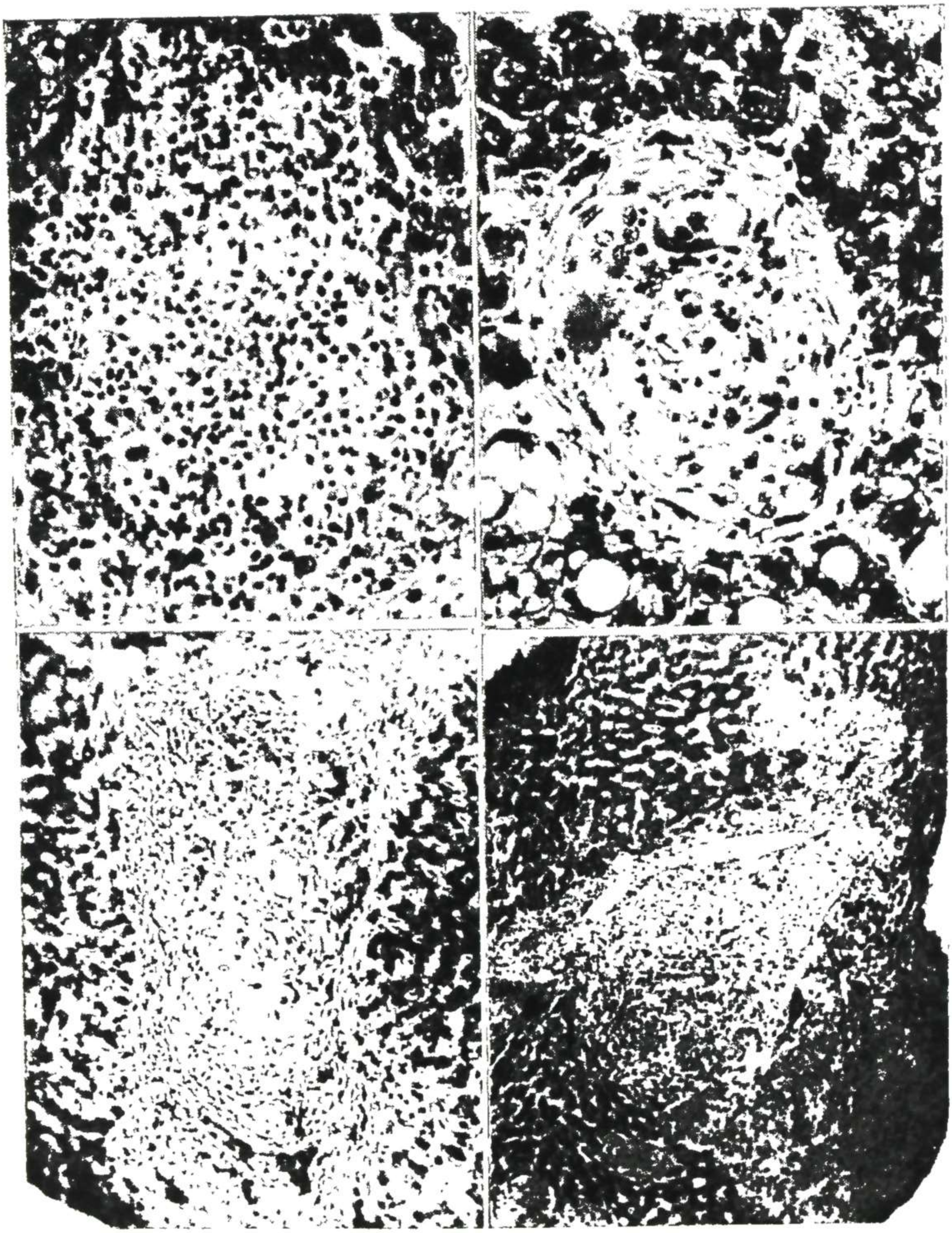


Fig. 18 (top left).—Hepatic granulomas in sarcoidosis. Irregular intralobular lesions with poorly defined margins and considerable lymphocytic infiltration; reduced from × 440.

Fig. 19 (top right).—Sharply circumscribed intralobular lesion with connective tissue capsule. Note giant cell with large vacuole containing crystalline material; × 440.

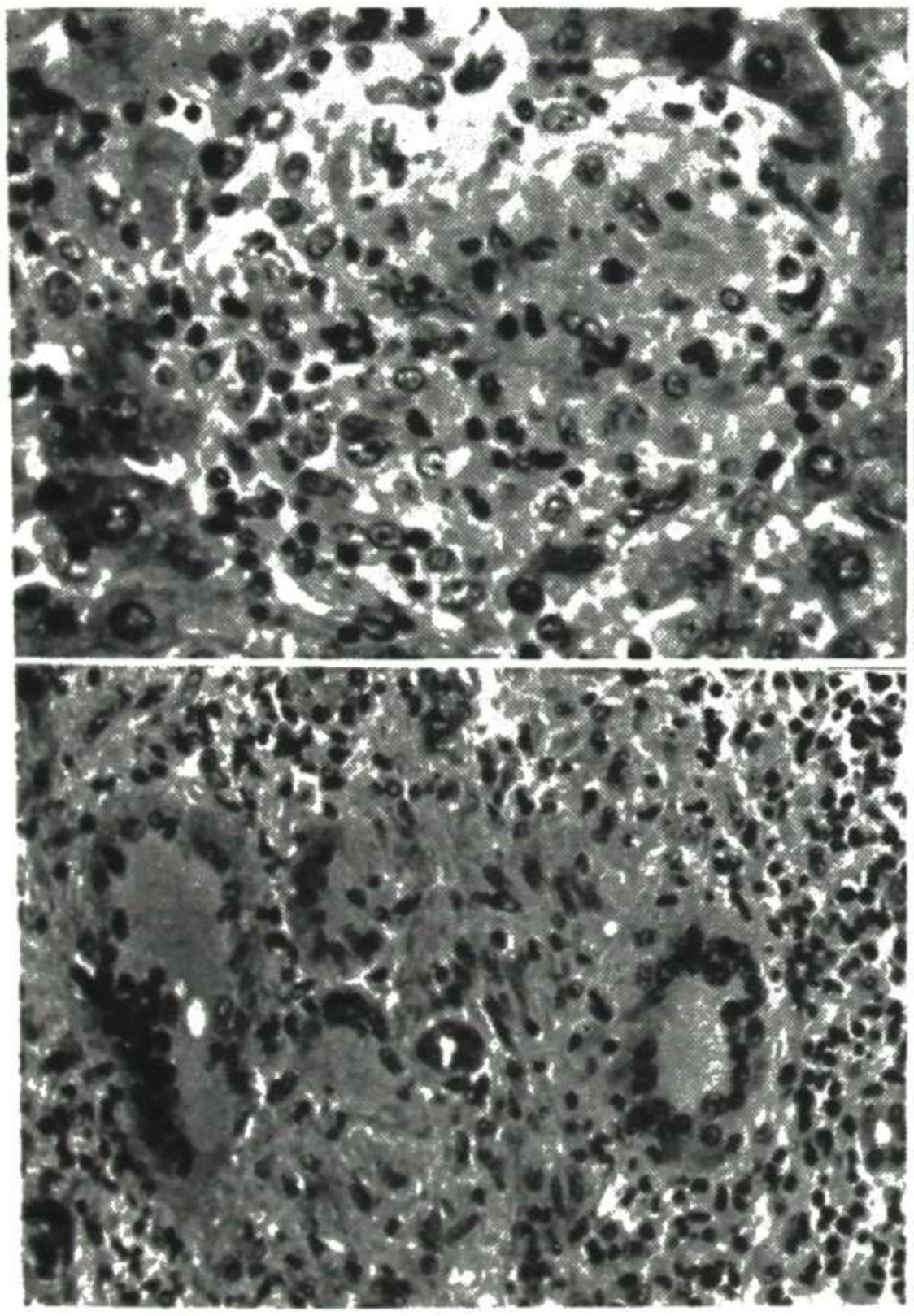
Fig. 20 (bottom left).—Sharply circumscribed lesion of portal zone with connective tissue capsule; reduced from × 220.

Fig. 21 (bottom right).—Large lobulated lesion of portal zone; reduced from × 125.

(Courtesy of Klatskin, G., and Yesner, R.: Yale J. Biol. & Med. 23:207-242, December, 1950.)

confirmed histologically in 15 patients. Moderate hepatomegaly was found in 11 of the patients, 6 of whom also had splenomegaly. Hepatic function tests demonstrated abnormalities in 12.

Liver biopsy revealed granulomas in all patients with sarcoidosis (Figs. 18-21). The ease with which they were demonstrated and the number of lesions in single sections suggested that the liver of such patients is heavily seeded with granu-



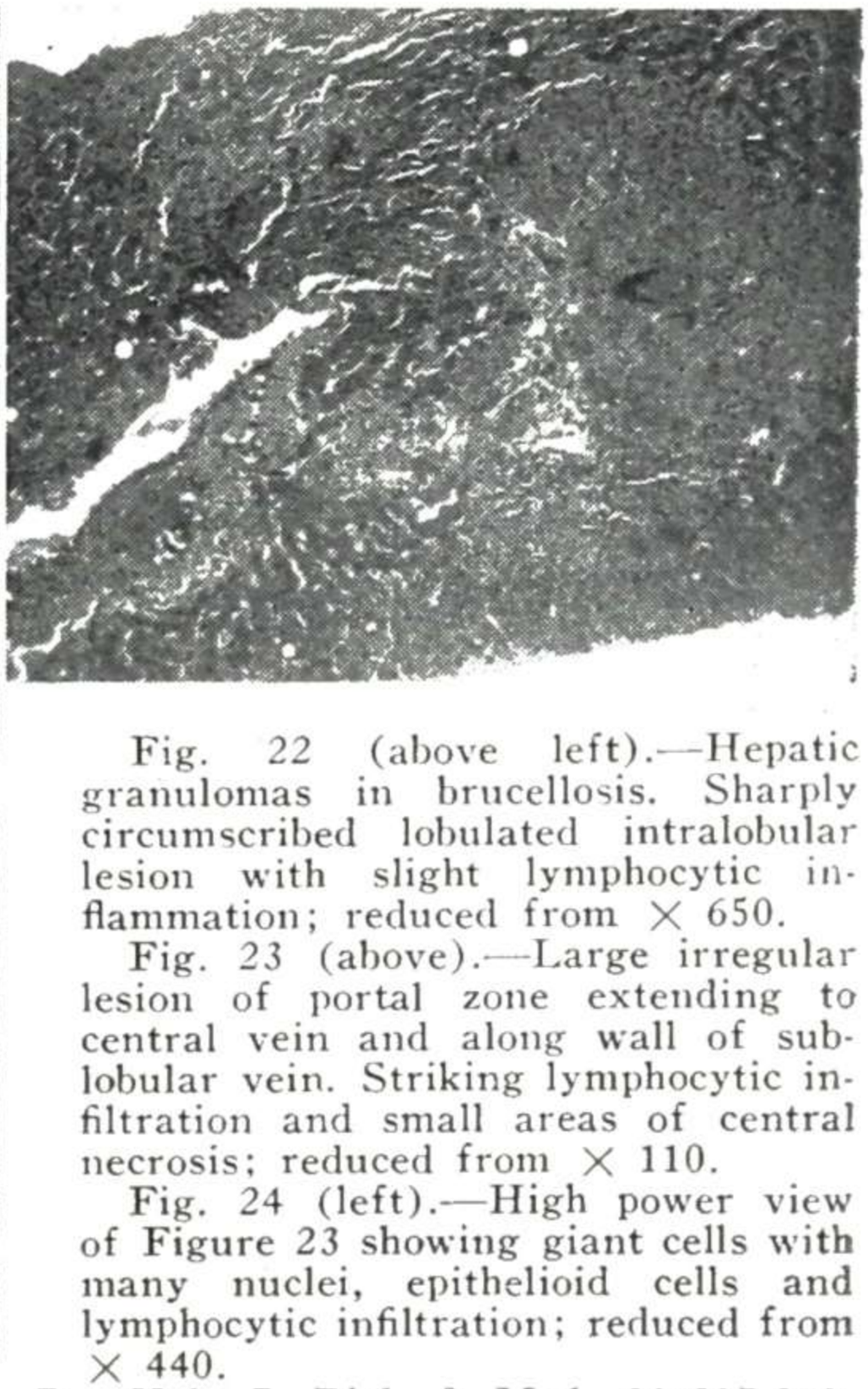


Fig. 22 (above left).—Hepatic granulomas in brucellosis. Sharply circumscribed lobulated intralobular lesion with slight lymphocytic inflammation; reduced from × 650.

Fig. 23 (above).—Large irregular lesion of portal zone extending to central vein and along wall of sublobular vein. Striking lymphocytic infiltration and small areas of central necrosis; reduced from × 110.

Fig. 24 (left).—High power view of Figure 23 showing giant cells with many nuclei, epithelioid cells and lymphocytic infiltration; reduced from × 440.

(Courtesy of Klatskin, G., and Yesner, R.: Yale J. Biol. & Med. 23:207-248, December, 1950.)

lomas. Size of the lesion tended to remain submiliary. The borders of the lesions were sharp, in contrast with those in patients with tuberculosis or brucellosis which were often irregular or lobulated, suggesting coalescence of multiple lesions. The lesions in sarcoidosis were located in both the parenchyma and portal zones, as in tuberculosis and brucellosis. They were composed of masses of epithelioid cells but their appearance was not characteristic of sarcoidosis. Although inflammatory cells were few compared with the numbers seen in tuberculosis and brucellosis, there were too many exceptions for this to be a reliable criterion for histologic differentiation. Typical Langhans or foreign body giant cells

were found in all cases, but neither the number or type was of value in differentiation. Schaumann bodies were not observed, and in only two cases were there crystalline inclusions. A fine reticulum network was demonstrated in the six cases of sarcoidosis studied. Necrosis was of minor extent in three cases. Intrasinusoidal reticuloendothelial hyperplasia was common in all granulomatous diseases. A thin, collagen envelope which gave the appearance of encapsulation to some of the lesions was noted in six cases of sarcoidosis.

Sarcoid-like hepatic lesions were noted in tuberculosis, erythema nodosum, brucellosis, beryllium intoxication and "primary" liver disease and have been reported in syphilis, leprosy, viral and mycotic infections.

[In the 1950 YEAR BOOK, page 38, is an article on liver biopsy in sarcoidosis, and on page 52, an article on granulomatous diseases of the liver in larval ascariasis. The current article and the one that precedes it give further information concerning granulomas which may be observed in the liver. Ultimately there may be clarification of the diagnosis of granulomatous lesions in biopsy material. Studies of functional disorders are reported by Shay *et al.* elsewhere in this YEAR BOOK.—Ed.]

NEOPLASIA

Antigenicity of Sarcomas Undergoing Atrophy in Rats. Margaret Reed Lewis and Paul Myron Aptekman[1] (Wistar Inst.) found that atrophy of sarcomas due to occlusion of their blood supply after 5-11 days of growth in susceptible rats protected the hosts from further growth of transplanted sarcoma tissue. To determine whether the atrophying sarcoma tissue might act as an antigen and whether transplantation into susceptible rats would bring about development of resistance to growth of transplanted tumors in the recipient, the authors utilized a special method of attenuating the tissue.

Sarcomas which originated in the host's own strain (native tumor) and were 100 per cent transplantable were used. After 10-11 days of growth, the blood supply was occluded, with resulting atrophy of the tumor. Two, three and four days after the vascular occlusion, tumor tissue was removed and transplanted by subcutaneous injection into susceptible rats. Considerable reaction took place at the injection site and resulted in formation of various sized cysts containing thick, turbid material. The cysts were absorbed after 8-14 days. Tumors failed to grow in any of the susceptible rats. Three

(1) J. Immunol. 67:193-195, September, 1951.

weeks later viable sarcoma tissue was implanted in these animals. The tissue failed to grow in 70 per cent of the rats which had received implants of modified sarcoma tissue which had undergone atrophy for two days and in 100 per cent of the rats receiving implants of tissue which had undergone atrophy for three to four days. Animals proved to be resistant to the challenge tumor injection were inoculated one to two months later with large amounts of viable sarcoma tissue to test their immunity.

Injection into susceptible rats of tumor tissue which had atrophied due to lack of adequate blood supply for two to four days brought about in the recipients a state of resistance to growth of implanted viable tumor tissue. Serologic studies failed to demonstrate antibodies in the serum of rats immunized in this way. The antigenicity of sarcoma tissue attenuated in various other ways was tested. None of them proved antigenic.

Progressive Tumor Resistance in Successive Generations of Inbred Immunized Rats. Paul Myron Aptekman and Margaret Reed Lewis[2] (Wistar Inst.) immunized successive generations of inbred rats and studied the influence of this procedure on the response of their offspring to immunization. A methylcholanthrene-induced sarcoma no. 231 to which rats proved 100 per cent susceptible was used for preparation of a vaccine and for transplantation. The following two methods of immunization were employed: (1) subcutaneous injection of an alcohol extract of tumor tissue for vaccination against tumor growth, after which resistance of the treated animals was challenged by implantation of a small amount of viable tumor tissue; (2) implantation of tumor grafts into normal rats, followed by intratumoral injections of tumor extract after the grafts had grown to a small size. Only rats which were proved to be immune were used for breeding.

Subcutaneous injection of an alcoholic tumor extract produced immunity in 50 per cent of the rats of nonvaccinated parents. Three lines of subcutaneously treated rats were inbred through 11, 10 and 5 generations respectively. In the 9th, 10th and 11th generations of one line of inbred rats, only 1 of 91 rats failed to respond to the vaccine. The rats from a second strain also showed a pronounced increase in response

(2) Science 114:577-579, Nov. 30, 1951.

to vaccination. In the third strain only 2 of 37 rats from the 4th and 5th generations failed to develop immunity in response to vaccination. The inbreeding of rats apparently did not lessen their susceptibility to the growth of the tumor used, and only 46 per cent of the offspring of untreated parents, corresponding to the last three generations of immunized parents, proved to be immune.

Immunity developed in 78 per cent of the rats of untreated parents after intratumoral injections of vaccine. Three lines of intratumorally treated rats were inbred for 12, 11 and 6 generations respectively. A total of 254 rats proved to be 100 per cent immune. In the later generations of the intratumorally treated rats, the primary tumor graft implanted previous to treatment grew slower than in earlier generations. The tumors of these offspring also responded more favorably to injection of vaccine, and fewer injections were necessary to treat small tumors than in the earlier generations.

Litter Seriation Phenomena in Fibrosarcoma Susceptibility: Contribution to Subject of Cancer Susceptibility in Relation to Age. Leonell C. Strong[3] (Yale Univ.) injected methylcholanthrene into litters of several generations of inbred mice. Only animals dying with chemically induced fibrosarcoma were studied. Mice in successive litters showed a difference in susceptibility to chemically induced fibrosarcoma (latent period) and in characteristics of malignancy (survival time and invasiveness). There seemed to be an inverse relation between survival time and latent period. Invasiveness of the tumor was reduced in mice of both sexes as litter seriation increased. The fibrosarcoma invaded the abdomen less frequently in mice of both sexes in successive litters. Survival time of mice bearing chemically induced fibrosarcoma with latent periods of less than 100 days gradually increased in litters of older mothers.

The results indicate that there are inherited factors in cancer susceptibility and certain attributes of malignancy that cannot be completely controlled by the accepted method of inbreeding. These characteristics (susceptibility, survival time and invasiveness) are influenced by some subtle mechanism which changes during the life time of the mother and is selectively handed down to her progeny in successive litters by some mechanism other than the chromosomes or genes. Trans-

(3) J. Gerontol. 6:340-357, October, 1951.

mission may involve cytoplasmic inheritance. The phenomena of litter seriation or of the age of the mother influencing biologic characteristics of her progeny is known to occur in other unrelated conditions.

[This and the preceding two articles indicate that further information can be expected from the study of experimental sarcoma, perhaps adding to or altering some of the views developed in the past in the study of carcinomas.—Ed.]

Carcinogenesis in Parabiotic Rats: Tumors of Ovary Induced by Acetylaminofluorine in Intact Females Joined to Gonadectomized Litter Mates and Reaction of Their Pituitaries to Endogenous Estrogens were investigated by F. Bielschowsky and W. H. Hall[4] (Univ. of Otago). A normal female rat joined in parabiosis to a gonadectomized partner goes into continuous estrus. Only the pairs of rats which survived parabiosis for at least 16 weeks were included in the study. Control groups of intact females joined to gonadectomized litter mates were not treated with 2-acetylaminofluorine (A.A.F.). The intact female partner received 4 mg. by stomach tube about three times a week for 10-25 doses. Single female rats were also given injections of the agent. Except for two animals killed when a palpable tumor developed, all were permitted to survive for 52 weeks.

There was no indication that A.A.F. given to the intact female animals affected the gonadectomized litter mate. Changes occurred in the ovaries of the parabiotic intact rat. Normal corpora lutea gradually disappeared. Healthy, cystic and atretic follicles made up the bulk of the ovary of the intact rat. Ovaries were four to five times normal weight 20 weeks after parabiosis was produced. Microscopically, cystic follicles lined by granulosa cells or a mixture of granulosa and lutein cells were common at this stage. Cysts with smooth walls, containing clear or slightly turbid fluid, were often found. These were not distinctly neoplastic. Ovarian tumors developed in about 50 per cent of the intact parabiotic rats which were given injections of A.A.F. Except for one with changes in both ovaries, tumors were unilateral. Grossly, the tumors were made up of solid white areas with reddish brown, blood-filled cystic structures. In all but 3 of 14 ovarian tumors which developed, granulosa cells were the prevailing type. In the early stages of development, the granulosa cell tumor appeared as a hemorrhagic cyst with a fibrous connective tissue wall. Papil-

(4) Brit. J. Cancer 5:331-344, September, 1951.

lary processes containing granulosa and lutein cells projected into the cavity. In progressive lesions, these proliferated and filled the whole cavity. As the tumors developed, they were found to be composed almost entirely of granulosa and lutein cells. Small cystic spaces were present in the agglomerations of granulosa cells and, when frequent, produced a folliculoid pattern. Some histologic variation was present in several tumors. One showed a tubular pattern with colloid-like material in the lumen and formation of glomerulus-like structures. In another tumor there were two kinds of cellular components. One was very bizarre and pleomorphic. Intermingled with these elements were nests of much smaller cells of epithelial character. Many features resembled those of choriocarcinoma. Invasion and metastases were present.

Morphologic signs of endocrine imbalance, present in all intact female animals joined to a gonadectomized rat, were principally manifestations of hyperestrinism. They included endometrial changes, hyperplasia of the breast, atrophy of the thymus, hyperplasia of the adrenal cortex and enlarged pituitary. In most intact parabiotic rats the anterior lobe of the pituitary was symmetrically enlarged. Some animals surviving more than 25 weeks showed an irregular nodular enlargement. These nodules were adenoma composed of granular or nongranular eosinophilic cells. There were no obvious tumors in the ovaries of intact parabiotic rats which were not given A.A.F. Ovarian tumors were not demonstrated in any intact female rat which had lived separately and received A.A.F. Tumors developed occasionally in other organs. In two of the single rats receiving A.A.F., adenocarcinoma of the breast was found. In practically all the rats treated with it, benign cystic cholangiomas were present. In the intact partners, they were usually larger and more widespread than in the single animals.

Granulosa cell tumors were produced in half of the intact parabiotic female rats given injections of A.A.F. The tumors arose from granulosa cells surviving the death of the ovum. Papillary ingrowths from the wall of these cystic follicles are early manifestations of neoplastic development.

The follicle-stimulating hormone secreted in excess by the pituitary of the gonadectomized litter mate is considered the factor essential for development of the tumor.

Study of Pituitary of Rats with Gonadal Tumors Produced by Biskind's Method (intrasplenic implantation of gonads in castrated animals) is reported by F. Lacour and M. Guérin[5] (Paris). These tumors are said to be caused by hyperstimulation of the pituitary that is no longer inhibited by gonadal hormones, while the hormones produced by the implants are inactivated in the liver. The pituitary of 11 female and 2 male rats bearing such tumors was studied by means of Romeis' staining technic with Krésazan orange which distinguishes six types of cells.

Pituitary castration cells, seen in 3 rats with no tumor or only a very small one, were not found in 10 in which the tumor was well developed. Apparently the secretion of the implant, at first completely neutralized by the liver, became so considerable that it began to act on the pituitary. This occurred at times before any of the genital organs gave evidence of excessive hormonal stimulation.

Disappearance of castration cells in three cases in which parovarian cysts were produced militates against the embryonal origin of these cysts and suggests a metaplastic origin from granulosa cells as well as functional activity of these cysts; indeed, transition forms between ciliated and granulosa cells were observed.

Joint Action of Chemical Carcinogen and Neoplastic Virus to Induce Cancer in Rabbits: Results of Exposing Epidermal Cells to Carcinogenic Hydrocarbon at Time of Infection with Shope's Papilloma Virus are reported by Stanfield Rogers and Peyton Rous[6] (Rockefeller Inst. for Med. Research). Areas of rabbit skin previously made hypersensitive with turpentine were scarified, inoculated with the Shope papilloma virus and covered with a dressing that contained 20-methylcholanthrene or 9:10-dimethyl-1:2-benzanthracene.

The papillomas which subsequently arose often appeared later, were fewer and remained less vigorous than those due to action of the virus alone. After several months, and more or less abruptly, a majority became carcinomatous, often at several locations, whereas with few exceptions the control growths underwent no such alteration. The carcinomas were of the usual type which arise from epidermal cells infected

(5) Bull. Assoc. franç. étude cancer 38:425-430, 1951.
(6) J. Exper. Med. 93:459-488, May, 1951.

with the virus. In control tests, 9:10-dimethyl-1:2-benzanthracene conferred latent neoplastic potentialities on uninoculated epidermis. The chemical carcinogens caused malignant growths to arise from many virus papillomas which were retrogressing after many months of proliferation. Their effects were so strong that some arose under circumstances ordinarily unfavorable to malignant change. It was concluded that the virus and hydrocarbons acted jointly in their carcinogenic capacities.

Isolation of Filtrable Virus in Hydatiform Mole in Process of Transformation into Chorioepithelioma is reported by Roland de Ruyk.[7] The mole was obtained by curettage four weeks after abortion. It was crushed and centrifuged; a Seitz ultrafiltrate was prepared which contained the equivalent of 3 Gm. tumor/100 cc. water. Control experiments were carried out with some of the filtrate which had been boiled for 10 minutes and with placental filtrates. Chorioallantoic membranes and amniotic cavities in chicken embryos were inoculated.

Only the unboiled filtrate produced any changes. In the ectodermic layer of the chorioallantoic membrane there was cellular degeneration with formation of inclusion bodies; in the mesoderm there were sarcomatous formations of connective tissue and characteristic modifications of the vascular endothelium. The entoderm showed papillary tumor-like formations. On the amniotic membrane there were tumors derived from cells of the amniotic surface, which seemed to metastasize to the liver extensively. Moreover the amniotic membrane was transformed into a vesicular mass, similar to the morphologic macroscopic appearance of the hydatiform mole. All these lesions were consistently produced on passage through successive embryos. Electron microscopic studies showed virus-like bodies in the amniotic lesions and acellular extracts of hydatiform moles, but not in extracts of normal placenta.

The results are difficult to explain other than by the presence of a filtrable virus, which might be an etiologic agent in production of hydatid mole and chorionepithelioma.

[That results in the fowl embryo can be extrapolated to the human disease is open to question. Certainly, the identification of a virus in this connection must be more exact than has been done by the author. Confirmatory studies are required with a view not merely to establishing the

(7) Bull. Assoc. franç. étude cancer 38:52-71, 1951.

action on the fowl embryo but also to determining whether such action can be expected from other cases of hydatiform mole or choriocarcinoma. —Ed.]

Histochemical Interpretation of Radiosensitivity in Normal and Neoplastic Tissues: Role of Nucleic Acids. Lucien Cornil and André Stahl[8] (Marseille) studied various tumors with (1) the Feulgen technic for detection of thymonucleic acid and (2) the Brachet technic for demonstrating ribonucleic acids. The latter consists in finding basophilia of various cellular constituents and observing its disappearance after the action of ribonuclease. In basal cell carcinoma a large nucleus, rich in thymonucleic acid, occupied most of the cellular space. Since the cytoplasmic ribonucleic acid content was relatively small, the thymonucleic/ribonucleic acid ratio was elevated in these cells. Lymphoblastoma, also a radiosensitive tumor, gave the same results. Columnar cell carcinoma of the gastrointestinal tract, however, showed a medium Feulgen reaction but contained large quantities of ribonucleic acid, so that the thymonucleic/ribonucleic acid ratio was much smaller than in radiosensitive tumors. Similar results were obtained in amelanotic melanoma.

[The authors maintain that radiosensitivity is proportional to the cellular content of nucleic acids and is greater as the ratio of thymonucleic acid to ribonucleic acid is higher; therefore the technics they use might be employed as a guide in treatment. This requires extensive substantiation. —Ed.]

Systemic Effects of Tumors in Rats. R. W. Begg[9] (Dalhousie Univ.) studied the effects of Walker carcinomas or Jensen sarcomas of various sizes in rats. Since tumors have been reported to produce adrenal stimulation and exhaustion, determinations were made of liver catalase activity, hemoglobin, thymus and adrenal weight, ascorbic acid and cholesterol content, all related to adrenal function. The weights of control and experimental animals were similar, and the weights of organs were thus assumed to be comparable.

The earliest effects produced by a tumor were hypertrophy of and loss of ascorbic acid from the adrenal, followed by anemia. There was no diminution of liver catalase in animals bearing tumors forming 5 per cent of body weight, but half the liver catalase activity was lost when tumor formed 15-30 per cent of body weight. The drop in liver catalase following adrenalectomy in rats is but half as large as that observed in

(8) Presse méd. 59:933-935, July 4, 1951.
(9) Cancer Res. 11:341-344, May, 1951.

the tumor-bearing animals; thus adrenal hypofunction is not the chief factor in the anemia and loss of catalase activity in the tumor-bearing rat. With increase in tumor size there was progressive increase in weight of adrenals and fall in adrenal ascorbic acid, cholesterol and sudanophilia, suggesting a trend toward adrenal exhaustion and failure. Thymus tissue decreased in size, but involution of thymus has been observed in mice with lymphoid hyperplasia and seems independent of the pituitary-adrenal axis.

[The time has long since passed when neoplasms can be looked upon as only local lesions. The following article also emphasizes this fact.—Ed.]

Studies in Antibody Response of Mice to Tumor Inoculation. P. A. Gorer[1] (Guy's Hosp. Med. School) used suitably absorbed human serum to detect antibodies not disclosed by previous methods. Ordinary "saline" agglutinins and agglutinins active in high concentrations of mouse serum can be demonstrated in mice by tumor inoculation. When heated human serum was used, hemagglutination, with or without a considerable prozone phenomenon, was observed. With fresh unheated human serum there was hemolysis but no agglutination. Better results were obtained if the cells to be tested were suspended in human serum before coming in contact with the antibodies. Fresh guinea pig serum enhanced agglutination in some instances.

Use of these methods in study of cells from mice bearing a foreign strain of tumor suggested that ability of the tumor to grow is due to its high resistance to the action of antibodies.

Conception of Tumor Autonomy Based on Transplantation Studies: Review. Harry S. N. Greene[2] (Yale Univ.) states that early in its growth, spontaneous rabbit tumor can survive in the primary host or in other animals bearing similar tumors but is readily transplantable in the normal animal only after metastasis. Heterologous transplantation of spontaneous uterine and breast tumors in rabbits to a normal animal of different species paralleled homologous transfer, and tumor which grew in normal unrelated rabbits also grew when transplanted from the original rabbit to guinea pigs. The growth was generally slow in the beginning but increased to parallel that of the spontaneous tumor of the new host. The ability to grow in normal animals was obtained simultaneously by

(1) Brit. J. Cancer 4:372-379, December, 1950.
(2) Cancer Res. 11:899-903, December, 1951.

spontaneous and transplanted tumors. In the early stage, survival seemed to depend on the special constitutional status of the spontaneous tumor-bearing animal which is not present in normal animals.

Transfer of early spontaneous mammary tumors of C3H mice to unrelated mice or to another species was unsuccessful. After metastasis of the primary tumor, both homologous and heterologous transplantation was successful.

Investigation of human tumors was limited to heterologous study. Of 123 human tumors transplanted to the anterior chamber of the eye of guinea pigs, 65 grew. All tumors known to have metastasized were autonomous. When only local nodes were involved and organic metastasis was not apparent, 39 per cent were autonomous. Without lymph node involvement or recognizable metastasis, transplantation was successful in only 29 per cent. The relation between autonomy and metastasis suggests that autonomy like metastasizability is a late stage in tumor development. The interval between successful tumor transfer to animals and death of the patient averaged 5.5 months. In the unsuccessful transplants, the patient died about 34 months after the attempted transfer.

It is concluded that with referenec to biologic properties, cancer of rabbits, of mice and of man is not a sudden transformation in normal cells but the final stage in a developmental process.. During the greater part of its course, continued existence of the tumor is conditioned by factors peculiar to the tumor-bearing subject. Autonomy, or the ability to survive in the absence of such factors, is a late development, followed by rapid acceleration in the fatal course of the disease. Little is known about the factors on which tumor development depends. In some instances there is indication that they are endocrinologic. Rabbits bearing certain mammary and uterine tumors show widespread endocrine changes suggestive of the continued action of estrogenic hormone. When normal rabbits, subjected to long-continued administration of estrogen hormone, were inoculated with mammary tumors or by a uterine tumor under comparable circumstances, the transplanted tumor survived and grew. In these special cases the constitutional state incident to the long action of estrogenic hormone probably supplied the factor essential to continued tumor existence. There has been no evidence of the operation

trogenic hormone in development of tumors of other or-

gans. The effect of castration or administration of estrogenic hormone in patients with prostatic tumors suggests that such tumors may depend on androgenic hormone.

Neither determination of the mitotic index nor morphologic study of a tumor was of value in assessing its ability to grow in normal animals. The degree of differentiation or organization appeared to bear some relation to growth rate but had little pertinence as an indication of autonomy.

Early embryonic tissue, like cancer, can grow in alien species. Unlike cancer, such tissue loses its autonomy with continued development and, by midgestation, transplantation reaction reverts to that of normal tissue. In both primary and experimental hosts, embryonic tissue undergoes differentiation, whereas cancer does not. Such a shift from a state of autonomy to dependency was not observed in tumors, but attainment of autonomy and metastases are coincidental and the interval of time available for such a development is sharply limited in the living body. Tissue culture of certain neoplasms suggests that such transition is possible in tumor cells.

[This review is of considerable importance in relation to the understanding of the biology of neoplasia. This fact and the distinction of the author have justified the preparation of an abstract, but it must be admitted that no abstract can do complete justice to the original article. —Ed.]

Anemia of Cancer Patients and Its Relation to Metastases to Bone Marrow. Shu Chu Shen and F. Homburger[3] (Tufts College) report that 60.1 per cent of 193 cancer patients had definite anemia, most of mild or moderate degree. Of the patients without anemia, 33.8 per cent had evidence of bony metastases; of those with anemia, 20.7 per cent. Of 50 patients with metastases, 48 per cent had anemia; of 143 without metastases, 64.3 per cent. Apparently, incidence of metastases to bone marrow is no greater in cancer patients with anemia than in those without anemia. Furthermore, incidence of anemia is no greater in the presence of metastases than in their absence.

Fifty-six per cent of the cases of anemia were of the myelopathic type, 12.9 per cent were of the myelopathic type complicated by blood loss and 28.5 per cent were due to blood loss alone. Anemia due to hemolysis occurred in 2.6 per cent. There were no cases of nutritional anemia. Most cases of severe anemia were due to blood loss. About two thirds of the pa-

(3) J. Lab. & Clin. Med. 37:182-198, February, 1951.

tients with myelopathic anemia and no blood loss showed no evidence of osseous metastases. In the myelopathic groups hypochromia and microcytosis were definitely less pronounced than in the anemias associated with blood loss. In general, the blood picture of the anemia of cancer differed in no obvious way from that of anemia associated with chronic infection.

In cancer patients with anemia, cobalt therapy may increase erythropoiesis regardless of metastases to bone. This study indicates that anemia associated with cancer is seldom due to bone marrow replacement by neoplastic tissue.

Studies on Mechanisms of Metastasis: Distribution of Tumors in Various Organs in Relation to Distribution of Arterial Emboli. Dale R. Coman, Robert P. deLong and Morton McCutcheon[4] (Univ. of Pennsylvania) prepared neoplastic cell suspensions by forcing tissue from Brown-Pearce rabbit tumor through a sieve, then fixing the suspensions in formalin and staining them with iron hematoxylin. Preparations were suspended in saline and 0.8 cc. was injected into the left side of the heart. In animals killed after one to three minutes, sections from various organs were stained with eosin. The injected cells appeared dark blue against a pink background. In each organ the number of single and clumped stained tumor cells was counted in the sections and their distribution, whether in capillaries or arterioles, was noted. Tumor concentration was expressed as cells and clumps per square centimeter. After injection of living tumor cell suspension, a second group of rabbits was killed in one to three weeks. Gross and microscopic metastases were determined and the adrenals, diaphragm, iris, kidney, masseter muscle, pituitary, spleen, testis and thyroid gland studied.

In some organs there was a great difference between the number of stained tumor cells per square centimeter of the first group and number of tumors per square centimeter in the second group. In the iris and pituitary, visible tumors were too numerous to count. Few metastases were found in the spleen, thyroid and muscle. In some organs there was correlation between the frequency distribution of tumor and of stained cells. The spleen and thyroid showed fewer tumors than would be expected from the number of emboli. If the stained cells in capillaries only were counted, these values showed much closer correlation to the number of living tumors

(4) Cancer Res. 11:648-651, August, 1951.

in all organs studied. In the sections, early tumor growths appeared almost invariably to have arisen in capillaries. The tumor cells used in this experiment seemed to have difficulty in penetrating the walls of the arterioles. In organs such as spleen and thyroid in which embolic cells are principally arrested in arterioles, metastases are rare. Few embolic stained cells were found in the capillaries of the spleen and thyroid. Young tumors were numerous in the kidney and nearly always occurred in the glomeruli, originating from tumor cells in the glomerular capillary loops or from the distal end of the afferent arteriole where it breaks up into capillaries. In other organs a similar origin in the capillaries rather than arteries was always noted. Stained tumor cells were rare in the muscle. Stained cells were found in the capillaries and the larger vessels in the body of the iris. Tumors arose from the same location. Tumor growth became rapidly confluent in the pituitary with lost identity of origin. Stained cells were found in the sinusoids oftener in the posterior than in the anterior lobe. Both stained cells and early tumor were found chiefly in the cortex of the adrenal close to the capsule.

Apparently the number of tumor metastases in the various organs depends on the number of embolic cells lodging in the capillaries. The frequency distribution of spontaneous metastases of Brown-Pearce tumor in rabbits is in agreement with the experimental evidence. There is no support to the theory that favorable conditions in the organs form the basis for increased frequency of metastases whereas unfavorable conditions in other organs account for infrequent metastases. The size of the emboli does not seem to influence the establishment of metastases. In all organs, tumors arose when most of the emboli consisted of single cells or small clumps of two to four cells. This is contrary to the concept that sizable clumps rather than single cell emboli encourage tumor development.

[It is gratifying to have an explanation of metastasis based on objective observations not tinged by rather vague impressions as to the suitability of field for growth in an organ or tissue where metastases develop. The frequency of metastasis to bone marrow, as has been developed by study of material removed by puncture methods, is not covered in the article as far as I can see, but the vascularity of marrow would fit well in the picture of distribution as disclosed.—Ed.]

Significance of "Tissue Pressure" of Normal Testicular and of Neoplastic (Brown-Pearce Carcinoma) Tissue in Rabbit. J. S. Young, C. E. Lumsden and A. L. Stalker[5] (Univ.

(5) J. Path. & Bact. 62:313-333, July, 1950.

of Aberdeen) utilized a refined manometric method for estimating tissue pressure in normal testicular tissue and neoplastic tissue implanted and growing in the contralateral testis of rabbits. Tissue pressure of the tumor was substantially greater than that of the normal testis. With time, tissue pressure of the tumor increased, whereas that of normal testis remained stationary. Injection of small volumes of normal saline solution or digital compression elevated hydrostatic pressure in both testes.

Results suggested that entrance of malignant tumor cells into the lumen of a vessel may be a physical phenomenon which results from increased extravascular or tissue pressure. Induction of local anesthesia near a tumor may increase the risk of disseminating tumor cells by increasing extravascular pressure and by injuring the walls of vessels so that tissue fragments may find an entrance through them. Furthermore, palpation of tumors may increase tissue pressure so that entrance of tumor cells into the lumen of vessels is facilitated.

[This series of observations fits in well with those outlined in the preceding article. Although clinical experience and experimental work has not shown that biopsy aids in the dissemination of tumors, this work re-emphasizes the danger of exposing tumors to repeated palpation and even massage. The following article elaborates on these principles.—Ed.]

Dynamics of Parenchymatous Embolism in Relation to Dissemination of Malignant Tumors were studied by J. S. Young and Harry D. Griffith[6] (Univ. of Aberdeen). It was assumed that all tissues exemplified the fundamental principles of a differential pressure system in that they consist of vascular tubes invested by a semisolid medium. The pressure of the medium may differ from that of the fluid inside the tube. On this basis a hydrostatic model was constructed to study the factors involved in the entrance and exit of fluids containing suspended bodies through holes in the wall of a collapsible tube.

Experiments showed that bodies suspended in a fluid medium surrounding a collapsible tube with a hole in its wall cannot enter the lumen of the tube so long as the internal pressure is greater than the external, but that in the reverse situation the bodies enter the tube. Hence it was concluded that formation of parenchymatous emboli consisting of fragments of normal tissue is probably determined by a shift of the differential pressure so that the extravascular exceeds the

(6) J. Path. & Bact. 62:293-311, July, 1950.

intravascular. The extravasation of blood into malignant tumors indicates that the intravascular pressure of their blood vessels is high in relation to the tenuity of the vessel wall. Rupture of the vessel and extravasation of blood into adjacent tissue provide a means by which tumor cells may enter the vascular channels, if the extravascular pressure exceeds the intravascular. Therefore, emboli of normal or tumor tissue may arise on the basis of hydrostatic relationships rather than from invasive growth of cells. Tumor cells may enter the lymph-vascular channels by the same means.

Role of Vertebral Venous System in Metastasis of Cancer to Spinal Column: Experiments with Tumor Cell Suspensions in Rats and Rabbits are reported by Dale Rex Coman and Robert P. DeLong[7] (Univ. of Pennsylvania). On the basis that metastases depend on availability of tumor emboli rather than on organ susceptibility, a study was made to explain the frequency with which cancer of the prostate, breast and thyroid metastasizes to the lumbar vertebrae. Three routes are possible: (1) embolic tumor cells enter the canal system and pass through pulmonary vessels into the arterial system, thereby reaching the vertebrae; (2) tumor emboli become established in the lung and form secondary lesions which in turn metastasize, and (3) cancer cells from the breast and pelvic region may enter the veins communicating with the extensive vertebral venous plexus.

METHOD.—Suspensions of viable tumor cells were injected into the femoral veins of rats and rabbits while slight abdominal pressure was applied. Control animals were given injections similarly except that abdominal pressure was not applied. The animals were later killed and distribution of tumor studied. Tumor cells in vertebral veins were assumed to have passed directly from the caval system into the vertebral system. Emboli in arterial branches were accepted as having reached the vertebrae by passing through the lung.

In 12 of the 14 experimental rats, tumor appeared in the vertebral veins. None showed tumor in the vertebral arteries. The two rats with no tumor of the vertebral veins had tumor in the lungs. All but one animal with vertebral vein involvement also showed tumor in the lung. Of 16 control animals, 15 showed tumor in the lungs only. One control animal had tumor in the spinal canal in the lumbar region.

Microscopically, the tumors usually arose from emboli in

(7) Cancer 4:610-618, May, 1951.

the larger thin-walled vertebral veins in the spinal column on the anterolateral surface of the vertebral body. They tended to extend into the bodies of the lumbar vertebrae through the numerous pores in the thin anterior wall of the vertebral body. The vertebral canal was invaded in several animals and the spinal cord in three.

Results in the rabbits were similar. Four of the seven experimental animals had tumor in the vertebral veins and lumbar spine. No arterial emboli were found. All experimental and control rabbits had tumor in the lungs. The vertebral vessels were not involved in the control group.

Results were in accord with the concept that the frequency of spontaneous tumor metastases to the vertebral column from pelvic tumor in man depends on the entrance of tumor cell emboli directly into the vertebral venous system, by-passing the lungs.

[The earlier work of Batson was supported by careful anatomic observations and, in the experience of those who performed autopsies, seemed to be entirely valid. It is of value to have experimental confirmation.—Ed.]

Study of Behavior of Human Thyroidal Tumors Transplanted into Anterior Chamber of Guinea Pig's Eye. Brown M. Dobyns and Beatrice Lennon[8] (Boston) studied the outcome of transplantation of fragments of 23 human thyroid tumors and 3 normal thyroids into the anterior chamber of the eyes of guinea pigs. The animals were observed for 13-827 days. Most of the normal thyroid tissue and many of the benign lesions were absorbed relatively promptly. Various transplants appeared to be dormant for long periods. A few disappeared only to reappear and increase in size. Of the 32 transplants of normal thyroid tissue, 10 remained visible for as long as 90 days, but none showed gross evidence of growth. No growth occurred in 12 transplants from two hyperplastic adenomas. All transplants from a Hürthle cell adenoma were absorbed within 90 days. Transplants from Hodgkin's sarcoma did not survive. Seventeen transplants from two rather primitive fetal adenomas classified morphologically as benign showed: gross survival without growth, 9; temporary disappearance then reappearance, 3; survival of viable tumor cells for 424 days, 2. Multiple transplants from five different papillary carcinomas of a low degree malignancy survived grossly in numerous instances and a few appeared to grow. Histologic

(8) Ann. Surg. 134:984-998, December, 1951.

examination 233 days after inoculation revealed tumor cells in one transplant which had reappeared. Numerous transplants of metastatic tumor from two patients with follicular adenocarcinoma remained unabsorbed for long periods. One showed slight growth and was successfully retransplanted, and surviving tumor cells were demonstrated in one other.

Some of the transplants from undifferentiated carcinomas grew or survived for long periods. There was always a latent period of several months before growth appeared, and even then growth was slow compared with that of malignant tumors in other organs. Those which grew most vigorously filled the entire anterior chamber and showed spontaneous necrosis. Differentiation of the transplant was sometimes more highly developed than in the original tumor, and one instance of extremely undifferentiated thyroid carcinoma showed increased degrees of differentiation in serial retransplants.

Some of the tumor transplants formed acini containing colloid. Attempts to demonstrate radioactive iodine in the transplanted viable tumors was unsuccessful, even after total thyroidectomy in the experimental animals.

[This study and the two that follow give valuable information about heterologous transfer of tumors. A general survey of the matter has already been given (p. 62).—Ed.]

Significance of Anterior Chamber in Tumor Transplantation: Nature of Tumor Growth beyond Anterior Chamber. E. J. Eichwald and H. Y. Chang[9] (Univ. of Utah) report that when mouse neuroblastoma C1300 was transplanted into the anterior chamber of the eye of female mice of C57 brown strain, the tumor grew progressively in three fourths of the animals. The periocular tissue and subcutaneous tissue of the head were invaded in most instances. After transplantation into the subcutaneous tissue of the abdominal wall, the tumor grew in only one fifth of the animals.

In an attempt to interpret this observation, the authors carried out further experiments on mice of this strain. Primary tumor cells were inoculated into the anterior chamber of 82 mice, with growth in 83 per cent; into the abdominal subcutaneous tissue of 84 mice, with growth in 18 per cent; into the cranial subcutaneous tissue of 81 mice, with growth in 21 per cent, and into the conjunctiva of 92 mice, with growth in 26 per cent. These results indicate the periocular and cranial connective tissue are no more susceptible than the tissue of

(9) J. Cancer Res. 11:811-813, October, 1951.

the abdominal wall to the growth of this tumor in the C57 strain of mice.

Tumors growing in the anterior chamber and in the anterior abdominal wall of a group of mice were removed after 37 days and transplanted into the subcutaneous tissue of the anterior abdominal wall of other mice. After 61 days, tumor from the anterior chamber and subcutaneous tissue was again transplanted into the abdominal subcutaneous tissue of other mice. The different sites of origin of the tumors used for inoculation did not significantly change the incidence of growth. These results indicate that adaptation of the tumor to hosts of the same strain is not the cause of growth beyond the eye after transplantation into the anterior chamber.

Neuroblastoma C1300 was transplanted into the anterior chamber of the eye of another series of mice, and the tumors which grew were removed from some of the animals on the eighth day and from others on the seventh day after inoculation; these in turn were transplanted into the subcutaneous tissue of the abdominal wall. In another group of animals the extraocular invasion was removed and transplanted into the subcutaneous tissue of the abdominal wall. Tumor growth after autologous retransplantation to the abdominal wall was observed in only 1 of 61 mice. This result indicates that autologous adaptation is not the cause for the observed tumor growth beyond the anterior chamber.

It appears that once the tumor has become established, it can overcome the resistance of the subcutaneous tissue and grow as well outside as within the anterior chamber. It follows that the low resistance in the anterior chamber is essential only to the growth of newly transplanted tumor to which the subcutaneous tissue is resistant.

Tumor Transplantation to Subdural Space of Heterologous Hosts. E. J. Eichwald, G. J. Goodman and H. Y. Chang[1] (Univ. of Utah) transplanted Mouse sarcoma 37 to the subdural space of 14 guinea pigs. A bone flap was cut, leaving the dura intact, and the tumor was deposited by needle injection. In animals killed the first day after transplantation the bulk of the tumor was necrotic, and free tumor cells were found penetrating the arachnoid and spreading through the subarachnoid space. Growing tumor was found in all guinea pigs killed thereafter and in the animals which died. By the

(1) Proc. Soc. Exper. Biol. & Med. 78:72-74, October, 1951.

end of the first week, a solid layer of tumor tissue occupied the subarachnoid space and rows of tumor cells infiltrated the brain along the perivascular spaces. Areas of necrosis and fibrosis were present in the upper levels of the tumor. Two weeks after inoculation a large tumor mass was present in the subarachnoid space which depressed and invaded the brain, with gross extension to the proximity of the ventricle. The last surviving animal died 21 days after transplantation. Autopsy showed hemorrhage and necrosis of the brain and abundant well preserved tumor tissue.

There was no evidence of regression of tumor in the brain at the end of 21 days after transplantation as compared with tumor transplanted to the anterior chamber, which usually begins to regress by the end of the second week.

Metastases Simulating Mammary Cancer in Prostatic Carcinoma under Estrogenic Therapy have been observed by J. H. Campbell and Sam D. Cummins[2] (Shreveport, La., Charity Hosp.).

Man, aged 69, was hospitalized with acute urinary retention. A suprapubic prostatectomy was attempted and the pathologic report was adenocarcinoma of the prostate. Orchiectomy was refused and the patient placed on daily doses of diethylstilbestrol. Examination 1½ years later revealed findings consistent with metastatic carcinoma of prostatic origin involving the vertebrae and pelvis. A year later there was bilateral gynecomastia; bilateral orchiectomy was performed. After five months, the patient was readmitted because of multiple painful subcutaneous nodules scattered over the body. Both breasts were enlarged and contained multiple irregular, hard, tender, movable nodules, uniformly located. Nodules removed from each breast showed undifferentiated adenocarcinoma. The patient became progressively worse and died within a month. He had received a total of 6,730 mg. diethylstilbestrol. Autopsy disclosed primary adenocarcinoma in the region of the prostate with metastatic nodules in both breasts, the subcutaneous regions over the abdomen, the liver, adrenals, spleen, kidneys and the wall of the right ventricle of the heart. Metastases were also found in the ribs and vertebrae.

The cytoplasm and nucleus of the carcinoma cells in the breast nodules were stained dark brown by the lead sulfide in the acid-phosphatase method of Wolf, Kabat and Newman. The lining cells of the ducts also revealed acid-phosphatase activity but were not so intensely stained as the carcinoma cells. Intense impregnation of the cancer cells from the prostate showed their acid-phosphatase content.

The validity of the theory that estrogens induce carcinoma

---

(2) Cancer 4:303-311, March, 1951.

of the male breast during therapy for disseminated carcinoma of the prostate is questioned on the basis of these findings. Review of 11 similar cases of primary breast carcinoma originating during estrogenic therapy for carcinoma of the prostate discloses that specific methods of differentiation have not been used previously.

[The development of gynecomastia following estrogenic therapy for carcinoma of the prostate is well established, but the mechanism is not fully understood. Of itself, gynecomastia is not disposed to neoplastic development. This report emphasizes the fact that any claim for development of neoplasia in gynecomastia should be fully supported.—Ed.]

Spontaneous and Complete Regression of Extensive Pulmonary Metastases in Case of Chorionepithelioma is reported by Walter R. Johnson[3] (Univ. of Michigan).

Woman, 43, para VI, gravida VII, was first seen on July 19, 1949, complaining of vaginal bleeding. Menstrual periods had been normal until amenorrhea developed in March. A normal five day period occurred in March and what was thought to be a normal period began in April. A few days after the end of this bleeding episode, there was onset of daily vaginal spotting, which was present on admission. She had no history of pulmonary symptoms, but there were increased weakness, fainting spells, anorexia and weight loss. A firm, nontender, movable mass could be felt arising from the pelvis and extending about 4 cm. above the symphysis pubis. Bimanual examination of the uterus disclosed it to be enlarged about three times normal size, with a firm mass 3 cm. in diameter extending from the right posterolateral wall. Total hysterectomy and bilateral salpingo-oophorectomy were performed. Microscopic examination of sections taken from a pale blue uterine nodule on the right posterolateral wall revealed the appearance of malignant chorionepithelioma infiltrating well into the musculature. There was a hypertrophic decidual reaction on both ovaries, without evidence of lutein cysts. Result of an Aschheim-Zondek test performed two days postoperatively was positive. Stereoscopic x-ray examination of the chest revealed widespread metastatic neoplasm of both lung fields.

When seen in September 1949, she was feeling well and had gained 21 lb. Pelvic examination revealed a firm neoplastic nodule about 2.5 cm. in diameter palpable high in the rectovaginal septum. Biopsy was not performed. X-ray examination of the lungs again revealed extensive bilateral pulmonary metastases. December 1949, pelvic examination was completely negative and chest x-rays showed complete disappearance of metastases. The Aschheim-Zondek test gave a negative result. When last seen in October 1950, she was in excellent health.

[Certain of the earlier reports of complete regression of malignant tumors have not been supported to a great degree by autopsy observations. The evidence presented here points strongly to the regression of this tumor, but without postmortem examination it is impossible to accept the view that the tumor has entirely disappeared.—Ed.]

---

(3) Am. J. Obst. & Gynec. 61:701-704, March, 1951.

Malignant Melanoma in Negro: Review of Literature and Report of Nine Cases are made by George C. Morris, Jr., and Robert C. Horn, Jr.[4] (Univ. of Pennsylvania). In addition to these nine cases in North American Negroes, 430 in both African and American Negroes have been reported. Calculations based on data obtained from a number of sources indicated

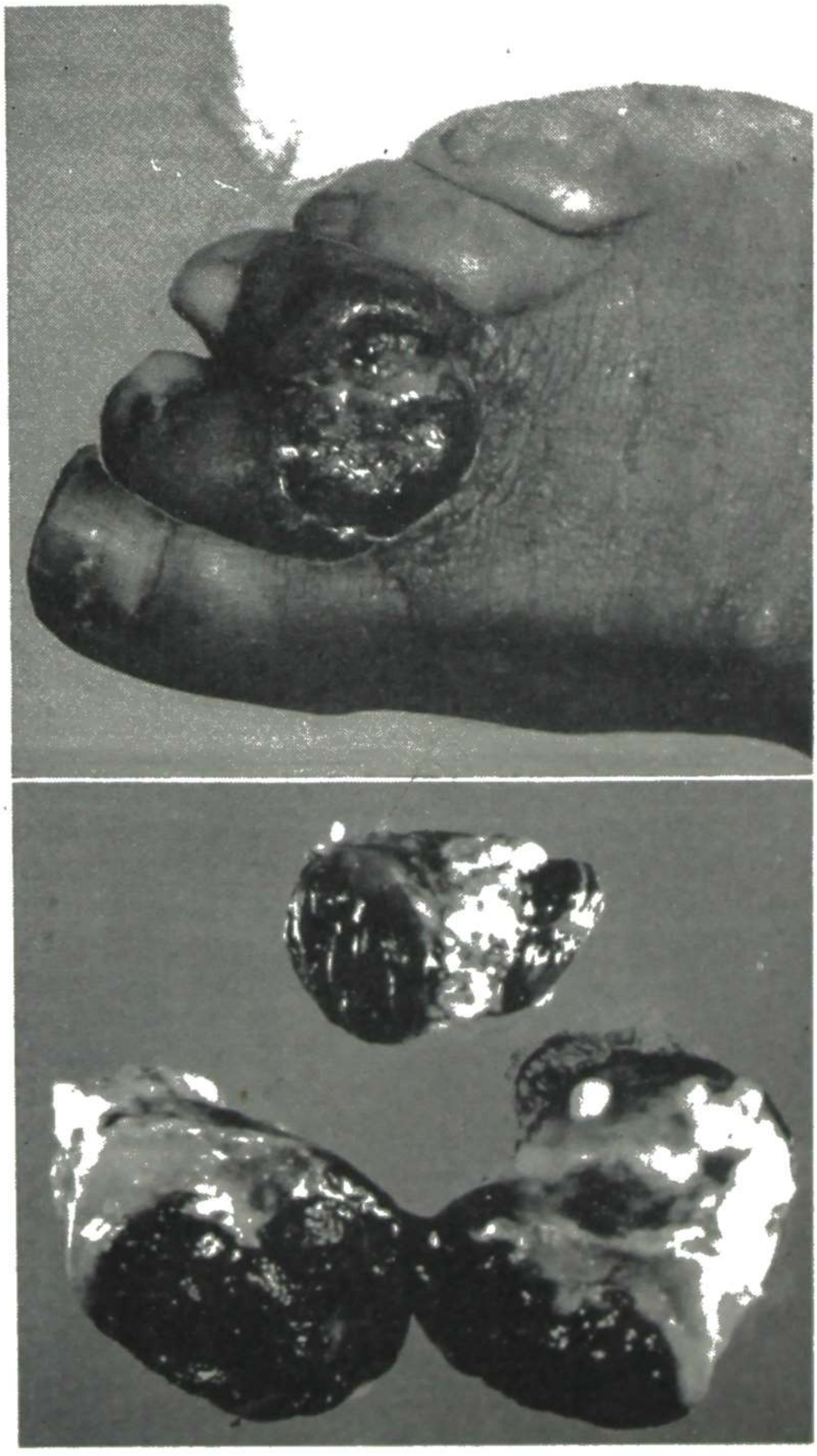


Fig. 25 (top).—Primary malignant melanoma.
Fig. 26 (bottom).—Heavily pigmented metastases in inguinal lymph nodes.
(Courtesy of Morris, G. C., Jr., and Horn, R. C., Jr.: Surgery 29:223-230, February, 1951.)

(4) Surgery 29:223-230, February, 1951.

that the incidence of malignant melanoma is 1.8-4.4 times as great in the white race as in the American Negro.

Average age of 48 Negroes for whom this factor was known was 45.2. There was a slight predominance of males. Of 287 malignant melanomas, 177 were primary on the foot (Fig. 25) and 36 originated elsewhere on the legs. Of the 46 cases in which the metastatic sites were indicated, 41 spread to the regional lymph nodes initially (Fig. 26) and 9 showed blood-borne metastases also. From the available data and the present cases it was apparent that the first manifestation of spread is involvement of regional lymph nodes.

Chromatin-Melanin Relationships in Malignant Melanomas. E. Meirowsky and L. W. Freeman[5] (Indiana Univ.) observed development of pigment in melanoma in formalin-fixed, paraffin-embedded preparations. The nucleolus and the intranuclear vacuoles were the first structures to become melanized. Complete nuclear melanization may be found in the "clear type" cells or regular melanoma cells. Fragments of pigmented nuclei and nucleoli extruded into the cytoplasm form chromidia. Melanized chromidia are abundant in cells showing mitosis. After becoming melanized, both chromidia and nuclei are extruded. The extruded nuclei and nuclear fragments retain a basophilic membrane. The retained or extruded nuclei and chromidia frequently appear to be budding after they become melanized. Nuclei in the process of budding maintain their chromatin structure. Occasionally cells were found with melanin in the cytoplasm but none in the nucleus.

These observations indicate that melanin formation occurs only in cellular structures consisting of or derived from chromatin. In light of recent histochemical discoveries, it is suggested that nucleoprotein may be the precursor of melanoprotein.

Histogenesis of Granular Cell Myoblastoma (Granular Cell Perineural Fibroblastoma?) was studied by A. G. Everson Pearse[6] (Postgrad. Med. School of London). Histochemical studies in six cases showed that the granules in myoblastoma cells contain a large amount of lipoid, small amount of protein and some glycol groups. Absence of ribonucleic acid indicates that these cells are not involved in protein synthesis.

---

(5) J. Invest. Dermat. 16:257-260, April, 1951.
(6) J. Path. & Bact. 62:351-362, July, 1950.

A characteristic of granular cell myoblastomas which has not been emphasized is the invariable presence of a diffuse collagenous framework. Usually a "brush" of reticulin fibers is found at both poles of isolated, single myoblastoma cells. The broken portions of collagen bear the same relation to the tumor cells as do the surviving muscle cells in the lingual variety of the tumor. Apparent transitions are visible in both.

When comparisons are made with normal collagen, more than the normal complement of fibroblasts is found in the collagenous stroma of the lesions. In the tumor a much higher proportion of fibroblasts contain periodic acid-Schiff-positive or sudan black-positive granules in the cytoplasm at the poles of the nucleus than is seen in fibroblasts in normal collagen. Intermediate stages can be observed. Apparently the mature granular myoblast is derived from a cell which has the long nucleus of the fibroblast and its characteristically shaped body containing a few of the specific granules at either pole. There is a close resemblance between the nucleus of the young fibroblast and that of the younger granular cells. Although not diagnostic, both often contain two dark-staining polar masses, presumably karyosomes.

The combined histochemical and morphologic evidence indicates that granular cell myoblastomas originate from fibroblasts rather than from neural, muscular or histiocytic cells. The enlargement of the tumor and its infiltrative quality are regarded as due to centrifugal spread of the granular cell change in fibroblasts.

[The use of special stains often aids materially in interpretations. Whether the interpretation here presented will stand the test of time is not certain, but at least it throws some doubt on the identity of the granular cell myoblastoma with the general group of neurofibromyomas. —Ed.]

Is Mycosis Fungoides a Reticuloendothelial Neoplastic Entity? Edward P. Cawley, Arthur C. Curtis and James E. K. Leach[7] (Univ. of Michigan) reviewed 10 cases diagnosed as mycosis fungoides and subsequently studied at autopsy.

The family history was notable in one case because the patient's mother also died of mycosis fungoides and in another because of the occurrence of two cases of leukemia and one of pernicious anemia in the patient's family. Clinically, all 10 patients presented the usual conglomeration of cutaneous

(7) Arch. Dermat. & Syph. 64:255-272, September, 1951.

lesions. Average duration of life was 5.3 years after diagnosis was established.

Hematologic examination showed no typical changes although several patients had moderate to pronounced eosinophilia. Organ examination at autopsy showed involvement, other than cutaneous, of various lymph nodes in seven, bone marrow in five, spleen in four, and of heart, lungs, kidneys and liver in two patients each. Solitary organ involvement included the appendix, adrenals, dura mater, aorta, diaphragm, breasts, tongue, testis, urinary bladder, pancreas, tonsils, salivary glands and thyroid gland.

Microscopically the dermal infiltrate was the diagnostic kernel of each cutaneous lesion. In one case the pathologic change was the polymorphous cutaneous infiltrate described as characteristic for mycosis fungoides. In the others, reticuloendothelial cells were the basic components of the lesion, and these were examples of Hodgkin's disease (3), lymphoblastoma of reticuloendothelial cell type (3) and lymphoblastoma not characteristic of lymphosarcoma or leukemia (3).

Although mycosis fungoides has been regarded as almost exclusively a cutaneous disease, the authors conclude that the disease is of reticuloendothelial origin and should be classified among the lymphoblastomas. It is a clinical but not a pathologic entity.

Miscellaneous

Morphologic Aspects of Paraproteinosis during Course of Plasmacytomas: Lesions of Autonomic Nervous System; Manifestations of Paraproteinosis in Alveolar Cells of Lungs. In about 12 per cent of patients with this disorder, skeletal lesions cannot be detected by x-ray or sometimes even at autopsy. G. Tverdy[8] (Antwerp) draws attention to the presence of granules in the alveolar cells of patients who present few symptoms and have negative bone roentgenograms. The cells are large (15-20 μ) and contain several large granules (2-3 μ) in the cytoplasm similar to Russell bodies. They are found in alveolar edema and sputum, where they can be of diagnostic importance. The granules have a pronounced affinity for acid stains, which can be observed grossly.

Tverdy reports a case in which there were few symptoms,

(8) Schweiz. Ztschr. allg. Path. 14:66-80, 1951.

negative roentgenograms and absence of the Bence-Jones reaction. The cells were observed. The diagnosis was finally confirmed by sternal puncture. In addition a homogeneous substance had infiltrated the interstitial tissues and vessel walls. The substance showed striking affinity for Congo red but did not take any of the other stains characteristic of amyloid; it was evidently related to the paraprotein present in this condition. The nerve fibers and ganglions of the sympathetic system showed similar deposits, which were similar to those reported in the literature in a group of conditions associated with neurologic symptoms referable to central or autonomic nervous system or peripheral nerves. In none of the previously reported conditions was plasmacytoma diagnosed, but the occasional absence of radiologic evidence of bone lesions may account for this.

Symposium on Amyloidosis: Secondary (Typical) Amyloidosis in Quadriplegics; Report of Four Cases is made by Murdock S. Bowman and Ernest S. Redfield[9] (U.S.N.). The disease which presumably caused the amyloidosis was, in all patients, chronic suppurative pyelonephritis, with decubitus ulcers possibly being an added factor.

The patients showed amyloid involvement of the liver, spleen, kidneys and adrenals, the usual finding in secondary amyloidosis. Microscopically, amyloid was seen in the walls of the arterioles in each of these organs. In the liver it was also found in the walls of the sinusoids; in the spleen, it was present in the corpuscles, and in the kidneys the glomerular tufts were involved. In three patients slight involvement of the pancreas or gastrointestinal tract was detected, indicating the tendency for overlapping of the primary (atypical) and secondary types of distribution.

Amyloidosis in Still's Disease. J. A. James and F. G. Bolton[1] (Royal United Hosp., Bath) report a case.

Boy, 4, had painful, flitting arthritis of the knees, wrists, ankles and cervical spine, associated with severe systemic symptoms, for 18 months. Flexion contractures of the hips and knees developed. Axillary and cervical lymph nodes were enlarged. A transitory pericardial rub was heard on several occasions. Intermittent fever, pronounced polymorphonuclear leukocytosis, severe anemia and increased sedimentation rate were present. Urine showed protein and casts. Total plasma protein value was 4.15 Gm./100 ml., albumin being 2.86 Gm. and globulin 0.96 Gm.

(9) U. S. Armed Forces M. J. 2:715-722, May, 1951.
(1) Ann. Rheumat. Dis. 10:250-254, September, 1951.

At autopsy, decided periarticular thickening of many joints was seen. The pericardial sac was obliterated by fibrous adhesions. The heart weighed 135 Gm. There was no evidence of valvular disease. The liver was greatly enlarged, weighing 1,644 Gm. Microscopic examination revealed diffuse amyloidosis and fatty change in the liver. Amyloid was deposited in the malpighian bodies and around the vessels of the spleen. There were large deposits of amyloid in all glomerular tufts of the kidneys. The mitral valve was normal. Some myocardial fibers were indistinct and appeared to be infiltrated with amyloid.

Tissue Changes Following Use of Plasma Substitutes. Frank W. Hartman[2] (Detroit) studied the pathologic changes resulting from introduction of the four exogenous macromolecular substances most commonly available for emergency intravenous administration: gelatin, dextran, pectin and polyvinylpyrrolidone. The first three have large molecules with high molecular weight. Reduction of molecular size, without changing the shape of the molecule, to a size and dimension approaching the molecule of albumin and globulin was carried out before injection. None of the four substances are metabolized in the body. They are eliminated from the blood by the kidney with relative rapidity in amounts up to 70-80 per cent. The compounds are inert and are phagocytized by the reticuloendothelial cells and infiltrate the endothelium of blood vessels as well as the parenchymal cells of liver and kidney.

Intravenous injection of a 6 per cent solution of gelatin into mice produced nephrosis of short duration. The lesions were similar to those described for sucrose nephrosis. The epithelial cells of the proximal convoluted tubules showed a granular, finely vacuolated swelling which diminished the size of the lumen.

After intravenous injection of 6 per cent dextran solution into mice, there was decided retention of the substance in the tissues. The lymph nodes, liver, kidneys and blood vessels were involved. Foam cell production was striking in the lymph nodes. Granular and vacuolar changes occurred in the liver cells. Swelling, vacuolation and desquamation of the epithelium of the proximal convoluted tubules were evident in the kidneys. The blood vessel walls, especially in the lungs, were infiltrated by foam cells.

When a 1 per cent solution of pectin was injected intra-

(2) A.M.A. Arch. Surg. 63:728-738, December, 1951.

venously into mice at three day intervals, retention occurred in the reticuloendothelial cells of the lymph nodes, parenchymal cells of the liver, tubular epithelium of the kidneys and, to a less extent, in the lungs and blood vessels. The animals allowed to live remained in good condition.

After the third injection of 3.5 per cent polyvinylpyrrolidone into mice, foam cell formation was noted in the lymph nodes. After the seventh injection, retention was well marked in the liver, kidney, bone marrow, lungs and blood vessels. The material appeared as granules and vacuoles. In the kidneys, tubular epithelium desquamated to form cell casts. Blood vessel changes consisted of swelling, vacuolation of the endothelium and palisade formation with mural thrombus formation and rupture.

After repeated or large intravenous injections, these four substances are taken up by the reticuloendothelial cells, endothelium of the blood vessels and parenchymal cells of the liver and kidney. When one substance tends to embarrass a single organ, a second substance might be used alternately. Total dosage should be limited in any short period to prevent excessive retention.

[The study of what are now called plasma expanders is intensive and widespread in this and other countries. From estimations of mass casualties, it is evident that blood and blood derivatives would not be available in sufficient amounts to meet the needs. The problem appears pressing and urgent. The fact that several of the macromolecular substances are deposited in the tissue is established by this report. That such deposit is enough of a handicap in the event that plasma expanders must be used is not clarified. Whether the deposit immediately following injection will have sequels over the course of a long time is not known. It is unfortunate that autopsies on human beings have not been in sufficient numbers to justify conclusions.—Ed.]

Poisoning by Dinitro-Orthocresol: Report of Eight Fatal Cases Occurring in Great Britain is presented by P. Leslie Bidstrup and D. J. H. Payne.[3] Dinitro-orthocresol is a yellow crystalline solid used in aqueous solution as an insecticide, fungicide and as a selective weed killer in cereal crops. Early symptoms of poisoning are fatigue, excessive sweating, unusual thirst, anxiety and restlessness. Increased rate and depth of respiration, tachycardia, hyperpyrexia and coma may be followed by death within a few hours. All cases of fatal poisoning occurred during hot weather.

Ages in the eight cases ranged between 24 and 40. Agricultural use of the drug provided exposure in seven and manu-

(3) Brit. M. J. 2:16-19, July 7, 1951.

facture in one. Exposure varied from two to six weeks, during hot weather. Death occurred within 12 hours after the acute onset in all. Yellow staining of the skin, particularly palms and soles, was consistently noted. Urine was chrome yellow. Hair, especially in the pubic and frontal regions, showed yellow discoloration. Conjunctivas were normal. Rigor mortis developed rapidly, frequently within an hour after death. Autopsy findings included pulmonary hyperemia and edema, scattered petechiae, gastric erosion and cloudy swelling of the kidneys. In 2 subjects exposed for a month, there was striking absence of subcutaneous and omental fat. Bone marrow was hyperplastic, normal medullary fat being replaced by red cellular substance.

The pharmacologic effects of the chemical are similar to those of dinitrophenol. There is stimulation of general cellular metabolism, an effect accentuated by heat. The chemical also increases the basal metabolic rate. There is an increase in oxygen consumption and in aerobic glycolysis. Glycogen disappears from the liver and muscles. The increase in metabolism is greater than could be accounted for by the fever. The clinical picture in fatal cases resembles thyroid crises. Death is thought to be due either to heat stroke or to cerebral edema.

Dinitro-orthocresol is absorbed through the skin, by ingestion and by inhalation. Rate of excretion in human beings is remarkably slow and toxicity results from the cumulative effect.

CARDIOVASCULAR SYSTEM

Endocardial Fibroelastosis: Report of Two Cases is made by Fred C. Collier and Paul D. Rosahn[4] (New Britain, Conn., Gen'l Hosp.). Eleven other reported cases are reviewed. In five cases there was a history of maternal infection during pregnancy which resulted in the affected infant and in one of a maternal illness of questionable etiology.

Most patients were under age 27 months and nine were under 5 months, one being a premature infant. All died in cardiac failure. Seven had associated cardiovascular anomalies other than dilatation or hypertrophy of the cardiac chambers. In five of these the other abnormalities were located in the great

(4) Pediatrics 7:175-181, February, 1951.

vessels and in the other two there were developmental anomalies of the heart chamber. Fibroelastic thickening of the endocardium was observed in the left ventricle of all; the change was in both the left auricle and ventricle in 10. None of the usual evidences of inflammatory reaction were present in the hearts. Even the thickened endocardium occurred diffusely, with an orderly arrangement of fibroelastic elements which did not suggest that inflammation was the basic lesion.

A likely hypothesis is that the changes are due to a developmental abnormality. Since infectious, dietary and immunologic disorders may cause congenital malformations in experimental animals, it is possible that they may also initiate similar changes in man. More careful review of maternal histories might disclose more cases of maternal illness during pregnancy. When the mechanism of production of developmental abnormalities is being considered, it is important to differentiate a true aberration in the germ plasm from the effect of environmental factors on fetal development. In reviewing the pathogenesis of this condition, the two mechanisms cannot be differentiated.

Endocardial Sclerosis: Review of Changing Concepts with Report of Six Cases is presented by Henry W. Edmonds and Walter B. Seelye[5] (Seattle). The cases were typical of a syndrome characterized by hypertrophy of the left side of the heart, thickening of the mural endocardium of the left ventricle and varying distortion of the aortic and mitral valves. Clinically, there were cardiac enlargement demonstrable by x-ray, nondiagnostic murmurs and sudden death in infancy. Only one patient had evidence of congestive heart failure.

The most striking anatomic feature was moderate to pronounced thickening of the mural endocardium, generally best developed over the anteroseptal surface of the left ventricle, but sometimes involving the whole left ventricle and the atrium also. Microscopic examination demonstrated dense collagenous fibrous tissue instead of normal endocardium, obviously a change of considerable duration and possibly referable to the time of actual formation of the heart.

The enlargement of the heart seemed out of proportion to the valvular deformity. This can be explained only on the

(5) Pediatrics 7:651-659, May, 1951.

basis of intramyocardial congestion caused by occlusion of capillary drainage into the ventricle. It seems more likely that the lesions result from primary maldevelopment than from inflammatory distortion of tissue differentiation. In either case an antenatal origin is assumed because of the youth of the patients in comparison with the age of the lesions. Cases of left-sided endocardial thickening with valve deformities, such as these, may have a theoretical common denominator in terms of segmental variation in tissue differentiation. Extensive fibroelastosis in the truncus segment of the embryo produces normally differentiated aortic and pulmonic trunks. Similar but less pronounced fibroelastosis in a portion of the bulboventricular loop would represent heterotopia resulting in the lesions of endocardial sclerosis.

[A concluding note to this article indicates that Farber has substantially retracted his earlier support of inflammatory pathogenesis and favors developmental origin. In this and the preceding article are explanations as convincing as anatomic studies will permit. However, the valvular deformity present suggests conservatism in excluding inflammation as the cause in all cases. Indeed, the next article suggests that the disorder might be included in the "collagen diseases." How many other diseases are ultimately to be included in that vague category is problematic. —Ed.]

Endocardial Fibroelastosis. William T. Hill and William A. Reilly[6] (Univ. of Arkansas) call attention to the close resemblance of this entity and the collagen diseases.

Negro girl, 2 months, had fever, cough and intermittent cyanosis for two weeks. She was malnourished and dehydrated. Myocardial damage was suggested by ECG. Autopsy showed the heart diffusely enlarged, the greatest enlargement involving the left ventricle. The endocardium of the atrial, ventricular and valve surfaces appeared dense, grayish white, thickened and tough. The pulmonary, aortic, tricuspid and mitral valves were stenosed by a process in which the edges of the valve were strikingly thickened, edematous, soft and myxomatous. The valve edges projected high above the bases of the valve rings. The chordae tendineae were neither shortened nor thickened. Microscopically there was some interstitial myocardial edema. The muscle fibers were hypertrophic. The endocardium was conspicuously thickened by interlacing bundles of fibrous connective tissue and elastic fibers. This tissue showed pronounced edema. The valves were tremendously thickened by pale, pink-staining, amorphous fibrinoid material found in the connective tissue spaces. Special stains showed changes similar to those described as characteristic of fibrinoid degeneration. The results of stains on the degenerative process of the endocardium and heart valves were as follows: (1) Massons' trichrome stain, bluish green with red nuclei; (2) muci-

(6) A.M.A. Am. J. Dis. Child. 82:579-586, November, 1951.

carmine, red-pink; (3) toluidine blue, metachromatic; (4) crystal violet, dark purple; (5) phosphotungstic acid hematoxylin, pale yellow-orange; (6) van Gieson, orange-red.

Clinical Implications of Marfan's Syndrome are reviewed by Arthur Alan Fischl and Jack Ruthberg[7] (New York City). Numerous organs are usually involved. Fingers and toes are long and tapering, the arms may reach to the knees and webbing of fingers is common. Subcutaneous fat is reduced, giving the impression of malnutrition. Patients are usually "double jointed," owing to relaxation of ligaments. The ears are pointed, the palate arched and a peculiar mournful facial expression is caused by the long drooping jaw and thin face. Kyphosis, scoliosis and sternal deformities as well as lung malformations may contribute to the high incidence of pneumonia, a common cause of death. Secondary sex characteristics develop poorly and the basal metabolic rate is low. Mental retardation is rare. Bilateral dislocation or subluxation of the lens is present in half the cases; the pupils dilate poorly with atropine and show iridodonesis. Congenital cardiovascular anomalies such as intra-auricular septal defects and coarctation or aneurysm of the aorta are common.

Few autopsies have been reported. Of three cases presented by the authors, in patients aged 21-32, one was autopsied. In the eye there was round cell infiltration of the optic head and choroid, intact retina, atrophic ciliary body with hyalinization of ciliary processes and subluxated lens and a normal filtration angle. The heart was soft and flabby, hypertrophic and enormously dilated; there was a saccular aneurysm beginning at the base of the aorta. An aortic coarctation was seen just beyond the left subclavian artery; at this point the ductus arteriosus was a fibrous cord. Microscopically, there were fatty degeneration of the myocardium and disorganization of the elastica of the aorta. Foci of necrosis and degeneration and some cystic areas were noted at the aneurysm. There were passive congestion of liver, spleen and kidney, a dermoid cyst in one ovary and chronic salpingitis.

[This and the succeeding articles focus attention on this peculiar syndrome; exactly what constitutes the syndrome as now interpreted is difficult to envision. For example, arachnodactyly may refer to the condition of the extremities and, in some instances, may merely indicate a long, slender person. The idea that, whatever it is, it is associated with congenital cardiovascular anomaly is not borne out by these reports of other torms of cardiovascular disease.—Ed.]

(7) J. A. M. A. 146:704-707, June 23, 1951.

Aortic Aneurysm Associated with Arachnodactyly. Arachnodactyly is a condition characterized by deformity of the extremities from lengthening and narrowing of the bone, often combined with various other malformations. Congenital cardiac lesions are commonly associated. M. F. Moses[8] reports on two women, aged 52 and 26, with arachnodactyly who also had aortic incompetence and congestive failure. At autopsy, aneurysmal dilatation of the ascending arch and multiple intimal tears of the abdominal aorta were found. There was also deficiency and rupture of the elastic fibers with vacuolization of the media. The changes probably represent an inherited congenital malformation of the aortic media.

"Myocarditis" and Hypoplasia in Arachnodactyly is reported by A. G. W. Whitfield, W. Melville Arnott and J. L. Stafford[9] (Birmingham, England).

Man, 35, with arachnodactyly, had symptoms resembling severe myocarditis and died in congestive failure. At autopsy the heart weighed 910 Gm. The valves appeared normal. Microscopic study revealed diffuse myocardial fibrosis. The valve leaflets showed no histologic evidence of rheumatic disease. An area of yellow fatty deposit in the left auricular endocardium was composed of histiocytes in a loose myxomatous stroma. There was mild diminution in aortic circumference without significant histologic change.

Cardiovascular Disease in Marfan's Syndrome. Robert J. Marvel and P. D. Genovese[1] (Indianapolis) report a case.

Man, 29, was hospitalized with congestive heart failure which did not respond to treatment. One sister had features of arachnodactyly and a brother had died of dissecting aortic aneurysm. The patient was 6 ft., 7 in. tall, thin and acutely ill with orthopnea and cyanosis. Blood pressure in both arms was 150/50. He had cataracts in both eyes. Cardiac enlargement, poor heart tones and diastolic gallop were noted, with loud systolic and diastolic murmurs at the base, maximal in the third intercostal space at the left sternal border. Laboratory findings were essentially negative. He died of congestive heart failure and pulmonary embolism six weeks after onset of symptoms.

At autopsy all heart chambers were considerably dilated and the left ventricle was hypertrophied. The heart weighed 830 Gm. There was moderate fusiform dilatation of the ascending aorta with enlargement of the aortic ring. There were no abnormalities of the endocardium, valves or coronary arteries. Areas of fibrosis were noted throughout the myocardium. Microscopic examination revealed hypertrophy of the cardiac muscle fibers with small areas of focal necrosis and conspicuous interstitial fibrosis. There was increased

---

(8) Brit. M. J. 2:81-84, July 14, 1951.
(9) Lancet 1:1387-1392, June 30, 1951.
(1) Am. Heart J. 42:814-825, December, 1951.

carmine, red-pink; (3) toluidine blue, metachromatic; (4) crystal violet, dark purple; (5) phosphotungstic acid hematoxylin, pale yellow-orange; (6) van Gieson, orange-red.

Clinical Implications of Marfan's Syndrome are reviewed by Arthur Alan Fischl and Jack Ruthberg[7] (New York City). Numerous organs are usually involved. Fingers and toes are long and tapering, the arms may reach to the knees and webbing of fingers is common. Subcutaneous fat is reduced, giving the impression of malnutrition. Patients are usually "double jointed," owing to relaxation of ligaments. The ears are pointed, the palate arched and a peculiar mournful facial expression is caused by the long drooping jaw and thin face. Kyphosis, scoliosis and sternal deformities as well as lung malformations may contribute to the high incidence of pneumonia, a common cause of death. Secondary sex characteristics develop poorly and the basal metabolic rate is low. Mental retardation is rare. Bilateral dislocation or subluxation of the lens is present in half the cases; the pupils dilate poorly with atropine and show iridodonesis. Congenital cardiovascular anomalies such as intra-auricular septal defects and coarctation or aneurysm of the aorta are common.

Few autopsies have been reported. Of three cases presented by the authors, in patients aged 21-32, one was autopsied. In the eye there was round cell infiltration of the optic head and choroid, intact retina, atrophic ciliary body with hyalinization of ciliary processes and subluxated lens and a normal filtration angle. The heart was soft and flabby, hypertrophic and enormously dilated; there was a saccular aneurysm beginning at the base of the aorta. An aortic coarctation was seen just beyond the left subclavian artery; at this point the ductus arteriosus was a fibrous cord. Microscopically, there were fatty degeneration of the myocardium and disorganization of the elastica of the aorta. Foci of necrosis and degeneration and some cystic areas were noted at the aneurysm. There were passive congestion of liver, spleen and kidney, a dermoid cyst in one ovary and chronic salpingitis.

[This and the succeeding articles focus attention on this peculiar syndrome; exactly what constitutes the syndrome as now interpreted is difficult to envision. For example, arachnodactyly may refer to the condition of the extremities and, in some instances, may merely indicate a long, slender person. The idea that, whatever it is, it is associated with congenital cardiovascular anomaly is not borne out by these reports of other torms of cardiovascular disease.—Ed.]

(7) J. A. M. A. 146:704-707, June 23, 1951.

diagnosis in only 3. Aneurysms were found in the ascending arch in 14, descending arch in 3 and dissecting aneurysm in 8 patients. In four instances with gross evidence of aneurysmal dilatation or dissection there was no histologic report of the aortic wall. The remaining 11 with aneurysms presented histologic evidence of aortic media malformation. Fairly definite evidence of rheumatic valvular disease and/or endocarditis was described in 10 autopsy reports.

Nonspecific Pericarditis: Fatal Case. Malcolm C. McCord and James T. Taguchi[2] (Veterans' Admin. Center, Dayton, Ohio) believe that anticoagulant therapy may have contributed to death.

Man, 52, was in good health until 36 hours before hospitalization, when he had severe pain under the upper half of the sternum which subsequently spread to the entire retrosternal area and radiated to the back of the neck, left shoulder and down the left arm to the wrist. When hospitalized, he was acutely ill and apprehensive. Temperature was 98.8 F., pulse rate 84, respiratory rate 28 and blood pressure 100/75. There was neither cyanosis nor pallor. White cell count was 14,600, with 75 per cent polymorphonuclear leukocytes. On the 3d hospital day a harsh pericardial friction rub was heard over a wide area at the base of the heart. Supraventicular tachycardia developed on the 4th day, but responded to oral administration of quinidine. Subsequently an ECG showed a minimally elevated S-T segment in lead I, notching of the T waves and pronounced clockwise rotation of the heart. On the 12th day there was recurrence of chest pain, similar to that present on admission. Blood pressure was 94/70. He appeared to be in shock, was cyanotic, had cool extremities and was perspiring and anxious. After intra-arterial transfusion, cyanosis disappeared and blood pressure returned to measurable levels. By the 16th day, blood pressure was 106/90, but he removed the oxygen tent, walked across the hall to the washroom, collapsed and died immediately.

At autopsy the pericardium was dark purplish red; on incision, about 150 ml. free blood was found in multiple loculated areas in the pericardial cavity. The pericardium was greatly thickened and the visceral and parietal layers were densely adherent except in the loculated areas. When the parietal pericardium was peeled away, a shaggy, fibrinous, hemorrhagic surface was seen. The myocardium was of normal thickness, consistency and color. Cardiac valves and endocardium were normal. The coronary arteries were thin walled, smooth and patent. Microscopically, there was a heavy fibrinous deposit on the visceral pericardium which enmeshed many clumps of red cells. A heavy infiltrate of lymphocytes and an occasional polymorphonuclear leukocyte were present. There was proliferation of fibroblastic tissue into the fibrin and clotted blood. Cultures of the

(2) A.M.A. Arch. Int. Med. 87:727-731, May, 1951.

pericardial exudate showed no growth and a guinea pig inoculated with the material and killed two months later showed no evidence of tuberculosis. Acute nonspecific pericarditis was diagnosed.

The difficulty in differentiating nonspecific pericarditis from acute myocardial infarction is clearly shown in this case.

[Although it may be true that anticoagulant therapy played a part in the death of this person, it may also have played a part in the lesion described. At autopsy on another case, reported by M. Pomerance, E. Perchuk and J. B. Hoffman (A fatal case of idiopathic pericarditis, New York J. Med. 52:95-97, Jan. 1, 1952), acute inflammation was found in the epicardium and, to a lesser extent, in the myocardium. This does not accord with the description given here. There is no real certainty that it was idiopathic pericarditis. Four cases of acute benign pericarditis were reported by O. F. Rosenow and C. J. Cross (A.M.A. Arch. Int. Med. 87:795-807, June, 1951). Emphasis is placed on interpretation of the electrocardiogram, and the authors suggest that a preceding viral disease may be important in the etiology. Of additional interest is the paper by R. C. Parker, Jr., and H. R. Cooper (Acute idiopathic pericarditis, J. A. M. A. 147:835-839, Oct. 27, 1951), who had the opportunity of studying 22 patients, all of whom recovered. They outline the clinical manifestations and electrocardiographic records. They point to the benign but often relapsing course. They also indicate the likelihood of preceding acute upper respiratory infections. Of importance is the part which angiocardiography may play in differentiating between dilatation of the heart and pericardial effusion. Only with precise clinical diagnosis can the effectiveness of antibiotics be determined.—Ed.]

Histochemically Demonstrable Glycogen in Human Heart: Special Reference to Glycogen Storage Disease and Diabetes Mellitus. Robert W. Mowry and Raymond Bangle, Jr.[3] (Boston City Hosp.), stained glycogen in sections of heart by the periodic acid-leukofuchsin method. As a control, one of duplicate sections was treated with diastase digestion just before the staining procedure. Glycogen was identified in the myocardium as deep purplish red granules, usually concentrated on one side of the muscle fiber. Blocks from infants were fixed in absolute alcohol. Hearts of adults were fixed in a Formalin-alcohol mixture. Sections were graded according to the amount of glycogen present.

In 19 of 33 unselected infants, considerable glycogen was present in the myocardium, 6 having an amount equal to that in 2 patients with glycogen storage disease studied under similar conditions. Three of the six infants had cardiac hypertrophy. No cause could be found in two. Infants under 8 months showed more glycogen than older ones. No sex difference was apparent. The interval between death and autopsy, up to 12 hours, did not affect the amount of demonstrable glycogen.

(3) Am. J. Path. 27:611-625, July-Aug., 1951.

In the hearts of 63 nondiabetic adults, relatively little glycogen was found. Patients with myocardial infarction were avoided as it has been shown that such areas contain an excess of glycogen. Eight of 17 hearts from diabetic adults showed increased glycogen content, but amounts varied more widely than in the nondiabetic group. No relation was apparent be-

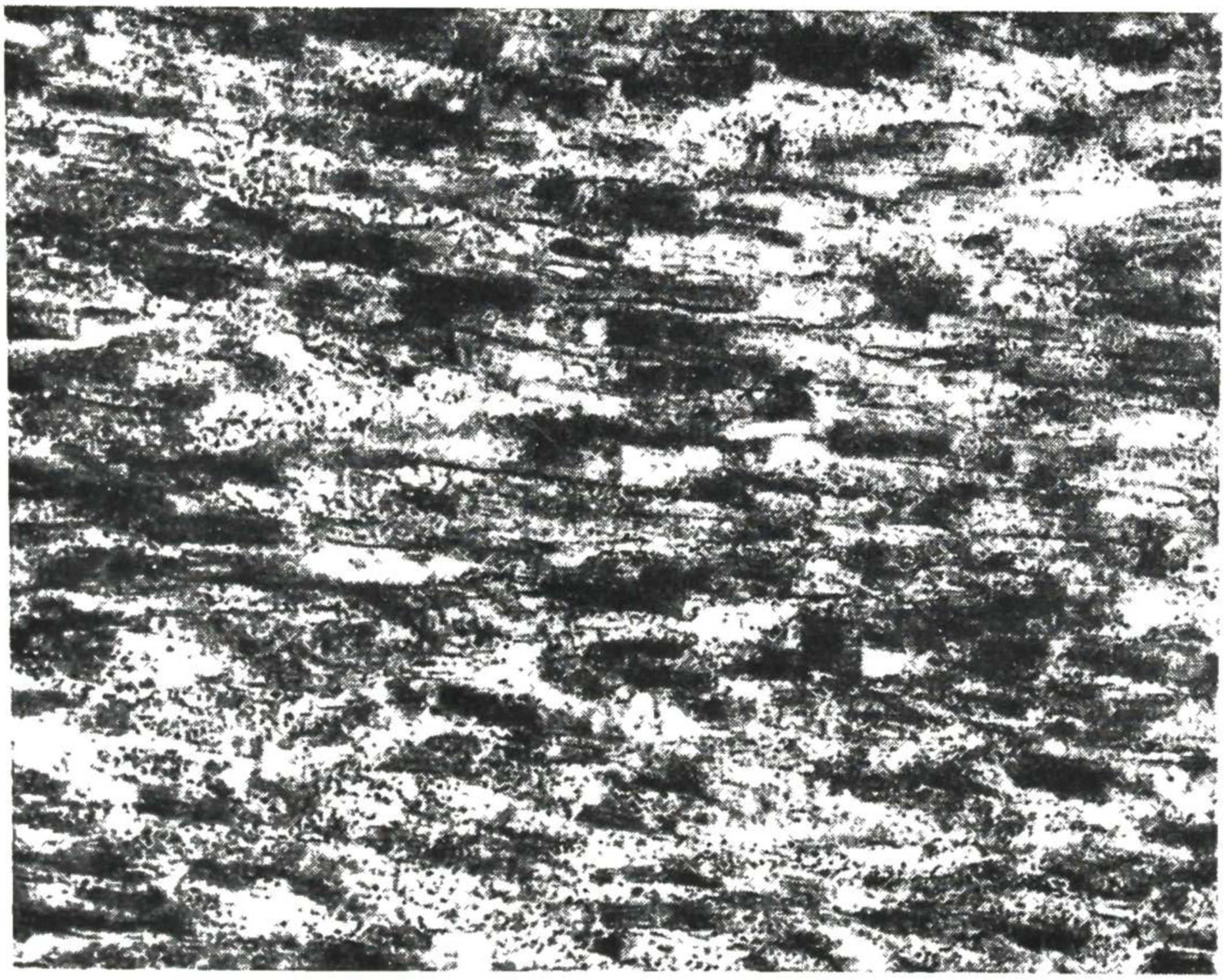


Fig. 27.—Myocardium of diabetic patient showing diffusely distributed glycogen. Periodic acid-leukofuchsin, without nuclear counterstain; reduced from × 300. (Courtesy of Mowry, R. W., and Bangle, R., Jr.: Am. J. Path. 27:611-625, July-Aug., 1951.)

tween the quantity of glycogen and severity, duration or treatment of diabetes. The interval between death and autopsy was of some importance in both groups, a decline in incidence and amount of demonstrable glycogen being observed with increasing time. Postmortem disappearance of glycogen in some cases was probably related to initial concentration.

Extensive glycogen infiltration of the adult heart seems confirmatory, if nonspecific, evidence of diabetes mellitus (Fig. 27). There is no indication that the presence of excess glycogen in the adult myocardium alters the function or size of the heart. Extensive glycogen infiltration of the heart is common

in infants. Whatever the mechanism controlling concentrations of myocardial glycogen in infancy, it has no definite relation to the factors that produce cardiac enlargement. Demonstration of abundant glycogen in infant hearts showing idiopathic hypertrophy does not justify the diagnosis of glycogen storage disease.

Heart in Hemochromatosis. Harold W. Keschner[4] (Veterans' Admin. Hosp., Coral Gables, Fla.) studied the clinical, pathologic and chemical changes in the hearts of 11 patients with hemochromatosis, including 2 with exogenous hemochromatosis or siderosis. Inorganic iron determinations were performed on the myocardium of the left and right ventricle of all 11 hearts. Control studies on five normal hearts showed the average iron content of the left ventricle to be 38.3 mg. and of the right ventricle 33.5 mg./100 Gm. dry tissue. The iron content of the myocardium of the patients with hemochromatosis was 2-19 times normal. Two of the 11 patients showed an increase of 10-18 times normal; in one there was a greater amount of iron in the right than in the left ventricle. The iron content of one patient with terminal heart failure did not exceed normal. In four of seven patients without significant cardiac symptoms, the iron content varied from 8 to 19 times normal. The highest values in the myocardium was found in the case of transfusional siderosis.

Various degenerative changes of the cardiac muscle were associated with a high iron content. These included disproportion of sarcoplasm to myofibrils, fragmentation and separation, pigmentation of fibers, fiber hypertrophy, nuclear displacement, pyknosis and karyorrhexis, cloudy swelling and vacuolar and hydropic degeneration. Fibrosis in varying degrees of severity was present in 9 of the 11 hearts. There was no significant correlation between the degree of fibrosis and extent of iron pigmentation. With Gömöri's method for demonstration of iron, reacting pigment appeared as fine, blue, dustlike particles and coarse blue granules. With hematoxylin-eosin, these appeared as golden brown and large, irregular, granular brown pigment.

Hemosiderin appeared to be laid down in a bipolar spindle-shaped formation around the nucleus, spreading longitudinally through the muscle fibers. Hemosiderin in connective tissue

(4) South. M. J. 44:927-931, October, 1951.

was scant. The histologic changes in exogenous siderosis were no different from those in the other cases in the series.

It is conceivable that cardiac disturbances due to chemical or physiologic changes might result from excessive iron storage in the myocardial fibers.

[Attention is called to the paper by Althansen *et al.* (A.M.A. Arch. Int. Med. 88:553-570, November, 1951) on hemochromatosis; this is a study of 23 cases from which several conclusions of interest are drawn. Exogenous toxins, alcohol, malnutrition, deficiency of protein or of vitamin B complex are ruled out as causes, but it is suggested that a constitutional factor may have an etiologic role. Excessive intestinal absorption of iron seems to be important, but changes in liver and pancreas may be responsible, and the possibility that all three may have a common cause is not excluded. Clinically, the hepatic cirrhosis appears to be relatively benign. They claim that the color of the skin is the result of thinning of the epidermis so that increased amounts of melanin in the basal layers become evident. This may well be true, but is not in accord with other reports that iron is demonstrable in the corium.—Ed.]

Myocardial Changes Following Shock. George W. Melcher, Jr., and William W. Walcott[5] (Columbia Univ.) produced shock in dogs by a variety of technics. In 22 of 29 surviving animals, significant lesions were found in the heart. In the seven without specific changes, shock was produced by different means, including various types of hemorrhagic shock, sublethal hemorrhage with stimulation of the sciatic nerve, traumatic shock and subcutaneous injection of histamine.

The earliest myocardial change, occasional muscle fibers showing loss of striation and deeply eosinophilic cytoplasm, was seen 24 hours after shock. The nuclei were often hyperchromatic and pyknotic. Two to seven days after shock, lesions were seen grossly in the form of scattered yellowish or gray areas in the myocardium. Most often, they were beneath the endocardial surface and in the papillary muscles. On cut section the foci appeared greasy and bulged above surrounding cardiac tissue (Fig. 28). Microscopically the muscle fibers were necrotic and surrounded by an inflammatory exudate of histiocytes, lymphocytes, plasma cells and occasionally polymorphonuclear leukocytes. Inflammation was most pronounced five days after shock; then it rapidly subsided. In sudan III preparations the focal myocardial lesions showed a large amount of lipoid-staining material. It appeared as finely dispersed droplets evenly distributed in the swollen muscle fibers. The fatty change was limited to single cells or small groups of

(5) Am. J. Physiol. 164:832-836, March, 1951.

adjacent fibers. The maximal amount of lipoid-staining material was seen three to five days after shock. It had entirely disappeared by the seventh day. In animals killed 10-14 days after shock, gross examination revealed whitish gray, linear streaks in the myocardium. Microscopically, occasional single muscle fibers or groups were surrounded by a few plasma cells, lymphocytes and giant cells of the foreign body type.

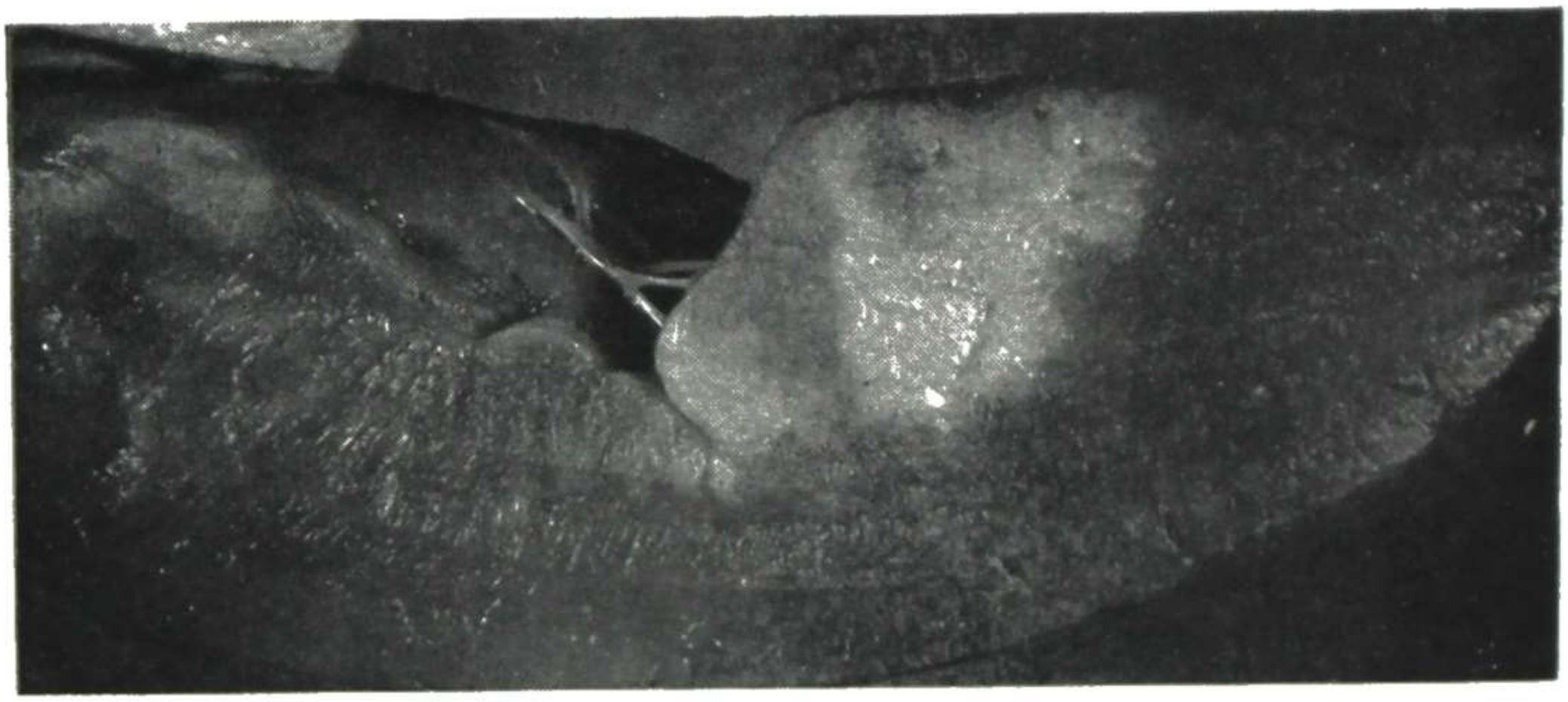


Fig. 28.—Papillary muscle of left ventricle of dog killed five days after induction of shock by bleeding. Almost entire muscle involved by fatty process. (Courtesy of Melcher, G. W., Jr., and Walcott, W. W.: Am. J. Physiol. 164:832-836, March, 1951.)

Mixed with the necrotic myocardial fibers were fine granules of material stained pale blue which resembled calcium. No definite lesions were seen grossly in animals surviving longer than 21 days.

The pathologic changes in the myocardium were attributed to shock. Animals that died during shock did not show similar lesions. The actual mechanism of production is obscure. The most likely explanation is hypoxia secondary to reduced coronary blood flow. If anatomic changes can be produced in shock, important functional alterations may occur which would affect the outcome in some instances.

[This and the following article emphasize the importance of the heart in shock. Heretofore several authors, on physiologic grounds, have indicated that cardiac disorder is of basic importance. However, the other phenomena, such as hemoconcentration, will have to be fitted into this concept in some satisfactory manner.—Ed.]

Studies on Metabolism of Cardiac Muscle from Animals in Shock. Walter J. Burdette[6] (Louisiana State Univ.) produced shock in rats by hemorrhage and application-release of tourniquets. The animals were killed in one to six hours and

(6) Yale J. Biol. & Med. 23:505-514, June, 1951.

hearts were rapidly removed. Myocardial glycogen, oxygen consumption, respiratory quotient, lactic and pyruvic acid values were determined in the Warburg apparatus before and after shock. The effect of potassium reduction and sodium iodoacetate on oxygen consumption was estimated.

Glycogen content expressed as milligrams of glucose/100 Gm. tissue decreased in both the heart and gastrocnemius muscle following shock. Average myocardial pyruvic acid levels were increased after shock. Lactic acid content of the heart was slightly increased in shock from hemorrhage but not significantly changed in animals to which the tourniquet was applied. No significant difference in average oxygen consumption of tissues of shocked and control groups could be detected. Presence of 0.25 mM. sodium iodoacetate in the medium was associated with a diminution of oxygen consumption in hearts of both shocked and control rats. The respiratory quotient of the hearts of shocked rats was slightly diminished. Glycolysis was increased in treated animals calculated from these data.

Metabolism of heart muscle is altered by shock. The condition of the myocardium is a factor in determining the outcome of shock; this probably becomes significant only after prolonged shock. Anoxia may account for the effect of shock on the myocardium, associated with a decrease in glycolysis.

The increased pyruvic acid content of the myocardium in shock may indicate that anoxia interferes with the tricarboxylic acid cycle of carbohydrate metabolism. Oxygen consumption is increased in shock; this was prevented by sodium iodoacetate. Addition of glucose to the myocardial substrate of the shocked and control groups was associated with increased glycolysis. The respiratory quotient was elevated after addition of glucose only in the shocked group. Lactic acid addition was associated with an increased respiratory quotient only in the controls. This suggests that utilization of glucose increases and lactic acid decreases in shock.

Reduction of potassium concentration had no consistent effect on oxygen consumption of either group. This may indicate that the effect of oxygen consumption of cardiac muscle is not due to elevated levels of potassium in the blood.

Fatal Myocardial Sarcoidosis. Raymond Yesner and Marvin Silver[7] (Veterans' Admin. Hosp., Newington, Conn.) re-

(7) Am. Heart. J. 41:777-785, May, 1951.

port the first death of a white man due to myocardial sarcoid. The eight previously reported deaths were in Negroes.

Man, 51, had a chronic cough in 1946. Chest x-rays showed bilateral hilar adenopathy, widening of the superior mediastinum and linear infiltration of the right lower lobe. The heart silhouette was normal. In 1949 he was hospitalized because of congestive failure, which responded to the usual treatment. About four months later he returned with severe congestive failure which did not respond to treatment and resulted in death.

At autopsy the pleural surfaces of both lungs were studied with tiny pink-gray nodules. Nodules were palpable throughout both lungs. The mediastinal lymph nodes were enlarged, firm and rubbery, with complete loss of architectural pattern. The heart was enlarged and throughout the myocardium there were numerous small, gray-white, discrete, irregular areas averaging about 4 mm. in diameter. The pleural and mediastinal nodules were cultured and injected into guinea pigs with negative results. Microscopically, there were widespread granulomas in the lungs, heart, lymph nodes, spleen, liver, pancreas and thyroid. Early lesions consisted essentially of epithelioid and multinucleated giant cells, some of which contained inclusion bodies similar to those described by Schaumann. No significant central necrosis was noted. Older lesions consisted of completely hyalinized, collagenous connective tissue. Both types were found in the myocardium, extending from endocardium to epicardium, but they were more irregular in outline and lacked sharp collagenous delineation. In the lung, alveolar septa and peritruncal fibrous tissue were thickened due to the healing of sarcoid granulomas. In the spleen there was thickening of the septa. In the liver, conspicuous increase in portal fibrous tissue suggested that sarcoid may be a possible cause of cirrhosis.

Role of Small Coronary Branches in Pathogenesis of Myocardial Infarction. The main branches are usually considered to be involved in myocardial infarction, but S. Hirsch[8] (Univ. of Brussels) believes that the smaller ones, acting as arteriovenous fistulas (which have been demonstrated histologically), play a major role. These glomus-like structures contain many polyhedral cells surrounding the lumen, which have been shown in certain species to secrete acetylcholine, and they are richly supplied with nerve fibers. One hundred rats which were submitted to severe emotional shocks by means of faradic currents showed, after 24 hours, considerable stasis in the myocardial capillaries and, in certain areas, periarterial infiltration and intimal lesions. Two to three days after the shock, modifications of muscle fibers and gradual evidence of their destruction appeared.

The role of the small vessels may explain the apparent

(8) Acta med. scandinav. 88:449-456, 1950.

divergence of autopsy findings in angina and infarction. The results of this experiment agree strikingly with those obtained by Selye; both suggest the theory that myocardial infarction is often an adaptation disease and angina an alarm reaction. Attention to stress due to psychic, toxic or allergic factors may therefore be more profitable than consideration of coronary pathology.

Mural Coronary. The anterior interventricular groove of the heart usually provides a shallow bed for the left descending anterior coronary artery. When there is a narrow inter-

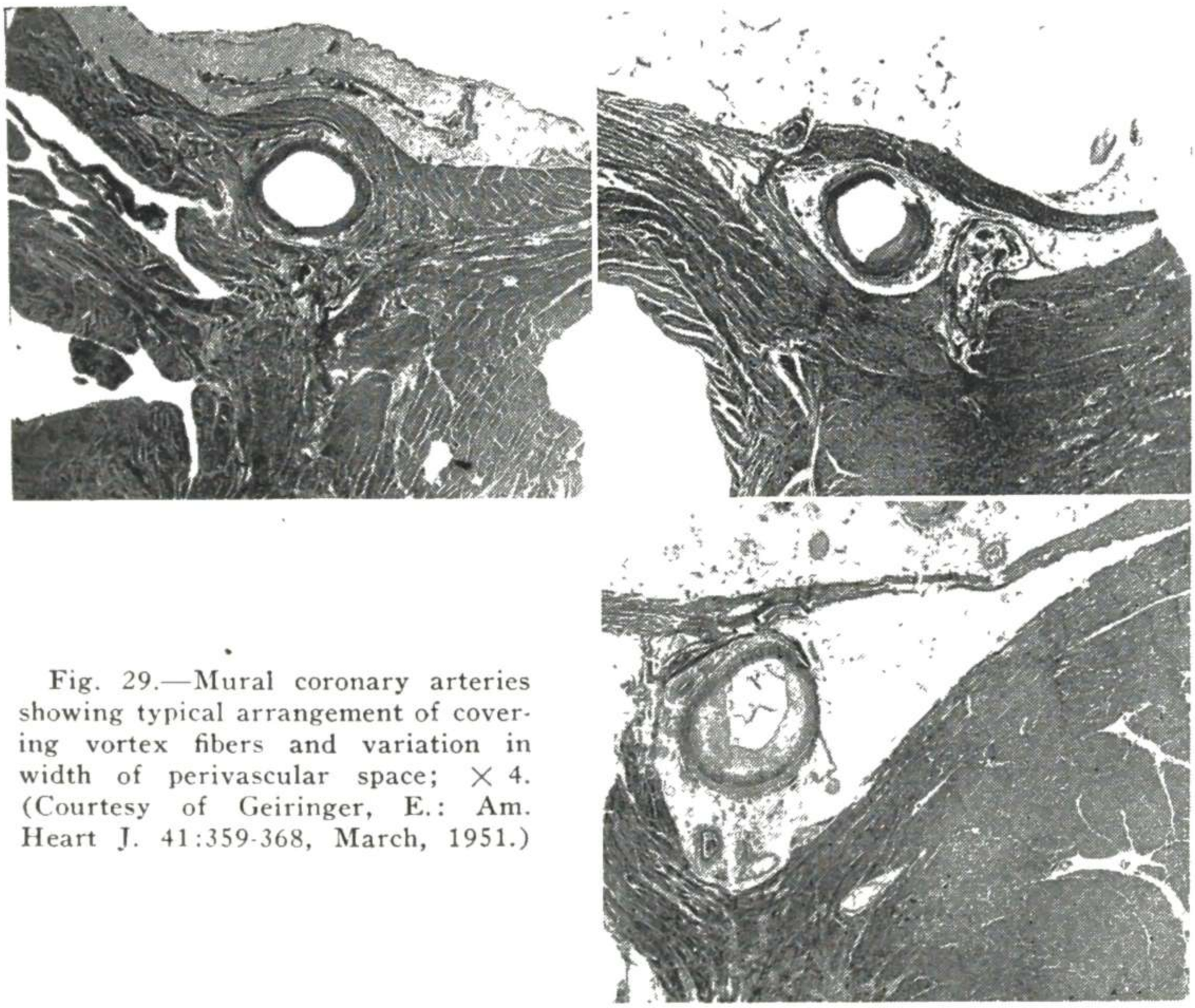


Fig. 29.—Mural coronary arteries showing typical arrangement of covering vortex fibers and variation in width of perivascular space; × 4. (Courtesy of Geiringer, E.: Am. Heart J. 41:359-368, March, 1951.)

ventricular groove the myocardium may be folded over the artery so that, although still epicardial in a strictly anatomic sense, it is intramuscular from a physiologic standpoint. E. Geiringer[9] (Edinburgh Univ.) classifies this type of artery as mural. Of 100 unselected patients examined at autopsy, 23 had gross evidence of this variation. The distance for which the vessel remained buried in the heart muscle varied from 5 mm. upward, and the intramuscular stretch was interposed at

(9) Am. Heart J. 41:359-368, March, 1951.

any part of its course. Microscopically the covering fibers were seen to run at right angles to the course of the vessel and to belong to the superficial layer of the myocardium, the so-called vortex fibers (Fig. 29). The perivascular space separating the muscular investment from the adventitia was narrow or very wide. There was no significant age or sex incidence.

To determine whether the muscular investment had any effect on the arterial wall, 100 paraffin sections of the upper third of the left anterior descending coronary branch of unselected consecutive patients were examined. Analysis showed that at the same age and sex, in hearts of the same weight, an epicardial left anterior descending artery of the same lumen as a corresponding mural branch tends to have a considerably thickened intima. Mural stretches of the artery were affected only rarely by atherosclerosis, whereas in comparable epicardial stretches this was common.

The effect of a myocardial investment is to reinforce the muscular action of the media. Others have shown that the effect of muscular contraction on an intramuscular artery is to open up the lumen and facilitate blood flow. Apparently intimal hyperplasia, being an internal buttressing effort against overdistention, becomes superfluous when external buttresses in the form of a muscular investment are provided. In such cases the lower incidence of atheroma is not surprising.

Comparison of Clinical and Pathologic Aspects of Coronary Artery Disease in Men of Various Age Groups: Study of 950 Autopsied Cases from Armed Forces Institute of Pathology is reported by Wallace M. Yater, Paul P. Welsh, John F. Stapleton and Mardelle L. Clark.[1] The patients were mainly male soldiers. Average age was 43.2; 68 per cent were 30.6-55.8. Negroes comprised 4.1 per cent of the group, and analysis showed that the disease occurs less often in Negroes than in white men.

The commonest site of gross myocardial infarcts in all age groups was the anterior wall of the left ventricle. This location was more frequent in the 18-29 age group than in the others. This would be expected since the left anterior descending artery alone was occluded most often in that group. Infarcts located in the apex and interventricular septum com-

(1) Ann. Int. Med. 34.352-392, February, 1951.

bined were also commoner in the youngest group. With age, there was increase in involvement of the anterior third of the interventricular septum alone and of the apex alone, in infarcts of the posterior wall of the left ventricles, and in occlusion of the right coronary and left circumflex arteries. Infarcts in other locations were relatively uncommon.

Although in 13 per cent of the cases only moderate narrowing of the lumens due to thickening of the coronary artery walls was reported, myocardial infarcts were noted in about 25 per cent, which suggests that more careful examinations might have revealed sclerotic or thrombotic occlusion of the vessels. Almost complete sclerotic occlusion alone of some part of one or more coronary arteries was found in 39 per cent; thrombotic occlusion alone in 23 per cent, and both sclerotic and thrombotic occlusion in 25 per cent. The left anterior descending artery was the one most frequently affected by all types of occlusion. Involvement of this artery alone decreased with age.

There were no gross myocardial infarcts in 61 per cent of the patients. Death without known occlusion of the coronary arteries occurred significantly more often in men without gross myocardial infarcts than those with infarcts. Mural thrombi in men with myocardial infarcts were commoner at age 50 and over (56 per cent). Rupture of the heart was about twice as common in men over 50 as in those under 40. Incidence of ventricular aneurysm increased from 12 per cent in those under 40 to 21 per cent in those over 50.

The number of associated lesions in all systems or organs increased with advancing age, particularly in men 50 or over.

[This is a brief condensation of the material in the original paper, to which interested readers are referred.—Ed.]

Thrombotic Thrombocytopenic Purpura: Disseminated Disease of Arterioles. Gordon C. Meacham, J. Lowell Orbison, Robert W. Heinle, Howard J. Steele and J. Alpert Schaefer[2] (Western Reserve Univ.) report clinical and pathologic observations in two patients with hemolytic anemia, thrombocytopenic purpura and arteriolar occlusions.

Case 1.—Woman, 54, had discoid lupus for 10 and hypertension for 4 years. Progressive anemia and icterus developed, with albuminuria, hematuria, leukocytosis, increased fragility of the erythrocytes and prolonged bleeding time. Clotting time was 7 minutes,

(2) Blood 6:706-719, August, 1951.

platelet count 17,280/cu. mm.; there was no clot retraction in 24 hours. The bone marrow showed erythrogenic hyperplasia with increased megakaryocytes but no platelet formation.

She died during splenectomy. Autopsy disclosed focal hemorrhages of the serosal and mucosal surfaces. The heart weighed 400 Gm. Microscopically there was widespread occlusion of arterioles, most frequent in the myocardium, adrenal, esophagus and lymph nodes. A few such lesions, found in the lungs, skin, skeletal muscle and spleen, appeared as amorphous granular eosinophilic material adherent to or continuous with the arteriolar wall. Their amorphous substance replaced part of the wall, and often the entire wall was thin and vaguely outlined. Elastic tissue and smooth muscle could not be demonstrated. Some of the occluded vessels presented an endothelial-lined crescent slit as the only remains of the lumen. Fibrin could not be demonstrated in the occlusive masses by phosphotungstic acid—hematoxylin stain. The mass and involved vessel wall gave a positive periodic acid Schiff reaction.

Case 2.—Woman, 43, had severe anemia, normal leukocytic picture and decrease in the platelets as estimated from the blood film. The bone marrow showed erythroid hyperplasia; megakaryocytes were normal in number and appearance. Splenectomy was performed for spherocytic hemolytic anemia. The spleen (500 Gm.) showed multiple old and recent infarcts. After operation, anemia improved. Three months later, blood pressure was 190/130. Three years later she had leukocytosis, platelet count of 59,000 cu.mm., mild anemia and myeloid hyperplasia of the bone marrow. Clot retraction was negative in 24 hours. There was temporary improvement after ACTH therapy with rise in platelet count. Relapse slowly developed during ACTH treatment.

Autopsy revealed numerous hemorrhages of all organs. One large hemorrhage of the brain measured $3 \times 3 \times 2$ cm. Several old infarcts occupied large areas of the cerebrum. The heart weighed 480 Gm. and the endocardium of the mitral leaflets and around the foramen ovale presented several fibrinous vegetations. Microscopically, there was widespread occlusion of the arterioles and small arteries by a process similar to that in Case 1. Serial sections disclosed in some instances that the material occluding the vessel lumen was continuous with similar accumulations located in the subintimal level. The occluded vessels were prominent in the cerebrum, leptomeninges, myocardium and spleen. In addition, there was a diffuse interstitial nephritis and moderate arteriolar nephrosclerosis.

Healing was sometimes observed (Fig. 30). In some instances, the occlusion contained numerous small mononuclear cells, but collagen formation was absent. Multiple aneurysms of the arterioles and precapillaries containing both the amorphous material and masses of proliferated endothelial cells were seen. Thrombopenia in this condition may not result from deposition of large numbers of platelets in occluded vessels but rather from some process similar to that producing

idiopathic thrombocytopenic purpura. Although platelets and the material occluding the lumen show similar staining reactions, there is no positive evidence that they are the same. The location of the material suggests that it arises within the ves-

Fig. 30.—Case 2. Section of healed occlusion in meningeal arteriole; reduced from × 255. (Courtesy of Meacham, G. C., *et al.*: Blood 6:706-719, August, 1951.)

sel wall, not within the lumen. Evidence is presented that the primary vascular lesion is a degenerative process in the arteriolar and capillary walls, rather than thrombus formation in the lumen of the vessel.

Aneurysms of Sinuses of Valsalva. G. R. Venning[3] (Cardiff, Wales) reports seven cases. One lesion appeared to be congenital, two were possibly congenital with superimposed endocarditis and four were due to endocarditis.

Case 1.—Man, 56, with progressive heart failure, gave no history of rheumatic fever or syphilis. He had collapsing pulse and

(3) Am. Heart J. 42:57-69, July, 1951.

blood pressure of 260/105. A continuous loud murmur was heard in the third and fourth interspaces at the left border of the sternum, associated with a systolic thrill. X-ray examination showed a large heart with prominent pulmonary arteries and expansile pulsation of the small intrapulmonary branches. The diagnosis was thought to be a communication between the aorta and right atrium. At autopsy the heart weighed 710 Gm. Both ventricles were hypertrophic. The right atrium was dilated. An aneurysm originated from the right coronary sinus of Valsalva and opened into the right atrium.

CASE 2.—Woman, 55, had progressive cardiac failure. Autopsy revealed bicuspid pulmonary and aortic valves. Bacterial endocarditis involved the aortic valve and had destroyed the posteroinferior portion of the larger (posterior) cusp. The sinus of Valsalva related to this cusp was in communication with a cavity 3 cm. in diameter in the membranous septum. An opening at the top of the cavity led into the left ventricle. The aneurysm bulged into the transverse sinus of the pericardium and into the conus arteriosus just below the bicuspid pulmonary valve. It bulged slightly into the right atrium above the septal cusp of the tricuspid valve where there was a small opening into the right atrium. Both openings were lined with vegetations. Thick fibrous tissue containing calcium deposits lined the aneurysmal wall. Calcium was also present in the aortic cusps. These findings indicate that the aneurysm in the membranous septum preceded the endocarditis. The associated bicuspid pulmonary and aortic valves suggested a congenital origin.

CASE 3.—Man, 64, died in congestive failure, with manifestations of infective endocarditis of the aortic valve. At autopsy the heart weighed 540 Gm. Both ventricles and the left auricle were dilated and hypertrophic. The aortic valve was distorted by calcareous deposits. From the right sinus of Valsalva a small aneurysm extended into the left ventricular wall just anterior to the pars membranacea septi. It was filled with blood clot. Histologically there was an acute inflammatory reaction around the thick fibrous wall. Calcification was associated with the aneurysmal wall as well as being present in a branch of the coronary artery which appeared to open into the sac.

Correct diagnosis of congenital and uncomplicated acquired aneurysm of the sinus of Valsalva is unlikely to be made during life unless rupture into one of the heart chambers brings about alteration in hemodynamics. Expansile pulsation of small pulmonary arteries makes fluoroscopy of value.

Congenital aneurysm of the right coronary sinus of Valsalva has been considered due to failure of the proximal and distal bulbar swellings to fuse in the embryo, which results in a fistula between the aorta and right ventricle. Aneurysms of the left sinus would be impossible if this were the only explanation. Congenital aneurysms may also result from a defect in formation of elastic tissue in the aorta, which occurs later in fetal development than does fusion of the bulbar swelling.

Special Article

STUDIES ON THE PATHOGENESIS OF ARTERIAL LESIONS*

By Russell L. Holman

The large number of papers published by Dr. Holman cannot be reviewed in this volume. So that the topic would be adequately discussed, Dr. Holman kindly consented to write this special article. We are indeed grateful to him.—Ed.

Obscurity shrouds the etiology and pathogenesis of most forms of arterial lesions. Current studies are concerned with the role of various substances in the circulation—cholesterol, lipoproteins, antibodies and hormones—that might affect the integrity of the arterial wall under normal or altered blood pressure. This unsettled state of our knowledge is briefly reviewed in the light of our experimental studies during the past 12 years. No attempt is made to review the voluminous literature on the subject.[1]

Arterial lesions that closely resemble those of rheumatic arteritis and periarteritis nodosa in man have been produced with regularity in dogs by feeding a standard high fat diet for eight weeks or longer, then inducing standard renal insufficiency.[2-6] The standard diet—calf liver 32 parts, sugar 25 parts, starch 25 parts and lipid substances 18 parts—is essentially a high fat, low protein diet with 43 per cent of its caloric value derived from fat, 7 per cent from protein and 50 per cent from carbohydrate. The various lipid substances that have been bioassayed are summarized in Table 1.

This standard diet has been fed for over a year, and no predictable lesions in the arterial system have ever been observed without some damage to the kidneys. Standard renal insufficiency induced in dogs on regular kennel diet has not resulted in arterial lesions. The sequence of high fat diet followed by renal insufficiency has been essential. All control data indicate that only these two factors are involved.

Bilateral nephrectomy and heavy metal injury have proved

---

*From the Department of Pathology, Louisiana State University School of Medicine, and the Charity Hospital of Louisiana, New Orleans.

These studies have been supported by grants from The John and Mary R. Markle Foundation, The Life Insurance Medical Research Fund and The National Institutes of Health and have been carried out in collaboration with Willard C. Hewitt, Margaret Swanton, Mary Lou Rutledge, Joyce Hinson, Joseph H. McCormick, Henry C. McGill, Julius Muelling, Suzanne A. Dugas, Chester K. Jones, Philip L. Harris and Bland Giddings.

equally effective in precipitating typical arterial lesions in properly fed dogs, but bilateral ureteral ligation, despite the induction of comparable degrees of azotemia, phosphatemia, acidosis and clinical "uremia," has repeatedly failed to do so.[7] Ablation of a metabolic activity of the proximal convoluted tubules has been prerequisite for the development of typical

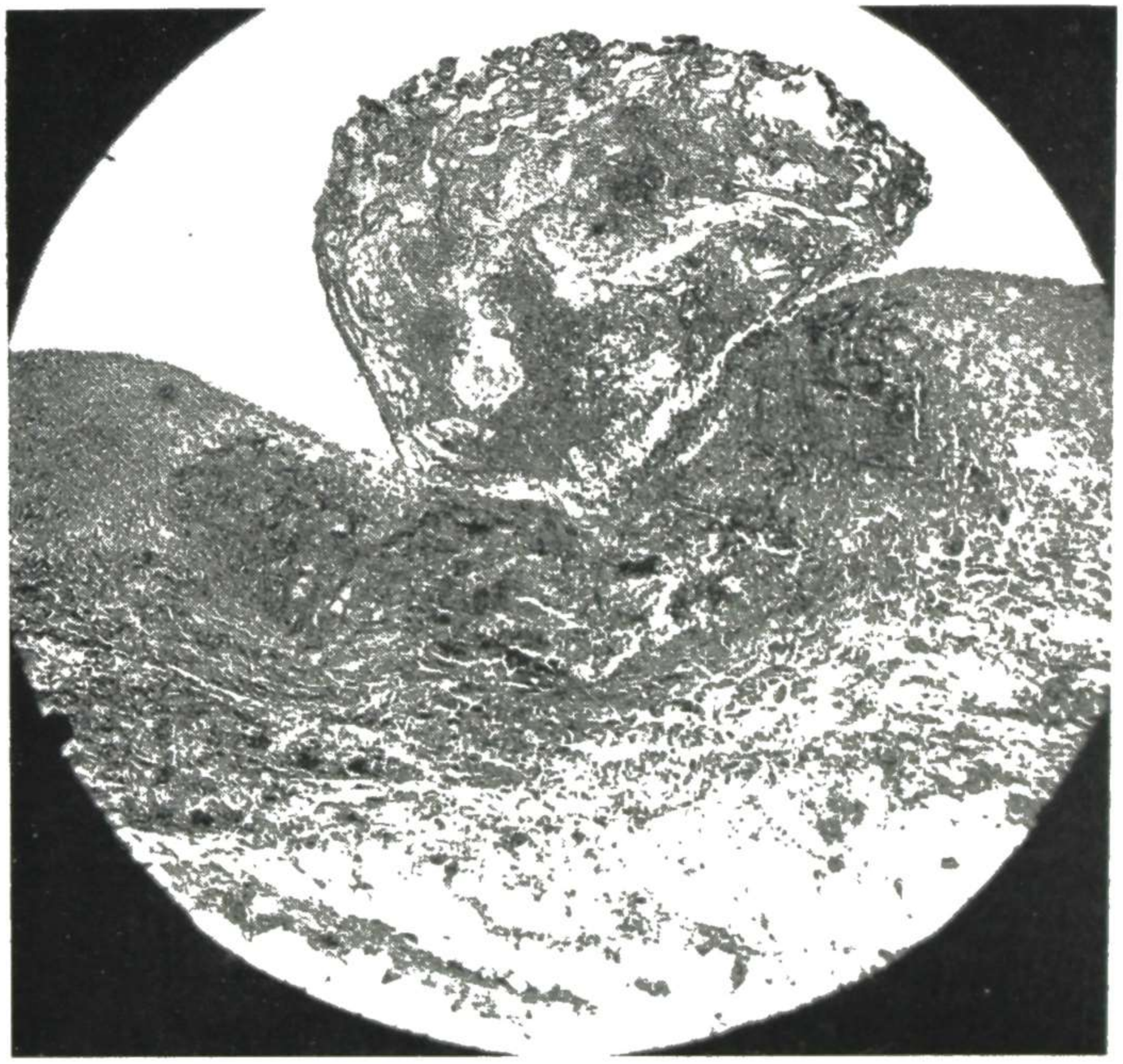


Fig. 31.—Acute necrotizing arteritis in an elastic artery; mouth of left subclavian artery. Pronounced disruption of musculoelastic framework with early aneurysmal outpouching is typical; thrombus formation on internal surface is exceptional. Hematoxylin-eosin stain; reduced from × 50.

arterial lesions. Concentration of this metabolic activity in the renal cortex has been indicated by the failure of damage to tissues and organs other than the kidney to produce arterial lesions in properly fed dogs.

The experimental problem has resolved itself into three parts: (1) the nature of dietary substance, (2) the renal factor, and (3) the pathogenesis of the arterial lesions.

All the data thus far accumulated have indicated "too much" of something in the diet, "too little" of something from

the kidneys, eight weeks of dietary toxicomponent and about eight days of renal insufficiency.

As can be seen in Table 1, certain samples of cod liver oil and all samples of creamery butter thus far tested have proved to be the most potent sources of dietary toxicomponent, and most of the chemical studies have been carried out on these two substances. The dietary substance has been shown to be relatively heat stable. It is not vitamin A or vitamin D. It

TABLE 1.—SUMMARY OF LIPID SUBSTANCES BIOASSAYED

Positive		Negative	
Animal		Animal	
Cod liver oil	45/62*	Lard	0/2
Cod liver oil†	42/43	Mutton tallow	0/2
Butter	20/20	Vegetable	
Shark oil	2/2	Corn oil	0/8
Sardine oil	1/1	Olive oil	0/2
Menhadin oil	1/4	Coconut oil	0/2
Vegetable		Cotton seed oil	0/2
Soy bean oil	2/4	Oleomargarine	0/4

*Number with typical arterial lesions/number in group.
†Excluding five inactive samples.

TABLE 2.—INFLUENCE OF VARIOUS EXPERIMENTAL PROCEDURES IN ARTERIAL LESIONS

Lesions aggravated by: Repeated injections of homologous plasma
Lesions unaffected by: Choline (50 mg./kg./day)
Lesions retarded or prevented by:

A. Physical	B. Chemical	C. Hormonal	D. Metabolic
Omission of toxicomponent for 1-4 weeks	Saponification Hydrogenation Antioxidants 1. Vitamin E 2. Diamylhydroquinone 3. Citric acid	Pregnancy Diethylstilbestrol Adenosine	Cholesterol

remains in the triglyceride fraction of lipase-treated butter.

Before the renal factor and the pathogenesis of the lesions are considered it is necessary to review briefly some of the experimental procedures that have influenced the incidence and appearance of the arterial lesions. These are summarized in Table 2.

Inactivation of the dietary toxicomponent by saponification and hydrogenation indicates that it is unsaturated fat acid. Prevention of the lesions by fat-soluble antioxidants such as vitamin E and diamylhydroquinone indicates that the oxidation or peroxidation of the unsaturated fat acid is the pathogenic mechanism.

Most of the data are consistent with the following hypothesis. Primary injury to the arterial wall is produced by the peroxidation of certain unsaturated fat acids. Normally this is prevented by fat-soluble antioxidants acting synergistically with one or more cofactors secreted by the proximal convoluted tubules of the kidney. Both citric acid and phosphoric

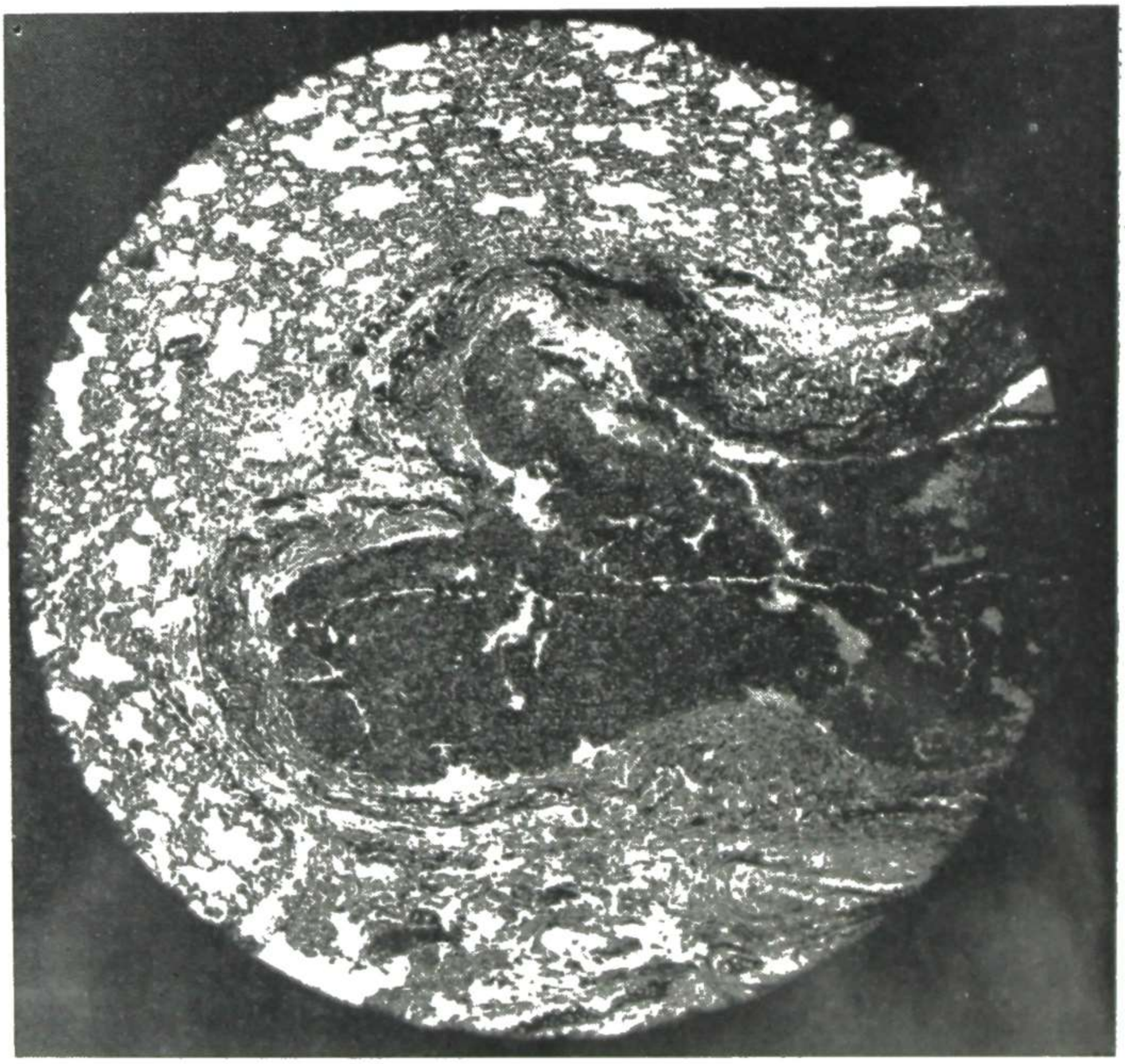


Fig. 32.—Acute necrotizing arteritis in a muscular artery; artery in lung. Extensive arteritis and periarteritis with early calcium impregnation of some of the necrotic elastic fibers. Hematoxylin-eosin stain; reduced from × 50.

acid are known to act synergistically with tocopherol and both are known to be formed by the kidney. Intravenous injections of sodium citrate have been shown to prevent the arterial lesions.[8] Adenosine triphosphate likewise prevented the arterial lesions, and this substance too is known to be formed in part by the kidney.[9] There must be multiple alternate metabolic pathways or safety valves by which this dietary toxicomponent may be diverted from the sites of vulnerability in the arterial wall. It is surprising that so many of these pathways lead from the kidney, but possibly this is the basis

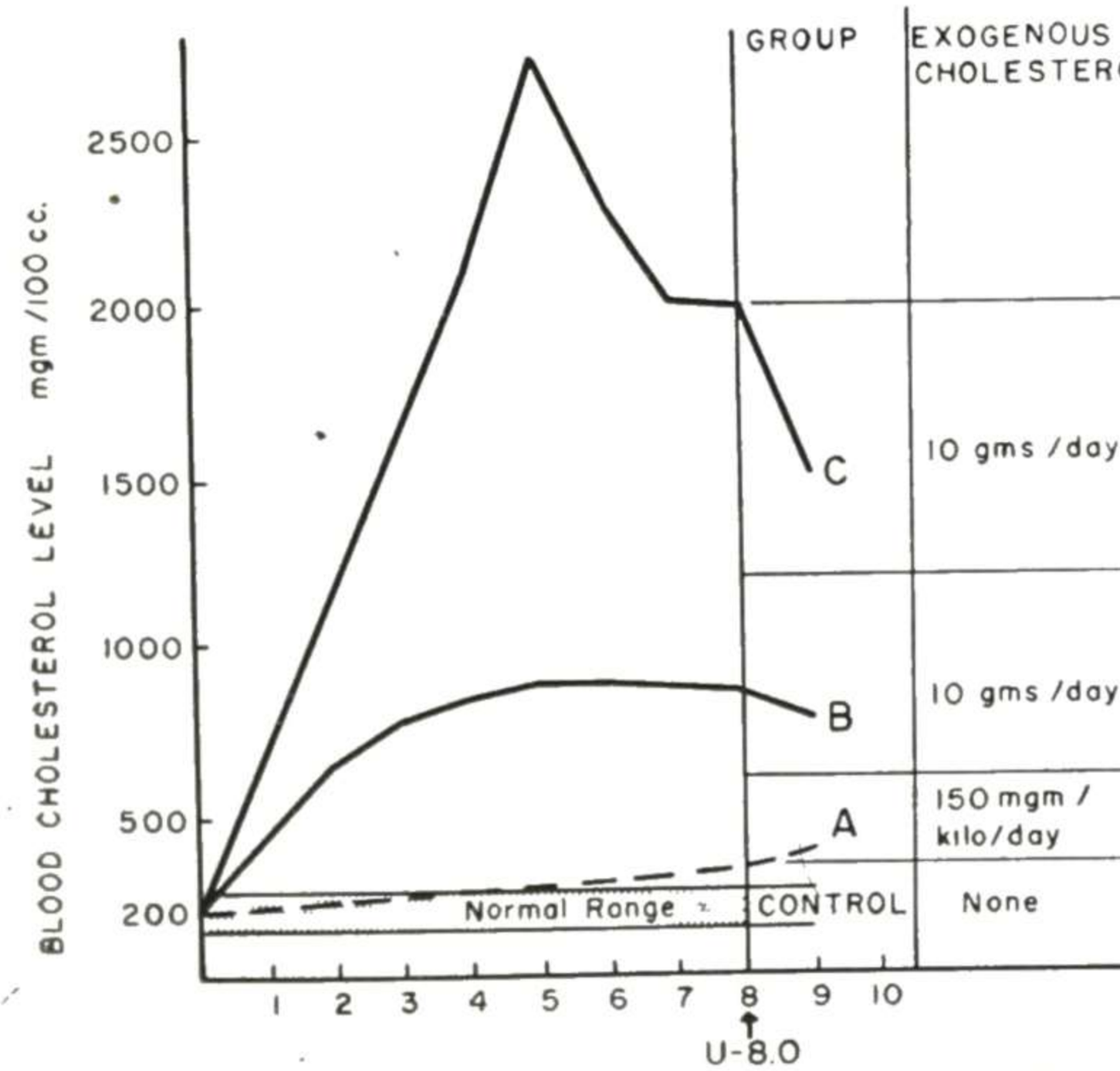
for the time-honored association between kidney damage and arterial lesions.

The possible bearing of these experimental lesions in dogs to arterial lesions in man is indicated in the following paragraphs.

Hypersensitivity. — The fact that simple omission of the dietary toxicomponent for one to four weeks eliminates the response of the arterial system to standard renal insufficiency constitutes strong evidence against hypersensitivity. The stage is set by diet and is reversible by change of the diet. At no time has there been any suspicion of an antigen-antibody reaction.

Hypercholesteremia.—Some of the surprising results showing that cholesterol added to the standard high fat diet prevented the typical arterial lesions are summarized in Table 3. Whereas 20 of 20 control dogs developed typical arterial

TABLE 3.—INFLUENCE OF EXOGENOUS CHOLESTEROL AND HYPOTHYROIDISM ON INCIDENCE AND CHARACTER OF ARTERIAL LESIONS



GROUP	EXOGENOUS CHOLESTEROL	THYROID STATUS	No. of LESIONS No. in GROUP
C	10 gms /day	Thyroidectomy	1/1 ATHEROMA
B	10 gms /day	Hypothyroidism Thiouracil (0.6 gm /day)	0/6
A	150 mgm / kilo/day	Normal	1/3
CONTROL	None	Normal	20/20

lesions on the standard experimental procedure, none of 6 dogs whose experimental procedure was supplemented by exogenous cholesterol and thiouracil (group B) developed arterial lesions, and only 1 of 3 dogs with no alteration of thyroid function and with only small additions of exogenous cholesterol (group A) developed arterial lesions. We are

attempting to repeat the single experiment (group C) in which exogenous cholesterol and thyroidectomy resulted in marked hypercholesteremia and the conversion of typical arterial lesions to atheroma. It would appear from this incomplete series

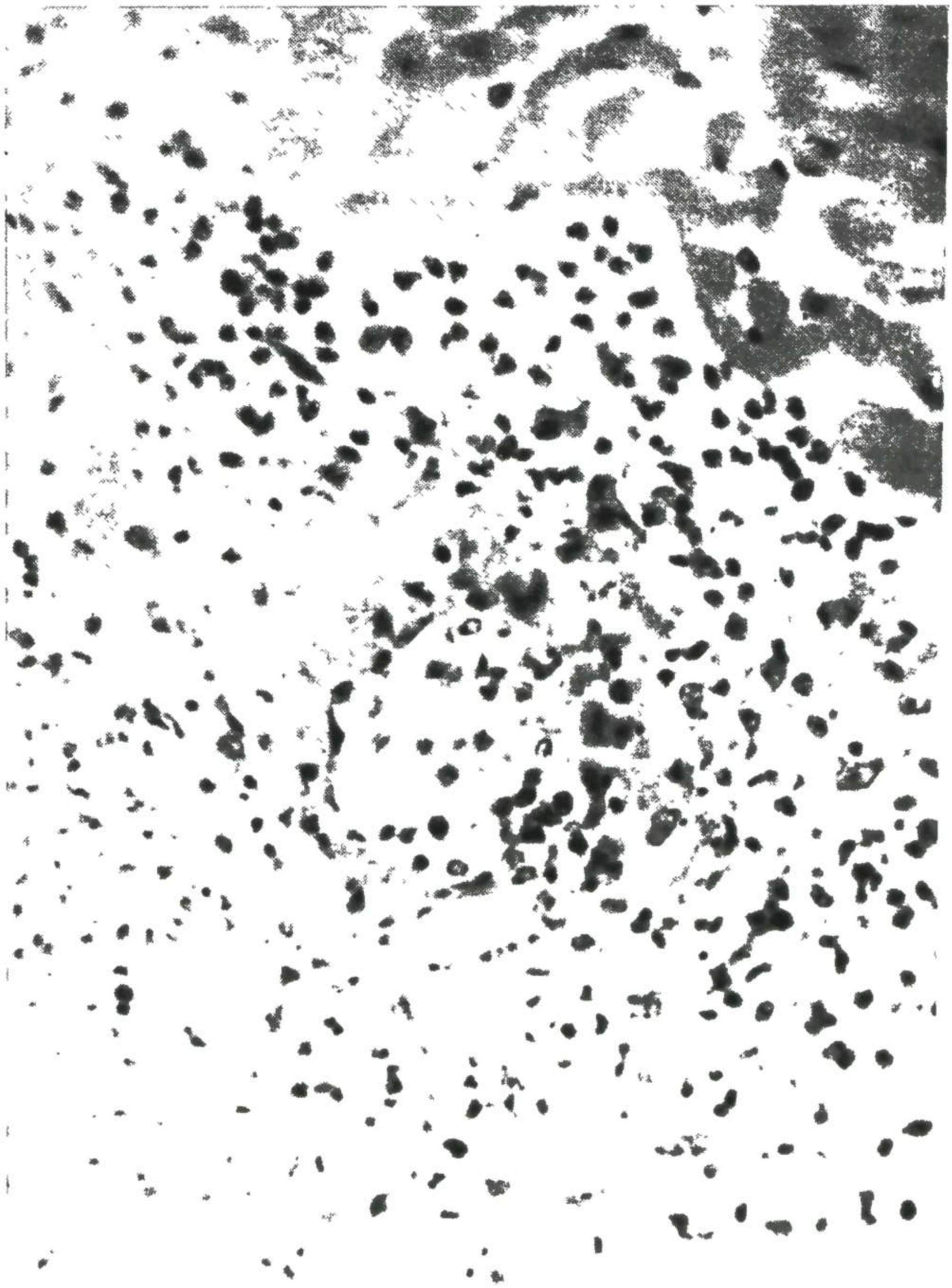


Fig. 33.—Acute necrotizing arteritis in a myocardial arteriole. Hematoxylin-eosin stain; reduced from × 320.

of experiments that acute necrotizing arterial lesions, no lesions or atheromatous lesions have been produced by controlling diet, cholesterol intake, thyroid activity and renal function. The evidence from this limited number of experiments points to a primarily protective influence of cholesterol

—possibly detoxification of toxic fat acid by esterification. Atheroma might result from excess of this protective activity. Time and additional studies may yet prove that cholesterol is the hero that puts out the fire rather than the culprit of arson.

Hypertension.—Serial blood pressure determinations were made on seven dogs throughout the experimental procedure.

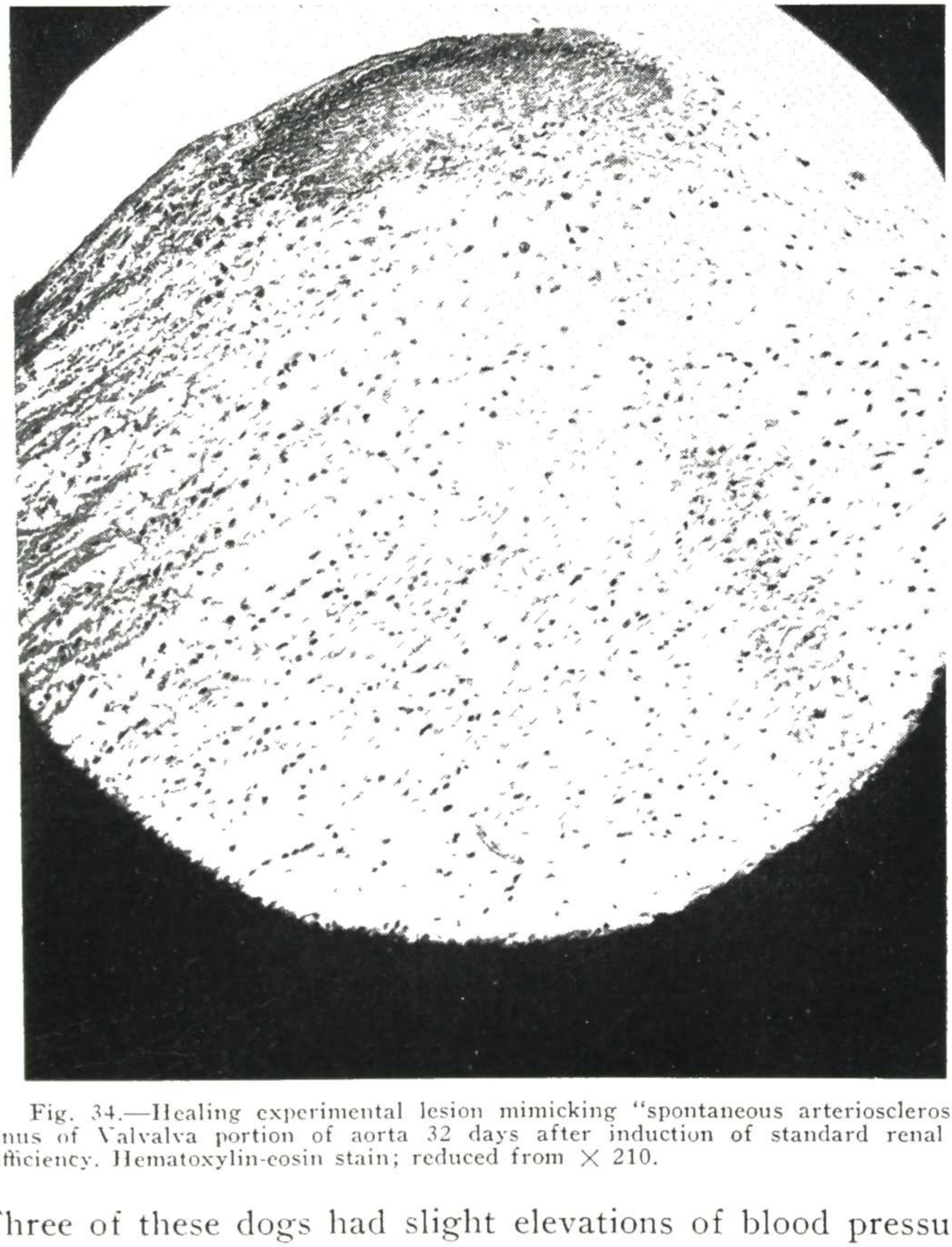


Fig. 34.—Healing experimental lesion mimicking "spontaneous arteriosclerosis." Sinus of Valvalva portion of aorta 32 days after induction of standard renal insufficiency. Hematoxylin-eosin stain; reduced from × 210.

Three of these dogs had slight elevations of blood pressure, but others with typical arterial lesions failed to show any elevation of blood pressure at any time. Apparently typical arterial lesions can develop in the absence of hypertension, but it would be surprising if hypertension did not aggravate the process.

Our experiments dealing with *age, sex, heredity, infection* and *hormones* have not been intensive, but the total data, derived from several hundred dogs, are appreciable and warrant the following brief comments. At no time has there been any evidence that the age of the experimental animal has influenced the incidence or appearance of the typical arterial lesions. Lesions have been produced with equal facility in both male and female dogs. All of the dogs used have been mongrels, hence a statement regarding the effects of heredity cannot be made at this time. Neither spontaneously occurring infections (such as distemper with extensive bilateral bronchopneumonia) nor artificially induced infections[7] (peritonitis and extensive cellulitis) have precipitated lesions in properly fed dogs. Pregnancy has definitely prevented the development of typical arterial lesions in six properly fed dogs[9] and diethylstilbestrol exerted an inhibitory effect in three dogs.[9]

Spontaneous Arteriosclerosis.—Possibly one of the most interesting features of these experimental arterial lesions has been the striking resemblance of some of the healing and healed lesions to the so-called spontaneous arteriosclerosis of dogs. By controlling the amount of heavy metal injected, dogs have been allowed to recover from kidney damage and have been followed up to 11 months. Several of the healing and healed lesions in this series have closely mimicked the so-called spontaneous arteriosclerosis of dogs (Fig. 34).

Dissociation of the experimental arterial lesions in dogs from the effects of age, sex, hypersensitivity, hypertension, hypercholesteremia and infection does not mean that these factors cannot play a role in some cases of arterial lesions, but to me it does mean that these factors are not the essence of so-called "collagen disease" lesions. Rather, our experimental results to date indicate that these factors are of secondary importance when compared to the direct injury produced by peroxidation of certain fat acids.

More than anything else, these experimental studies of the past decade have indicated the need for answers to two fundamental questions: (1) What factors integrate endothelium, reticulum, ground and cement substances, elastin, collagen, smooth muscle and areolar tissue into a functional tubular organ, and (2) what factors can upset this normal integration or equilibrium? Attempts to interpret human and experimental

lesions at this fundamental level will materially assist in elucidating the pathogenesis of arterial lesions.

REFERENCES

1. Klemperer, P.: Studies on collagen diseases, Am. J. Path. 26:505, 1950.
2. Holman, R. L.: Acute necrotizing arteritis, aortitis, and auriculitis following uranium nitrate injury in dogs with altered plasma proteins, Am. J. Path. 17:359, 1941.
3. Holman, R. L.: Necrotizing arteritis in dogs related to diet and renal insufficiency: V. Evidence for a dietary factor, Am. J. Path. 19:977, 1943.
4. Holman, R. L.: Prevention of experimental arteritis in dogs by vitamin E, Proc. Soc. Exper. Biol & Med. 66:307, 1947.
5. Holman, R. L.: Studies on the pathogenesis of arterial disease, South. M. J. 42:108, 1949.
6. Holman, R. L.: Factors regulating blood pressure, Tr. 4th Conf., Josiah Macy, Jr., Foundation, 1950, pp. 150-164.
7. McCormick, J. H., and Holman, R. L.: Studies on the pathogenesis of experimental necrotizing arteritis, Proc. Soc. Exper. Biol. & Med. 72:75, 1949.
8. Donnelly, G. L., and Holman, R. L.: The stimulating influence of sodium citrate on cellular regeneration and repair in the kidney injured by uranium nitrate, J. Pharmacol. & Exper. Therap. 75:11, 1942.
9. Unpublished data.

Experimental Production of Arteritis by Passive Sensitization. Sheldon G. Cohen, Lloyd D. Mayer and Leo H. Criep[4] (Univ. of Pittsburgh) passively sensitized rabbits with 5 ml. rabbit anti-horse serum and beginning ½ hour later injected 15 ml. horse serum (1:100) intravenously in divided doses. Major pathologic changes were confined to the lungs, the most constant ones being in the small pulmonary arteries and arterioles. They showed perivascular adventitial infiltration by eosinophils; to a lesser extent, lymphocytes and plasma cells, and a few polymorphonuclear leukocytes. The next most commonly involved organ was the heart. It showed slight subendocardial cellular infiltration by round cells and a few eosinophils.

When rabbits were given rabbit anti-horse serum alone, there was inconstant occurrence of an extremely light and scattered perivascular eosinophilic infiltration of an occasional small pulmonary vessel. The lesions were in no way comparable in extent to those in the first group of animals. When horse serum alone was given, lesions were found even less frequently. No lesions were found in rabbits given dog serum after passive sensitization with rabbit anti-horse serum. Lesions failed to appear in rabbits given bovine gamma

(4) J. Immunol. 66:487-496, May, 1951.

globulin after sensitization with rabbit anti-horse serum.

The lesions in the first group probably represent a manifestation of hypersensitivity which results from interaction of antigen and antibody in the tissues. The pulmonary localization of the severe lesion may be explained by the fact that the pulmonary arteriole is considered the "shock tissue" of the rabbit. The intravenous administration of antibody and antigen may also be a factor in the pulmonary localization. The results support the theory of specificity in relation to immunologic phenomena.

Special Article

ATHEROSCLEROSIS, LIPOPROTEINS AND CORONARY ARTERY DISEASE

By John W. Gofman, Hardin B. Jones, Thomas P. Lyon, Frank Lindgren, Dean Graham, Beverly Strisower *and* Alex Nichols*

A paper by J. W. Gofman and his associates that appeared in Circulation (5:119-134, January, 1952) and other publications are comprehensive and give in considerable detail the results of their investigations. To have the whole field covered in brief form, this special article was prepared by Dr. Gofman and his associates. We are grateful to them for furnishing this material.—Ed.

A wealth of information, both clinical and experimental, accumulated over the years, has provided undeniable evidence that atherosclerosis and its serious clinical sequelae, e.g., coronary artery disease, are in some way related to serum lipids. The major problems are:

I. Which serum lipids are actually related to atherosclerosis?

II. If certain serum lipids are associated with atherosclerosis, what is the nature of that association? Are the involved serum lipid constituents actually etiologic agents in the disease or are they a reflection of a metabolic disturbance which produces both serum lipid alterations and atherosclerosis independently?

III. Will knowledge of the status of a patient with respect to abnormality of serum lipids provide diagnostic or prognostic information?

IV. Will alteration of the serum lipids toward normal be of prophylactic and therapeutic value in atherosclerosis, especially in such sequelae as coronary artery disease?

*From the Donner Laboratory of Medical Physics and the Radiation Laboratory, Department of Physics, University of California, Berkeley, Calif.

Certain evidence has now developed concerning each of these problems. This evidence may be considered with respect to each problem listed.

I. The determination of which serum lipids are related to atherosclerosis depends on the ability to characterize the serum lipids in individual patients. By our application of ultracentrifugal methodology it has been possible to describe serum lipid transport in an individual patient in terms of a series of giant lipoprotein components. Essentially all of the chemical lipid constituents of serum (cholesterol, free or esterified, phospholipids, fatty acids and neutral fat) can be accounted for quantitatively in one or more of the ultracentrifugally measurable lipoproteins.

In the ultracentrifuge the lipoproteins, being of relatively low density, can be made to undergo flotation, since it is possible to render the solutions carrying them more dense than the lipoproteins by the simple expedient of adding salt. This allows separation of the lipoproteins from the dense serum proteins, such as albumin and globulins. Then in an analytical flotation run photographs are obtained which enable us to determine (*a*) what lipoprotein species are present and (*b*) at what concentration such lipoproteins exist in the serum of a particular human subject.

Since several species of lipoproteins may be present, we have found it useful to describe these lipoproteins by either of two means.

(*a*) *Flotation rate* in the ultracentrifuge under specified conditions. The units used are so-called Svedberg units (in honor of the inventor and pioneer of the ultracentrifuge method). Thus a particular lipoprotein may be named or characterized by its flotation rate S_f units (Svedbergs of flotation). (*b*) *Density of the lipoprotein* in grams/cubic centimeter. Since the various lipoproteins differ from one another in this property (in addition to other differences), it is often useful to describe or name a molecular species in terms of its density, e.g., a lipoprotein is spoken of as being in the 1.07 Gm./cc. class. An arbitrary, but useful, split has been made in the case of human lipoproteins at a density of 1.063 Gm./cc. All of higher density than this are referred to as high-density lipoproteins; those of lower density are designated low-density lipoproteins. It is this latter class, the low-density lipoprotiens, which will be considered.

In man the various types of low-density lipoproteins which may be present are now characterized, and information is accumulating as to their chemical composition and biologic interrelations. The human serum lipoproteins known to exist, together with their chemical composition, follow.

	S_f4 S_f6 S_f8 S_f10 S_f13 S_f17	S_f17-40	S_f40-40,000
Total cholesterol	~ 30%	decreasing steadily →	5%
Fraction of cholesterol esterified	~ 75%	decreasing steadily →	0%
Phospholipid	~ 25%	decreasing steadily →	5%
Protein	~ 25%	decreasing steadily →	5%
Glyceryl ester	← Absent or very low % in this range →	Increasing steadily →	75-85%

The crucial feature of distinction among human beings of various ages and clinical categories is the concentrations of the various classes of lipoproteins habitually present in the serum. Individual patients may be described by their "lipoprotein spectrum." The "normal" pattern and deviations therefrom follow.

"Normal" Pattern

1. Lipoproteins of S_f4 and/or S_f6 present at low or moderate concentrations. *Minimal* levels of higher S_f components except for transient elevations in S_f30-40,000 following fatty meals.

"Minimal" Defect

2. Lipoproteins of S_f4 and/or S_f6 at increased concentrations but without any increase in higher S_f4 components as compared with (1).

"Minor" Defect

3. Lipoproteins of S_f4 and/or S_f6 *plus* S_f8 in increasing concentration.

Progressively "More Severe" Defect

4. $S_f4 + S_f6 + S_f8 + S_f10$
5. $S_f4 + S_f6 + S_f8 + S_f10 + S_f13$
6. $S_f4 + S_f6 + S_f8 + S_f10 + S_f13 + S_f17$
7. $S_f4 + S_f6 + S_f8 + S_f10 + S_f13 + S_f17 + S_f17$-20
8. $S_f4 + S_f6 + S_f8 + S_f10 + S_f13 + S_f17 + S_f17$-20 + S_f20-40
9. $S_f4 + S_f6 + S_f8 + S_f10 + S_f13 + S_f17 + S_f17$-20 + S_f40-40,000. (In this group the S_f40-40,000 can be of transient existence following meals or may be sustained even postabsorptively.)

10. *"Most Severe" Defect*

As in (9) except that S_f4 and S_f6 may be depressed to quite low concentrations. (This may be regarded as a general shift toward higher S_f lipoproteins and is comparable to that which appears in rabbits in the later phases of cholesterol-Wesson oil feeding.)

The *physiology* underlying the presence of such molecules in serum appears to be that these lipoproteins represent, in part at least, a sequence of molecules involved in the normal metabolism of fat and fatty acids, with progressive transformation of molecules of high S_f classes into those of lower S_f classes.

The *pathologic physiology* underlying the presence of elevated concentrations of certain of these lipoproteins appears to be either (*a*) an abnormal rate of delivery of a particular lipoprotein to the serum, or (*b*) a partial metabolic block in the normal conversion of a particular lipoprotein to those of lower S_f classes. In either event the result may be a steady state *elevation* in serum level of that lipoprotein.

Our studies of patients with coronary artery disease (a major share of which is atherosclerotic in origin) have revealed beyond doubt certain critical facts.

1. Two classes of lipoproteins are elevated significantly and independently in patients with coronary artery disease as compared with "normals" of the same age and sex (some of whom, of course, have silent atherosclerosis). These classes are (*a*) the lipoproteins between S_f12 and S_f20 ("the S_f12-20 class"), and (*b*) the lipoproteins between S_f20 and S_f100 ("the S_f20-100 class"). Class (*a*) is not acutely influenced by food intake, whereas class (*b*) (especially the S_f35-100 group) may be acutely elevated following ingestion of fat-containing meals.

2. Both classes contribute, and independently, in the association with atherosclerosis.

3. Together, the S_f12-20 plus the S_f20-100 classes of lipoproteins contribute *essentially all* of the relationship of serum lipids with atherosclerosis, yet they represent, on the average, only 10-15 per cent of the total lipids of serum and, specifically, only 10-15 per cent of the cholesterol of serum. The cholesterol and other lipids in the remaining 85-90 per cent of serum lipoproteins provide no independent contribution to atherosclerosis.

4. Since only a small fraction of the cholesterol-containing lipoproteins are of importance in atherosclerosis, the variations in the remaining bulk of serum cholesterol serve more to obscure and confuse the relation of serum lipids to atherosclerosis than to clarify it. As a result the serum cholesterol determination is definitely an unsatisfactory guide to evalua-

tion of atherosclerotic potentialities. At any total serum cholesterol level, the S_f12-20 and S_f20-100 classes of lipoproteins are higher in patients with coronary artery disease than in normal subjects, over the range from *low* through *high* cholesterol levels. Conversely, when patients with coronary disease are matched with normal subjects at the same S_f12-20 + S_f20-100 levels, the serum cholesterol level fails to segregate the patients with coronary disease from the normals.

At *low* total serum cholesterol levels, patients with high S_f12-20 + S_f20-100 lipoprotein levels may be expected to be developing atherosclerosis. At *high* total serum cholesterol levels, patients with low S_f12-20 + S_f20-100 lipoprotein levels may be expected to be relatively protected against atherosclerosis.

5. In a classic *hypercholesteremic* group — patients with xanthoma tuberosum (known clinically to develop excessive atherosclerosis)—the S_f12-20 + S_f20-100 lipoproteins average 2-2½ times higher than in equivalently hypercholesteremic individuals who are clinically normal.

II. Although the association of the S_f12-20 and S_f20-100 lipoproteins with atherosclerosis is strong, there is no *direct* evidence that these molecules are etiologic in the sense that they produce atherosclerosis directly by deposition in some manner from serum. We consider the probability good that this is the case. In any event, until and unless evidence to the contrary arises, this hypothesis provides a fruitful basis for prophylactic and therapeutic studies in atherosclerosis.

III. Obviously the ability to predict in which "normal" individuals atherosclerosis is developing excessively will be of clinical value. Our data already show statistically significant association of elevated S_f12-20 levels with the development of coronary disease de novo in "normals." Studies now in progress will provide additional information on a much larger series this year.

Follow-up study of patients with established coronary artery disease shows statistically significant association of elevated S_f12-20 lipoprotein levels with early recurrence of myocardial infarction. There is thus established a prognostic import in the S_f12-20 lipoprotein level. It is likely that we will be able to demonstrate similar prognostic significance for the S_f20-100 lipoproteins.

IV. Certain factors, exclusive of frank disease states such

as diabetes, xanthomatosis, nephrosis, myxedema and hepatitis, are known to influence the level of the atherosclerosis-associated S_f12-20 and S_f20-100 lipoprotein levels.

a) *Obesity*, which is almost universally the result of excessive caloric intake. The association of obesity with elevation of the S_f12-100 lipoproteins (S_f12-20 + S_f20-100) is highly significant, although of moderate degree. This association may be of sufficient degree to explain the moderate clinical correlation of obesity with excessive atherosclerotic vascular disease.

b) *Dietary fat intake*. Acutely, the ingestion of a meal high in mixed fats produces elevations especially in the S_f20-100 lipoprotein levels. Chronically, restriction of dietary fat produces a fall in the S_f12-20 and S_f20-100 lipoprotein levels in a large proportion of, but not all, patients. In part, this effect is due to the usual association of reduced caloric intake on a fat-restricted diet. In part it appears also due, in some patients, to the reduced fat intake per se.

c) *Heparin administration*. Heparin is the most powerful agent we have encountered for shifting the serum lipoprotein pattern toward normal in human subjects and animals. The S_f20-100 lipoprotein class is generally wiped out within 30 minutes after the administration of 25-100 mg. heparin intravenously in man. The S_f12-20 class shows a transient elevation, followed by a decrease. Within 24 hours, however, the pre-heparin lipoprotein pattern is re-established in the great majority of human beings.

Chronic lowering of lipoprotein levels is possible in some human subjects by intermittent heparin injection. Much work remains to be done in establishing possible dosage forms and schedules.

Efficacy of lipoprotein alterations is related to two considerations. (1) A significant decrease in recurrence rate of myocardial infarction has been established in patients with established coronary artery disease whose levels of S_f12-20 lipoproteins have been significantly reduced by dietary fat restriction. Part of this protection may be associated with the alteration of lipoprotein level associated with the control of obesity. (2) Heparin administration has been shown by Graham *et al.* in our laboratory to protect rabbits against cholesterol-induced atherosclerosis.

Heparin administration to human beings in doses of 50-100

mg. once or twice weekly has been shown by Lyon and Yankley of our group to produce marked amelioration of angina pectoris. It cannot be stated at present that this heparin effect is or is not related to its profound ability to alter serum lipoproteins acutely.

The future development of this approach follows two lines: (1) further evaluation of the prognostic and predictive implications of elevated S_f12-20 and S_f20-100 levels, together with evaluation of the clinical efficacy of reduction of such levels in the management of atherosclerosis; (2) the understanding of the nature of the metabolic error which leads a sizable fraction of the human population to have elevations of the atherosclerosis-associated lipoproteins. The latter is of greater fundamental importance but may lag behind certain of the practical applications of the former.

Cholesterol, "Giant Molecules" and Atherosclerosis. An important relation exists between the cholesterol concentration in the blood plasma and development of atherosclerosis. However, there is not sufficient information on the usefulness of serum cholesterol measurements in diagnosing atherosclerosis or in predicting impending danger from coronary heart disease. Cholesterol does not exist in simple solution in the blood plasma but is associated in complexes with proteins and lipoids. Methods have recently been developed for estimating the amounts of such low density complexes by observing their flotation in the ultracentrifuge. It has been suggested that these "giant molecules," called G substances, are implicated in atherosclerosis.

Ancel Keys[5] (Univ. of Minnesota) analyzed the results of various studies to determine the value of blood cholesterol and G measurements as evidence of atherosclerosis. Qualitatively, the same kind of evidence which supports the relation of blood cholesterol to atherosclerosis also exists for G substances. Imperfect technical methods of determination result in a wide variation of G values. The analytic uncertainty for a single measurement of cholesterol is of the order of 5 per cent or more, whereas the uncertainty of a single measurement of G is of the order of $\pm$10 mg./100 ml. Since a large percentage of G determinations are less than 15 mg./100 ml., the effect of the possible discrepancy is apparent. Prediction of the resulting degree of atherosclerosis from blood analysis in

(5) J. A. M. A. 147:1514-1519, Dec. 15, 1951.

rabbits fed cholesterol showed a forecasting efficiency of 37 per cent with the use of G values and 50 per cent with total cholesterol measurement.

No satisfactory comparison of both G and cholesterol measurements on the same group of normal human beings and patients with atherosclerosis was available. In one investigation in which G and cholesterol measurements were made on patients with coronary disease, normal persons of a younger age group were used for controls. When the G concentration in serum and cholesterol serum values are combined, no information is obtained for discriminating between normal persons and persons with coronary disease that has not been evident from total cholesterol determinations alone. Neither measurement is a good discriminator. If one of these measurements has any advantage over the other in detecting or predicting coronary disease, evidence favors the total cholesterol measurement.

[Elsewhere, Dr. Keys states that the quantity of G substances (— 10 to — 20 Svedberg units of sedimentation) appears to be similar to that of the serum cholesterol (Human Atherosclerosis and the Diet, Circulation 5:115-118, January, 1952). Thus, he believes that the serum cholesterol level is a safe guide. An editorial in the *Journal of the American Medical Association* entitled "Blood Lipids and Atherosclerosis" (148:207, Jan. 19, 1952) reviews many of the studies which have been published. The concluding statement indicates the present state of affairs: "Despite the many unsolved problems and puzzling conflicts it presents, the rapidly expanding literature of this subject gives promise of an increasing understanding of the nature of atherosclerosis."—Ed.]

Macrophage Migration in Experimental Atherosclerosis. John H. Simonton and John W. Gofman[6] (Univ. of California) investigated the macrophage-transport hypothesis of atheromatosis, using rabbits as experimental subjects. Reticuloendothelial cells were labeled with a radioisotope and atherosclerosis was induced by cholesterol feeding. The animals were killed at intervals, depending on the length and amount of cholesterol feeding and state of the blood serum, and the distribution of the label was determined. If the aortic plaque tissue arose principally from migrated macrophages, the activity per gram of tissue should be greater in the aorta than in the liver.

High concentrations of the label were found in Kupffer cells and in splenic and marrow macrophages, but no significant increase was demonstrated in aortic atheromatous tissue. The little radioactivity observed in the aortic preparation

(6) Circulation 4:557-562, October, 1951.

probably represented phagocytosis of the isotope directly from the blood stream by the aortic cells. No evidence was found in microscopic preparations of aortic atheromatous tissue of the presence of labeled Kupffer cells or of other labeled macrophages from the spleen or bone marrow. Results indicate that macrophage migration is not a significant source of the foam cells in atherosclerotic lesions of rabbits.

Sustained Hyperlipemia Induced in Rabbits by Means of Intravenously Injected Surface-Active Agents. Aaron Kellner, James W. Correll and Anthony T. Ladd[7] (Cornell Univ.) gave rabbits a single intravenous injection of 20 per cent tween® 80 in amounts of 2.5 cc./kg. body weight. Blood cholesterol and phospholipid levels increased sharply, reaching peaks in 6-12 hours and returning to normal range in 24-48 hours. When injections were given twice daily, elevations of the levels could be maintained. In every instance there was a parallel increase in blood cholesterol and phospholipid content, phospholipid levels tending to be somewhat higher than the corresponding cholesterol ones. Similar results were obtained with single injections of triton A20, except that hyperlipemia persisted for 5-15 days.

Since blood cholesterol, phospholipid and neutral fat levels were elevated in these rabbits, it does not seem unreasonable to suppose that there may have been concomitant increases in other circulating lipids, e.g., steroid hormones and free fatty acids.

Surface-active agents provide the most convenient means for elevating the major lipid components of the blood serum in mammals. Whether they act directly by increasing the capacity of plasma to hold lipids in stable emulsions, or by interfering with enzyme systems in the blood or tissue which are essential for the intermediary metabolism of fats, or by other means, cannot be stated. Injection of surface-active agents may induce hypercholesteremia by augmenting the synthesis of cholesterol or by retarding its degradation. The fact that hyperlipemia develops rapidly after injection of these agents is consistent with the observation that there is a rapid turnover of lipids in the body. Lipemia produced by intravenous administration of these agents differs from that which follows feeding of cholesterol, but the method will serve as a tool for further study of experimental atherosclerosis.

---

7 . Ex r. Med. 93:373-383, April, 1951.

Lipid Metabolism and Atherosclerosis. R. Gordon Gould[8] (Chicago) discusses the relation of plasma and tissue lipids to arteriosclerosis and evaluates their significance from recent work on the subject. The passage of isotopic cholesterol from the liver to the plasma was measured after C^{14}-labeled acetate was given to dogs. Labeled free cholesterol, found in the plasma within a few minutes, had reached a maximum in an hour. No significant change developed in the total cholesterol level. Dogs killed one and four hours after administration of the preparation showed the same C^{14} free cholesterol content in both plasma and liver. The esterified plasma cholesterol contained little isotope at one hour. Apparently, free cholesterol is the primary product of synthesis in the liver and does not become esterified before entering the blood. Within a few hours the newly synthesized cholesterol molecules were equally divided between free plasma cholesterol and both red cells and plasma ester cholesterol.

Equilibrium between blood and liver cholesterol may occur in the opposite direction. Intravascular administration of C^{14}-labeled acetate was followed by exsanguination 16 hours later in one dog. Some of this blood was given another dog, with removal of the same quantity from the recipient to keep the total amount of cholesterol essentially constant. The recipient was bled and perfused with saline at various intervals and distribution of labeled cholesterol in the liver and other tissues determined. The labeled plasma cholesterol fell rapidly in the first few hours, much of it entering the liver cells. Equilibration between total plasma cholesterol and that of the liver was 50 per cent complete after eight hours and equilibration of free plasma cholesterol was even faster.

Movement of plasma cholesterol to extrahepatic tissue is very slow and may be an irreversible process. If large amounts of cholesterol are fed to experimental animals, three mechanisms may be possible whereby the animal maintains a constant concentration of cholesterol. (1) Absorption may decrease. (2) Endogenous synthesis may be inhibited. (3) Various methods of cholesterol disposal may be accelerated. The thyroid gland is one of the regulators of plasma cholesterol; the total body content of cholesterol is unchanged after thyroidectomy in animals despite a doubled serum cholesterol level. This suggests that thyroid action is concerned with the

. J. Med. 11:209-227, August, 1951.

distribution between plasma and tissue rather than with the synthesis or utilization of cholesterol.

Influence of Intravenously Administered Surface-Active Agents on Development of Experimental Atherosclerosis in Rabbits is described by Aaron Kellner, James W. Correll and Anthony T. Ladd[9] (Cornell Univ.). Rabbits fed cholesterol but not given injections of a surface-active agent showed slight elevations of serum cholesterol and serum phospholipid levels three weeks after experimental feedings had been started. After six weeks these levels were moderately elevated, and hyperlipemia persisted thereafter. Postmortem examination showed that five of seven animals had atherosclerosis.

In rabbits given tween® 80 intravenously but not fed cholesterol, pronounced hyperlipemia appeared more promptly than in the first group and the amounts of cholesterol and phospholipid in the serum were much greater. Phospholipid was regularly present in greater amount than cholesterol, in direct contrast to findings in the first group. None of the animals showed atherosclerosis of the aorta at autopsy.

In rabbits fed cholesterol and given tween® 80 intravenously, hyperlipemia occurred and was pronounced after three weeks. Cholesterol and phospholipid levels were appreciably higher in this group than in the previous two groups. Phospholipid levels were regularly higher than cholesterol levels. Only one of four animals showed atherosclerosis of the aorta post mortem. Similar changes followed substitution of triton A20 for tween® 80. Additional experiments in which tween® 80 was repeatedly given intravenously did not result in resorption of previously induced atherosclerosis in rabbits.

It is not possible to state whether the reduced incidence of atherosclerosis in the presence of pronounced and sustained hypercholesteremia is due to elevation of blood phospholipids, the injection of surface-active agents into the circulating fluids or to other factors. The elevation of phospholipid in the presence of surface-active agents possibly has played a role in this decreased incidence of atherosclerosis. That atherosclerosis did occur in some of these experiments suggests involvement of other factors in its pathogenesis.

Experimental Production of Lipid Deposition in Excised Arteries. Sigmund L. Wilens[1] (New York Univ.) studied the

(9) J. Exper. Med. 93:385-398, April, 1951.
(1) Science 114:389-393, Oct. 12, 1951.

filtration properties of human arteries, using excised iliac arteries from young persons who had died suddenly as a result of trauma. Pooled serum of human donors was placed in the arteries under known pressure and the fluid passing through the wall collected. Total cholesterol, total protein, albumin-globulin ratios, calcium, nonprotein nitrogen and chloride were determined on the original serum, the fluid remaining in the artery and the filtrate collected after passage through the vessel wall. At 20 mm. Hg pressure, no filtration occurred. At 30 mm., a slow rate of filtration was noted, and at increasing pressures the rate was correspondingly accelerated. The filtrate differed from the original serum in appearance and chemical composition. It was watery and pale brown and contained little or no cholesterol and relatively little protein. It contained 25-50 per cent less calcium than the original serum. Chlorides, nonprotein nitrogen and other inorganic substances were present in the same concentration as in the original serum and the retained fluid in the vessel lumen. The fluid remaining in the vessel lumen after filtration was viscid and dark yellow, with increased cholesterol (600 mg. per cent) was not uncommon. The protein content, especially the globulin fraction, was increased, and sometimes the albumin-globulin ratio was reversed. The calcium content was moderately elevated.

By calculation, it was found that 20-50 per cent of the cholesterol present in the original volume of serum filtered could not be accounted for by concentration within the lumen of the vessel. It was estimated that 2-38 per cent of the cholesterol in the filtration system had entered and been retained within the vessel wall. Similar calculation revealed that a small proportion of protein was lost during filtration and was presumably deposited intramurally. The relative amounts of cholesterol and protein retained did not depend on the pressure level of filtration. They did increase with the length of time of filtration.

When the artery was stained in toto with sudan IV after 36-48 hours of filtration at 200-300 mm.Hg, the entire exposed intimal surface was pale red. The amount of lipid deposited depended chiefly on the amount of fluid that had filtered through the vessels per unit of surface area. It also depended to some extent on the original thickness of the fibrous intima and, for this reason, was generally more pro-

nounced in the thicker common iliac than in the external iliac artery. At 75-125 mm., scanty lipid deposits were noted after 24 hours of filtration. In some instances the lipid appeared to spread uniformly throughout the entire thickness of the intima; in others it had concentrated at the internal elastic lamella, which often acted as a barrier against further penetration. There was no tendency to lipid droplet formation, and the lipid in the intima was not doubly refractive. In several experiments with high filtration pressures, stainable lipid material in appreciable amounts had diffused throughout the media and concentrated at its external margin.

It is possible that the smaller particles of lipid in the serum can enter the intima, whereas larger ones are rejected.

[In essence this is a study in vitro and discloses valuable information concerning permeability of these vessels for lipids. It will be noted that the main accumulation was uniform throughout the intima, but appreciable amounts entered the media. Ultimately, this may have some bearing on the problems of arteriosclerosis.—Ed.]

Studies in Experimental Atherosclerosis: Anatomic Alterations Induced by Intravascular Injection of Cholesterol Sols into Animals. Otakar J. Pollak and Bella Wadler[2] (Quincy, Mass., City Hosp.) used colloidal suspensions of cholesterol stabilized in partially deproteinized rabbit serum to avoid the damaging effect of a vehicle. Two different suspensions were injected, the coarse having micelle size of 0.2-0.4 μ and the fine 0.02-0.04 μ. Varying amounts were given intravenously and the rabbits killed at different intervals. In animals given one large dose (over 188 mg. cholesterol), widespread histologic lesions were found. Multiple emboli were seen in small pulmonary arterioles and minute focal necrosis was found in the lungs and brain. Evidence of cholesterol crystals was found in blood clots within many veins. Fatty change was noted in the central portion of the liver lobules, adrenal cortex and sometimes the renal glomeruli. Steatosis appeared in animals living more than 10 minutes after injections. Vascular alterations, constant in all animals, consisted of foam cell collections in the subintima of pulmonary arterioles and small arteries. In rabbits given less than 99 mg. cholesterol, only blood vessels were altered. Foam cell aggregates in the subintimal zone of arterioles and small and medium-sized arteries of the lungs were found in animals 30 seconds and 3 minutes after injection.

---

2 . Gerontol. 6:217-228, July, 1951.

Repeated intravenous injections of coarse cholesterol suspension in small amounts caused steatosis of the liver and fat deposits of the glomerular capsule and loop. Foam cell collections were present in pulmonary arterioles and small arteries. Apparently the size of cholesterol particles prevented free passage through the pulmonary capillaries. Some rabbits, given a single injection of the suspension containing small cholesterol particles, had no pathologic lesions. Others treated similarly had extensive vascular alterations, especially in the lung. Repeated injection of the fine particle suspension was always associated with pulmonary vascular lesions. Occasionally the coronary arteries and aorta were affected. Volume and amount of cholesterol were unimportant in influencing the extent of the change. When the interval between injections was 10 minutes, more lesions were produced than when injections were at 24 and 48 hour intervals. Survival time was also a factor in determining the presence and extent of vascular damage. When animals were killed after injection, changes were more frequent than in rabbits which survived five to seven days.

Two rabbits received coarse cholesterol suspension by intracardial injection. Both, killed less than five minutes later, had vascular lesions of the aorta and one presented subintimal foam cell collections in the pulmonary arteries.

In one group of rabbits the fine suspension was injected into the carotid arteries and abdominal aorta. Observations differed from those following intravenous injection. No lesions were found in the pulmonary vessels. Some animals had damage to the aorta and coronary and renal arteries. Renal arterioles and arteries were damaged in all rabbits with aortal injections. No vascular change was noted after intravenous injection of hypercholesteremic serum and material from an ovarian cyst rich in cholesterol. They had steatosis of the liver and fatty changes of the adrenal cortex and renal glomeruli. Multiple small collections of lymphocytes were found in the lungs, brain and myocardium. Fat emboli were widespread.

Intravenous injection of a fine suspension of colloidal graphite caused arterial changes similar to those found when small cholesterol particles were used. Localization of graphite particles corresponded to that of cholesterol. Endothelial cells loaded with these particles were seen in the subintima of arter-

ies. An identical change was demonstrated in the vessels of rabbits after intravenous injection of a fine colloidal suspension of sodium stearate.

Distribution of vascular lesions after injection of the material used in this experiment depends on the route of administration. The results suggest that colloidal particles of a certain size are precipitated on the vascular intima of rabbits when introduced directly into the circulation. The larger the particle size, the more severe the damage produced. The effect of cholesterol on the blood vessels is not specific but may be produced by injections of sodium stearate or graphite suspension. Cholesterol or its esters may be deposited secondarily in vessels damaged primarily by other macromolecular substances. Atherosclerosis induced by intravascular injection of colloid suspensions is probably the result of precipitation of the particles on the vascular intima. The initial lesion may be reversible, permitting removal and transportation of the foreign material from the primary deposits in the subintima to a secondary deposit in the reticuloendothelial cells of the liver and other viscera.

Intimal Vascularization and Atherosclerosis. Erich Geiringer[3] (Univ. of Edinburgh) examined 300 aortas and sections of 100 hearts including the first inch of the anterior descending branch of the left coronary artery. He found that avascularity of the intima was the rule to a critical depth of 0.5 mm. in the aorta and 0.35 mm. in the first inch of the anterior descending branch of the left coronary artery. The avascular intima is nourished directly from the main lumen by permeation of plasma constituents through the endothelium, as postulated by Virchow and demonstrated by others. Thickening of the intima does not increase the depth of the avascular area because transmedial vascularization progresses to the line of critical depth.

It is a common observation that the normal vascularity of the thin-walled arteries of young subjects is confined to the adventitia and that with advancing age and increasing thickness the outer two thirds of the media also take part in this vascularity. If the intima grows even thicker, vessels begin to appear in the inner third of the media and eventually penetrate the internal elastic lamina, thus becoming intimal.

Vascularization from the lumen occurs in plaques of

(3) J. Path. & Bact. 43:201-211, April, 1951.

thrombotic origin and is evidence of the thrombotic origin of such a plaque. Intimal vascularization from the lumen is found more commonly in the aorta than in the coronary arteries. These two forms of intimal vascularization are often associated in the same stretch of artery, and where they coexist they usually establish anastomoses.

Interference with or insufficiency of the blood supply of an atherosclerotic plaque will result in atheroma and foster new thrombus formation.

Special Article

AVIAN ARTERIOSCLEROSIS

By L. N. Katz, J. Stamler *and* R. Pick*

Numerous studies have been reported by Dr. Katz and his associates. It has proved impossible to abstract all of them; therefore Dr. Katz and his co-authors kindly provided this summary of their work. It yields much information on the basis of biology and physical chemistry. It may well be that the interpretations can ultimately be extrapolated to mammalian arteriosclerosis. We are deeply grateful to Dr. Katz and his associates for this valuable article.—Ed.

Avian species are uniquely suited for arteriosclerosis research, since they show spontaneous development of arterial lesions morphologically similar to human atherosclerosis.[1,2] Moreover, gross atherosclerosis can be readily induced in at least one avian species, the chick, by either cholesterol feeding or estrogen administration.†[3] Thus three different arterial lesions are available for analysis in the chick—the spontaneous, the cholesterol-induced and the estrogen-induced. Since our studies on avian arteriosclerosis have been confined almost exclusively to experiments in the chick, the discussion that follows deals only with this species.‡

Spontaneous arteriosclerosis in domestic fowl is typically located in the abdominal aorta. The characteristic gross lesion is an elevated, smooth, longitudinal, nonsudanophilic white or yellow ridgelike thickening, extending from the interrenal region to the bifurcation. In no case have we seen gross lesions of the foregoing type in the elastic aorta (the ascending aorta and arch).

---

*From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago.

†Since the forthcoming monograph, *Experimental Atherosclerosis,* by L. N. Katz and J. Stamler[3] has an extensive bibliography, no attempt is made here to compile references.

‡Limited experiments by our group in ducks indicate that this avian species is comparatively resistant to both cholesterol- and estrogen-induced hyperlipemia and atherogenesis.

Microscopically, the essential feature of the spontaneous abdominal aorta lesion is focal thickening of the intima by fibrous tissue. The overlying endothelium is intact. The fibrous tissue comprising the intimal thickening is young and cellular in regions of little proliferation and also at the surfaces of large plaques. On the other hand, the deeper portions of thick plaques are composed of acellular, hyalinized collagenous tissue exhibiting areas of mucoid degeneration.

In her studies of spontaneous lesions in domestic chicks fed for commercial marketing, Dauber[2] observed fusiform cholesterol slits, round calcific granules, sudanophilic material and large lipid-bearing foam cells in the deeper layers of occasional fibrous plaques. However, our recent studies indicate that such atheromatous changes are not seen in spontaneous lesions of birds reared in the laboratory throughout their life on a known diet§ devoid of a cholesterol supplement. Hence, the atheromatous changes noted by Dauber in spontaneous lesions of commercial chicks were probably a consequence of increased intake of dietary cholesterol. Based on our latest findings, it is likely that the spontaneous lesion is primarily an intimal fibrosis, i.e., a nonatheromatous arteriosclerosis.‖

The foregoing conclusion concerning the morphology of the spontaneous lesion has significance for the problem of the pathogenesis of this lesion. Is lipid deposition a primary event in its pathogenesis? Obviously, our inability to demonstrate lipid in the spontaneous lesion strongly supports the conclusion of both Fox and Dauber that this intimal fibrosis is not lipid-engendered. The pathogenesis of this lesion remains completely obscure.¶

Data concerning the incidence of chick spontaneous arteri-

---

§The chick starter mash we use is made up of corn, oats, wheat bran, wheat standard middlings, alfalfa meal, meat scraps, dried buttermilk, soy bean oil meal, bone meal and vitamins and minerals. This mash contains 18 per cent crude protein, 3-5 per cent crude fat, 54 per cent carbohydrate and approximately 0.06 per cent cholesterol.

‖Concerning the foregoing terminology, *"arteriosclerosis"* is a generic designation, referring to several distinct entities, among them atherosclerosis, Mönckeberg's medial sclerosis, hyperplastic arteriosclerosis, etc. Thus the term, *"the arteriosscleroses"* would perhaps be more appropriate. *"Atherosclerosis"* is primarily an intimal arteriosclerosis distinguished fundamentally by the lipid and cholesterol content of its typical plaque.

¶In addition to the foregoing spontaneous lesion in the abdominal aorta, Dauber described a lipid infiltrative process in the thoracic (elastic) aorta of hens, unassociated microscopically with atherosclerotic changes.[2] Insofar as atherosclerosis is defined as a pathologic lesion producing thickening of the arterial wall, this lipid infiltration is not truly atherosclerosis. It is probably a consequence of estrogen-induced hyperlipemia in mature, gonadally actice hens.[3] Further, Uchiyama described a primary medial calcification in the arteries of chicks.[2] Among the thousands of animals examined in this laboratory, this lesion has never been observed.

osclerosis present several significant features. Thus, among wild ground fowl, Fox found a 1-5 per cent incidence of spontaneous lesions.[1] In contrast, a much higher incidence, 20-50 per cent, has invariably been observed in younger domestic chicks. This difference between domesticated and wild fowl in the incidence of spontaneous lesions remains unexplained. Further, in his study of wild fowl, Fox observed a pronounced sex differential in the incidence of spontaneous lesions—a 9:1 proportion of male to female.[1] Limited data available from our recent studies on male and female domesticated chicks fed regular mash for 12-15 weeks suggest a similar sex differential.

Several studies in our laboratory have assayed the effects of various procedures on the spontaneous lesion in the abdominal aorta of chicks. Neither alteration of the neutral fat level in the diet or of the total caloric intake (semistarvation) nor administration of lipotropic factors (choline and inositol) had any effect on the incidence and severity of this lesion. Pancreatectomy, administration of desoxycorticosterone or thyroid hormone and induction of salt hypertension were also essentially without significant consistent influence. Substitution of a specially prepared, defatted, cholesterol-free mash did retard development of spontaneous lesions and moderately decreased their incidence and severity. The fact remains, however, that practically complete removal of cholesterol from the diet of chicks did not conspicuously inhibit spontaneous atherogenesis (see previous comment on pathogenesis of the spontaneous lesion).

The aorta is not the sole site of spontaneous arteriosclerosis in chicks. Recently, particular attention has been focused on spontaneous coronary lesions in this avian species. Intimal fibrous plaques have been demonstrated in the coronary arteries of chickens. These lesions are entirely free from lipids. Chronic stress or cortisone administration causes a decrease in their incidence. Their pathogenesis is unknown. Further, a spontaneous focal degenerative medial lesion has also been described in the coronary arteries of chicks. It has been suggested that this lesion is lymphomatosis of the coronary vessels. It is unlikely that this lesion is related to spontaneous intimal fibrosis or is a site of predilection for atheroma formation when cholesterol is added to the diet of chicks.

Estrogen-induced atherosclerosis in cockerels occurs in the brachiocephalic arteries in the upper thoracic (elastic) aorta

and sometimes in the upper abdominal aorta. The lesions develop after about nine months of estrogen-induced hyperlipemia, with hyperphospholipemia and hypercholesteremia. They are typical intimal atherosclerotic plaques of varying sizes, distinguished grossly from cholesterol-induced lesions (see latter), principally by their color, which may be bright lemon-yellow or orange rather than cream.

Microscopically these lesions are typically atheromatous or atherosclerotic plaques, with fibroblastic intimal thickening, sudanophilic foam cells of the macrophage type, lipid-bearing fibroblasts, extracellular lipid droplets and anisotropic cholesterol crystals. The intima and media of the aorta adjacent to such plaques are diffusely infiltrated by lipid.

In some estrogen-treated cockerels, lesions essentially similar to the foregoing are also present in the abdominal aorta. In addition, typical "spontaneous" smooth, ridgelike, longitudinal plaques are seen, differing grossly from the spontaneous lesions of untreated control birds only in their tendency to be a lemon-yellow color. Microscopically, unlike the usual spontaneous lesions, they contain considerable sudanophilic material and associated atherosclerotic changes, apparently superimposed secondarily on previously developed, purely fibrotic spontaneous intimal plaques (see below). Estrogen-induced avian atherosclerosis is unique in one other respect; i.e., no lesions are induced in the coronary vessels. This is a fact of particular significance in view of recent experiments on the effects of estrogens on cholesterol-induced atherosclerosis.

Studies on factors possibly influencing estrogen-induced atherogenesis demonstrated that it was uninfluenced by a low fat diet, by lipotropic factors or by orally administered aluminum hydroxide gel. However, desiccated thyroid hormone given orally did depress estrogen-induced atherogenesis.

Gross *cholesterol-induced atherosclerosis* of the aorta and great vessels may develop in chicks after as little as two weeks of experimental feeding. In contrast to the spontaneous lesion, the site of predilection of cholesterol-induced plaques is the ascending aorta and arch (elastic aorta of the chicks). In the earlier stages, before discrete plaques are identifiable grossly, the lining of the elastic aorta has a cream-white, smooth, glistening appearance. Subsequently, elevated nodules, raised longitudinal streaks and plateau-like plaques develop.

With high levels of dietary cholesterol (1-2 per cent) and prolongation of the experimental dietary regimen beyond a few weeks, the lesions become confluent. Pronounced sclerotic changes supervene, rendering segments of the aorta stiff and brittle. Gross narrowing of the orifices of the brachiocephalic and coronary arteries, and of the aorta lumen itself, results from these atherosclerotic plaques. Lesions in the brachiocephalic arteries, which are elastic arteries, usually parallel those of the thoracic aorta.

Cholesterol feeding also leads to an increased incidence and severity of gross atherosclerosis of the abdominal aorta. This effect on lesions in the muscular aorta tends to lag behind, compared with the intensified atherogenesis in the proximal thoracic (elastic) aorta. The abdominal aorta lesions of cholesterol-fed cockerels include large, yellow, elevated longitudinal plaques, grossly resembling the spontaneous lesions of birds not fed sterol-rich diets. In addition, small, elevated, pinhead-like nodules may be seeded over the abdominal aorta, particularly adjacent to the orifices of aortic branches. Irregular plaques resembling those seen in the thoracic aorta, as well as raised, rough, granular, yellow transverse lesions, are occasionally observed in the muscular aorta of birds with advanced atherosclerosis. Such involvement occurs with high dosages (1-2 per cent) and prolonged periods (15-26 weeks) of cholesterol feeding. In general, lesions in the iliac arteries parallel those in the abdominal aorta.

The cholesterol-induced lesions in the thoracic aorta exhibit a variable microscopic morphology, depending on their stage of development and severity. Early lesions consist of accumulations of large lipid-laden, cholesterol-containing foam cells with small pyknotic nuclei. These foam cell plaques are of varying degrees of severity, from a single layer of cells beneath the intact endothelium to a veritable foam cell cushion, several layers deep. The aorta adjacent to such a cushion may be diffusely infiltrated by extracellular lipid, but is otherwise unchanged from normal.* At this stage, special stains demonstrate no changes in the media and adventitia. This early lesion is "pure" atheroma. Apparently it is the initial lesion of cholesterol-induced atherosclerosis.

In chicks fed high dosages of cholesterol for long periods,

*The relation between diffuse lipid infiltration and focal atherogenesis remains one of the key problems of atherosclerosis research.

more advanced changes are observed. These processes include breakdown of foam cell plaques with total disappearance of foam cells or their conversion into "ghost" cells. Sometimes, necrosis of the centers of foam cell plaques occurs, with formation of "abscesses" containing cellular debris, fragments of nuclei, free fat, cholesterol crystals and heavy deposits of calcium in granules or plates. Concomitantly, fibroblastic proliferation and hyaline and cartilaginous metaplasia proceed; bone formation may occur; in the heavier plaques, fine vasa may develop.

The ridgelike, smooth, longitudinal lesions in the lower abdominal aorta of cholesterol-fed chicks have a microscopic pattern which is apparently a combination of spontaneous and cholesterol-induced atherogenesis. There are subendothelial fibrosis, hyaline thickening and atheromatous change, with cholesterol crystals, foam cells, atheromatous "abscesses" and marked early calcification. As in estrogen-treated birds, these atheromatous changes are probably secondarily superimposed on pre-existent spontaneous fibrotic lesions, which may be foci of predilection for lipid and cholesterol deposition and atherogenesis. As a result of this combination of spontaneous and cholesterol-induced atherogenesis, the severity of these lesions is significantly increased. Other lesions in the abdominal aorta tend microscopically to be very similar to the cholesterol-induced plaques in the thoracic aorta.

In summary, then, cholesterol-fed chicks exhibit the spectrum of changes in the aorta seen in atherosclerotic lesions of man, including foam cell plaques, necrosis and atheromatous abscesses, fibrosis and hyalinization, vasa formation, calcification and cartilaginous and osseous metaplasia. Ulceration of atherosclerotic plaques with thrombus formation is the only human lesion not yet observed in the chick.

In addition to the changes in the aorta, brachiocephalic and iliac arteries, avian cholesterol-induced atherosclerosis extensively involves other segments of the vascular tree. Gross and microscopic lesions are found in the heart valves, endocardium and coronary arteries. Similar lesions are also present in the blood vessels of the spleen, adrenal and thyroid glands and in the main renal arteries. Furthermore, the pulmonary arteries and systemic veins may be involved, in association with generalized organ lipidosis and cholesterosis.

Gross and microscopic atherosclerosis of the coronary arteries is prominent in cholesterol-fed chicks. Gross yellow-white plaques are frequently observed in the first few millimeters of the coronary arteries. Microscopic lesions include "pure" atheroma, with lipid-laden foam cells almost completely occluding the vessel lumen. More advanced lesions exhibit foam cell cushions as well as fibrotic intimal thickenings, foci of necrosis and calcification, compression of the adjacent media and apparent penetration of lipid into the media. These lesions are primarily intimal in origin.

Extensive studies have been carried out on factors influencing cholesterol-induced atherosclerosis in chicks: dietary neutral fat levels; chronic undernutrition; patterns of cholesterol, lipid and over-all nutritional intake; lipotropic and pancreatic factors (choline, inositol, lipocaic, antifatty liver factor, pancreatic enzymes, lecithin, etc.); agents influencing alimentary cholesterol absorption (aluminum hydroxide, plant sterols); thyroid and thyrotrophic hormones; estrogens, androgens, gonadotrophic hormones and gonadectomy; alloxanization, pancreatectomy and steroid diabetes; salt and desoxycorticosterone (DCA) hypertension; ACTH, DCA, compounds E and F (cortisone and hydrocortisone); heparin; plasma lipoprotein patterns (S_f levels); bird age, and others. Limitations of space do not permit even a summary outline of the results of these experiments (cf. Katz and Stamler[3]). In addition to the foregoing studies, it has been demonstrated that with cessation of cholesterol feeding both hypercholesteremia and cholesterol-induced lesions regress in chicks; therefore the lesion of atherosclerosis is definitely reversible.

Among the several experiments analyzing factors that influence experimental cholesterol atherosclerosis in chicks, one recent study yielding particularly significant results merits summary presentation here. This project encompassed an analysis of the effects of estrogen administration on cholesterol-induced atherosclerosis in cockerels. When cholesterol and estrogens were given concurrently, *coronary* atherogenesis was conspicuously inhibited, although cholesterol-induced aorta atherogenesis proceeded unaffected. A subsequent experiment showed that estrogen administration reversed coronary lesions previously induced by cholesterol feeding, even when cholesterol feeding was continued during the period of estro-

gen administration. Here again, estrogen reversal of cholesterol-induced coronary atherosclerosis was associated with no effect on aorta lesions.

Studies of plasma lipids in these experiments suggest that the lipid pattern, and particularly the plasma ratio of cholesterol to phospholipids (C/P ratio), may be a significant factor in coronary atherogenesis. These investigations further afford a lead to the possible mechanisms of the human sex differential in susceptibility to coronary atherosclerosis. Finally, they highlight an important lesson for atherosclerosis research. Hitherto most investigators of experimental atherosclerosis tacitly assumed that atherogenesis proceeds in different arterial beds according to essentially similar biologic laws. Hence most workers confined their studies to the aorta and interpreted their findings as valid for atherogenesis in the coronary, renal, cerebral and other arteries. The results of the foregoing experiments demonstrate this to be a fundamental methodologic error. Since estrogen inhibits coronary atherogenesis in cholesterol-fed cockerels without exerting any effect on aorta atherogenesis, it may be concluded that different laws determine atherogenesis in the aorta and coronary arteries. Therefore workers in experimental atherosclerosis cannot confine their observations to the aorta.

The importance of this methodologic point is highlighted by the fact that human morbidity and mortality result mainly from coronary and cerebral atherosclerosis. Studies of human material suggest that in *homo sapiens* as well, atherogenesis in the several arterial beds proceeds according to different biologic laws. Therefore the experimenter, aiming ultimately to eliminate disease and death due to atherosclerosis in the arteries of vital human organs, must study atherogenesis in these vessels of his experimental animals. He must attempt to elucidate the basis for the different atherogenic responses of the several arterial beds to a given experimental regimen. Hence, in our laboratory, studies of the coronary arteries as well as of the aorta are now a routine part of every atherosclerosis experiment.

In conclusion, the foregoing brief summary demonstrates that avian species, particularly the chick, are highly useful for the investigation of atherosclerosis. The following facts—that the chick is an omnivorous animal, that it spontaneously develops gross lesions closely simulating those seen in man,

that three types of lesions (spontaneous, cholesterol-induced and estrogen-induced) are available for study in the chick, that cholesterol-induced atherosclerosis can be produced in this species with minimal hypercholesteremia and organ lipidosis (a pattern of lipid derangement closely simulating that usually seen in human beings with atherosclerosis) and that extensive studies may be readily accomplished on factors influencing experimental atherosclerosis in chicks—all these facts highlight the value of this avian species for atherosclerosis research.

Acknowledgements.—Grants-in-aid from the Life Insurance Medical Research Fund and National Heart Institute of the United States Public Health Service constituted the principal sources of support for these studies. Additional funds were obtained from the Special Cardiac Fund of the Committee on Scientific Research, American Medical Association; the Chicago Heart Association; the Sam and Sarah Ehrlich Fund; the A. B. Kuppenheimer Fund; the E. J. Loewenthal Fund; the Herbert G. Mayer Fund; the Michael Reese Research Foundation; the Nelson Morris Fund; the Jeannette N. and Alex D. Nast Fund for Cardiovascular Research; the Emil and Fanny Wedeles Fund.

This report is based on the work of a large team during the last decade. In addition to the authors, the principals have included Deborah V. Dauber, M.D.; Louis Horlick, M.D., and Simon Rodbard, M.D., Ph.D. Other professional personnel were Drs. L. C. Akman, S. A. Carlen, M. Feldman, Jr., G. Gros, R. Harris, M. Hurwitz, M. Lowenthal, R. S. Megibow, A. J. Miller, A. Sanders, J. G. Schlichter and E. N. Silber. We are also indebted to the following technicians: L. Adams, E. Arnold, C. Bolene, G. Crowley, M. Dudley, W. Foote, L. Friedberg, D. Friedman, L. Havel, P. Johnson, E. Levinson and J. Meyer.

REFERENCES

1. Fox, H.: Arteriosclerosis in Lower Mammals and Birds: Its Relation to the Disease in Man, in Cowdry, E. V. (ed.): *Arteriosclerosis* (New York: Macmillan Company, 1933).
2. Dauber, D. V.: Spontaneous arteriosclerosis in chickens, Arch. Path. 38:46, 1944.
3. Katz, L. N., and Stamler, J.: *Experimental Atherosclerosis* (Springfield, Ill.: Charles C Thomas, Publisher, in press).

Essential Hyperlipemia is defined as a disorder of fat metabolism of undetermined origin, which is characterized by hyperlipemia of the retention type. It is often accompanied by hepatosplenomegaly, eruptive xanthomatosis and abdominal pain.

E. R. Movitt, B. Gerstl, F. Sherwood and C. C. Epstein[4] (Veterans' Admin. Hosp., Oakland, Calif.) review the 14 cases in the literature and report 3 additional ones. The patients were aged 1-47; most were male. Abdominal pain was a prominent symptom in seven and a significant reason for hos-

(4) A.M.A. Arch. Int. Med. 87:79-96, January, 1951.

pitalization in six, two of whom were operated on because of a diagnosis of acute abdominal emergency. The liver and spleen were palpable in nine. Some observers have suggested that quick deposition of fat in the liver is associated with abdominal pain. Characteristic xanthomatous lesions were observed in seven patients. Lipemic retinitis was reported in 10. None had jaundice.

During abdominal crises, two patients had pronounced leukocytosis, but in the rest white cell counts were not remarkable. Liver function and carbohydrate metabolism tests disclosed no unusual information. In all but two cases, "milky" or "creamy" appearance of the serum was reported. Total blood lipid values were greatly increased in all patients, the increase being mostly due to rise in the concentration of neutral fats. Cholesterol level was also often increased, at times greatly.

Biopsy of a few xanthomatous lesions showed no granulation tissue or giant cells, comparative scarcity of foam cells and an inflammatory reaction. Of three bone marrow specimens, only one showed fat-containing cells. Splenic puncture in one patient revealed no abnormal cells. Autopsy of the one year old patient showed almost total lack of histologic evidence of abnormal lipid deposits in the organs or reticuloendothelial system. Fat-containing cells were seen in the marrow, lymph nodes and spleen.

The clinical course is regarded as benign. No treatment method has proved of value. There was evidence of a familial tendency in two cases. Pathogenesis of this condition is obscure, but it may be related to faulty removal of fat from the blood by the liver or to a defective mechanism of fat deposition.

Isolation of Hypertensin from Circulating Blood of Normal Dogs with Experimental Renal Hypertension by Dialysis in Artificial Kidney. Leonard T. Skeggs, Joseph R. Kahn and Norman P. Shumway[5] (Cleveland) recovered hypertensin in significantly larger amounts from the animals in the early phases of experimental renal hypertension than from those with long continued elevation of blood pressure (chronic, benign, experimental renal hypertension) or normal dogs. A possible explanation for the fact that the amount of hypertensin recovered from the dogs decreased during the second 90

(5) Circulation 3:384-389, March, 1951.

minutes of dialysis is the tendency for blood pressure of hypertensive animals and human beings to fall somewhat when they are put at complete rest.

From the data it could not be concluded with certainty that hypertensin is the vasoconstrictor material responsible for elevation of blood pressure in benign experimental renal hypertension. They do suggest this possibility, however, as well as indicate that hypertensin may play an important role in maintaining elevation of blood pressure at least in the initial phases.

[The demonstration of hypertensin by this method is convincing. When such a method applicable to man is developed, the mechanism of hypertension will become clarified. Nevertheless, the next three articles indicate the complexity of the whole problem.—Ed.]

Production and Pathogenesis of Parabiotic Hypertension in Rat. Because in various experiments hypertension has resulted from renal lesions in one of a pair of rats in parabiosis, C. E. Hall and O. Hall[6] (Univ. of Texas) studied the effects of parabiosis itself on hypertension. Litter mates were matched, placed in parabiosis by the Bunster and Meyer technic and maintained on regular diet with 1 per cent sodium chloride for drinking. Blood pressure was measured weekly by the tail plethysmograph. In many cases, massive edema in one of the partners led to death; this manifestation was not related to elevation of blood pressure and could be reversed by shifting the animals to salt-free drinking water.

In 40 per cent of the surviving pairs one of the partners developed malignant hypertension in an average of three to four weeks. Preliminary experiments indicated that saline drinking fluid is not essential for development of hypertension and that the hypertension may be a result of the parabiotic state. Hypertension was preceded or accompanied by hypotension, often severe, in the parabiotic partner; in no parabiotic pair was there hypertension in both animals.

Rats were sacrificed after three weeks of hypertension. The adrenal cortices of both partners were much larger than those of normotensive parabiotic rats, but the adrenals of the hypertensive partner tended to be larger than those of the normotensive cotwin. Other pathologic changes were confined to the hypertensive partner. Cardiac enlargement was present in all; there were hypertrophy of individual myocardial fibers and hyalinization of cardiac arterioles, with

(6) A.M.A. Arch. Path. 51:527-538, May, 1951.

periarterial reaction strikingly similar to Aschoff bodies. The kidneys appeared flea-bitten and showed hypertrophy and sclerosis of the media of the small arterioles, sclerosis of some glomeruli and occasional rupture of a glomerulus with discharge of blood into a distended Bowman's capsule. These lesions were similar to those of malignant nephrosclerosis. Sections of pancreas and superior mesenteric artery revealed lesions similar to those of periarteritis nodosa, with arterial walls transformed into a homogeneous hyaline material or showing regions of necrosis with infiltration of adventitia by lymphocytes and eosinophils. If a humoral factor causes the hypertension, either it does not cross the parabiotic capillary anastomosis or it is rendered inactive when it does.

Nature of Hypertension Occurring in Nephrectomized Parabiotic Rat. J. M. Ledingham[7] (London Hosp.) investigated possible ways of producing hypertension in parabiotic rats and describes the vascular lesion found in the viscera of the totally nephrectomized partner. Total nephrectomy was performed on one member of a parabiotic pair in 13 instances; 12 rats showed hypertension 2-12 days after nephrectomy. The intact member of the parabiotic pair showed no change in blood pressure. Maximal duration of hypertension was 44 days. Postmortem examination was done in eight pairs of animals. The totally nephrectomized member was smaller in size and showed very little or no subcutaneous or peritoneal fat. Fluid retention was present in three of the totally nephrectomized, parabiotic animals. Weights of the heart and adrenals were increased in the totally nephrectomized member. Characteristic arteriolar lesions were found in the viscera of six totally nephrectomized parabiotics but not seen in the organs of the intact member. Lesions occurred in the arteries and arterioles of the heart, pancreas, mesentery, small intestine and liver. They consisted in all cases of periarteritis with massive infiltration of the adventitia with fibroblasts and small round cells; in severe cases there was swelling of the cells of the media and deposition of fibrinoid material beneath the endothelium (Fig. 35). There were foci of necrosis in the myocardium.

In six parabiotic pairs, one kidney was removed from both animals. Only one rat showed an elevated blood pressure. When the other kidney was removed from one member, the

blood pressure of the totally nephrectomized animal rose. In eight parabiotic pairs simultaneous excision of kidneys and adrenals from one member produced no rise in blood pressure in five pairs. After operation two animals had transient rise in blood pressure. There was terminal rise in the blood pressure before death in one rat lacking kidneys and adrenals. In one to two days after operation the ears, nose and feet of the operated member were pinker than the intact member. This

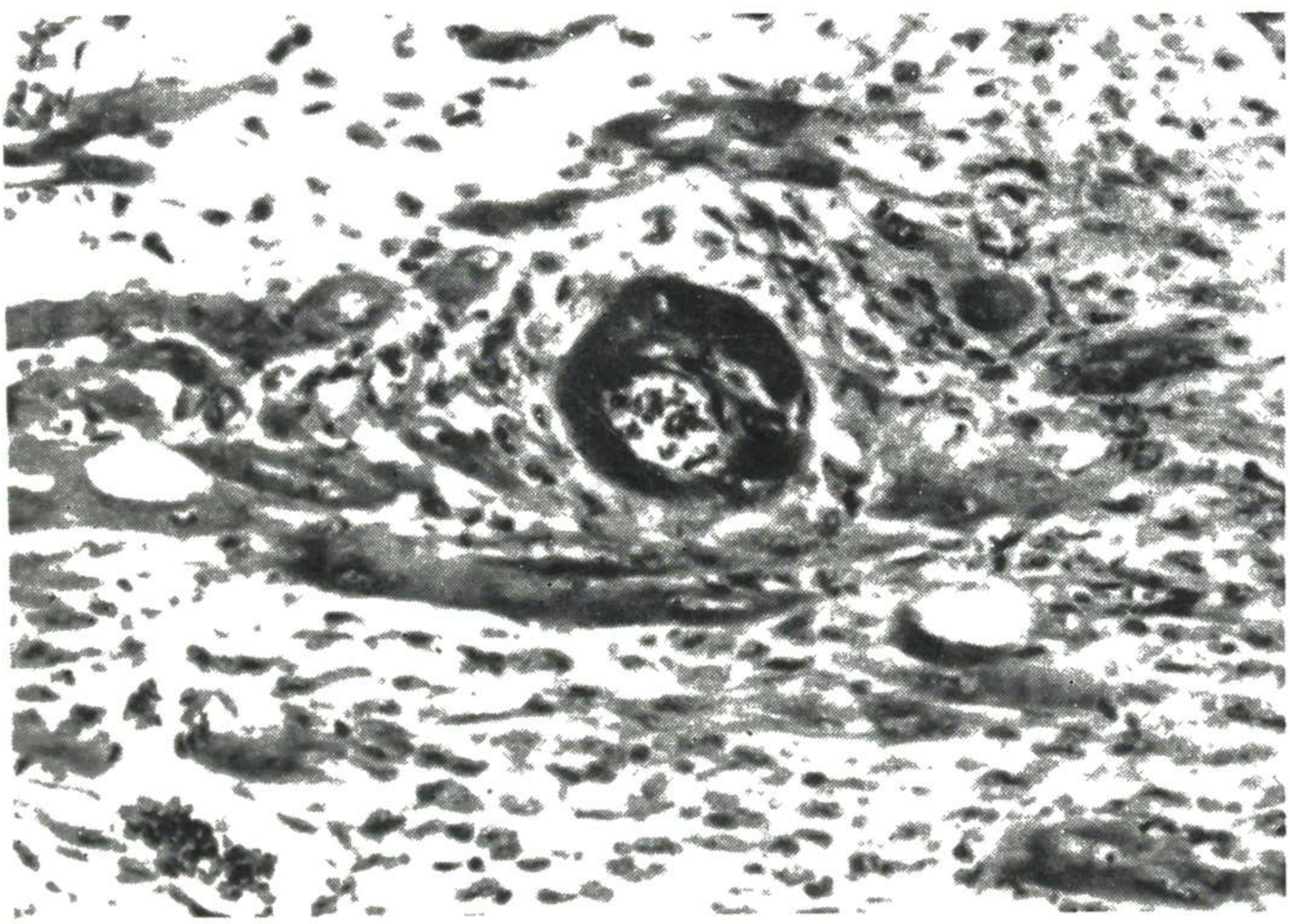


Fig. 35.—Arteriolar lesions in heart of the hypertensive nephrectomized member of a parabiotic pair. (Courtesy of Ledingham, J. M.: Clin. Sc. 10:423-439, November, 1951.)

was accentuated by anesthesia. The animals were very sensitive to cold. When adrenalectomy was done in five nephrectomized, parabiotic members the animals survived 2-32 days; during this time the blood pressure remained within normal limits, except for a transient rise in two animals. In seven parabiotic pairs total adrenalectomy of one member was done. In five of these pairs one kidney was removed from each member at the time of adrenalectomy of the single member. Blood pressure in both members remained essentially the same. Pink extremities were again noted in the totally adrenalectomized members. The thymus of each adrenalectomized member was two or three times heavier than the partner.

When DCA pellets were implanted in five of the adrenalec-

tomized, nephrectomized rats, all showed elevation of the blood pressure to high levels. The peripheral vasodilatation persisted. In four pairs of parabiotic rats the adrenals and kidneys were removed from one member and DCA pellets implanted in both animals. This resulted in increased blood pressure of both members, the nephrectomized member showing the greater degree of hypertension. Because DCA and adrenal cortical hormone have water- and salt-retaining properties, and this has been suggested as a factor in the production of hypertension, rats were injected intravenously with different solutions and blood components without producing an increase in blood pressure.

Totally nephrectomized animals of parabiotic pairs have an unstable blood pressure usually elevated at some period before death. Arteriolar lesions occur in the viscera of the nephrectomized animal but not in the intact partner. It appears that pressor factors operating in the nephrectomized partner of parabiotic rats are not derived from the intact member. The pressor factor was dependent on presence of adrenal tissue in this experiment and adrenalectomy abolished hypertension in the nephrectomized parabiotic partner but did not lower normal blood pressure in one member of a parabiotic pair when the kidneys were intact. Vasodilatation in the skin of the adrenalectomized parabiotic member was observed, both in the presence and absence of the kidneys. The phenomenon occurred without any fall in blood pressure and persisted when the blood pressure rose after implantation of DCA. This suggests that some factor from the adrenal controls the tone in the skin vessels and that this control is independent of the vasoconstriction which determines the blood pressure.

Adrenal Cortical Changes in Rats with Various Types of Experimental Hypertension are reported by Helen Wendler Deane (Harvard Univ.) and Georges M. C. Masson[8] (Cleveland Clinic). Adult male control rats of Sprague-Dawley and Wistar albino strains had adrenal glands which together weighed about 12 mg./100 Gm. body weight. Blood pressure averaged 104 mm. Hg. The zona glomerulosa appeared moderately fatty and was about 40 μ in width, whereas the zona fasciculata was broad and contained more lipid in its outer portion than farther inward.

(8) J. Clin. Endocrinol. 11:193-208, February, 1951.

Rats with both kidneys wrapped in silk showed a variable rise in blood pressure and relative enlargement of the adrenals. The zona glomerulosa was enlarged and laden with small lipid droplets which contained uniformly fine, birefringent crystals. The zona fasciculata appeared enlarged, with somewhat increased lipid content. Administration of desoxycorticosterone acetate to unilaterally nephrectomized rats given saline caused a pronounced rise in blood pressure; adrenal weights were increased in animals with severe vascular disease. The glomerulosa was narrow and fat free but the fasciculata appeared unusually fatty. Rats given compound S showed no alteration of blood pressure, adrenal weight or glomerulosal width. Administration of anterior pituitary powder resulted in moderate elevation of blood pressure and significant enlargement of adrenals. The glomerulosa was narrow and the fasciculata broadened and moderately fatty. When anterior pituitary powder and desoxycorticosterone were given concomitantly, hypertension developed more rapidly than with the pituitary powder alone. The adrenal glands were enlarged, the glomerulosa was of normal width or broader and the fasciculata exceptionally broad. Renin administration caused elevation of the blood pressure, slight enlargement of the adrenals, broadening of the glomerulosa and appearance of fat in the fasciculata.

Results suggest that desoxycorticosterone, anterior pituitary powder and encapsulation induce hypertension through separate physiologic pathways. In animals receiving saline with desoxycorticosterone or anterior pituitary powder, the reduced requirement for a salt-regulating hormone might account for involution of the glomerulosa. Enlargement of the glomerulosa probably signifies increasing output of salt-regulating hormones. Although the cause of hypertension in rats treated with anterior pituitary powder remains unknown, augmented output of salt-regulating hormones is probably not responsible. Secretion of 11-oxygenated hormones by the fasciculata may augment the hypertension induced by anterior pituitary powder.

Pathogenesis of Thrombosis. R. Jurgens (Basel) and H. Braunsteiner[9] (Univ. of Vienna) determined the agglutination of thrombocytes photoelectrically by preparing a suspension containing 100,000 platelets/cc. saline solution and plotting extinction coefficient against time. Various agents, such

(9) Schweiz. med. Wchnschr. 52:1388-1394, 1950.

as histamine, bacterial toxins, cobra and bee venom, were found to promote platelet agglutination even in the presence of anticoagulants (citrate, oxalate and heparin), preventing formation of fibrin. Platelets are known to have a negative electrical charge and to move to the positive pole in an electric field, and physicochemical conditions, such as pH, salt concentration and temperature, affected their agglutination. Studies with the electron microscope did not reveal fibrin around or on the agglutinated thrombocytes in the presence of heparin or citrate. Thrombocyte-free citrated plasma showed more rapid clotting on addition of calcium and agglutinated thrombocytes as compared with nonagglutinated thrombocytes, probably due to activation of thrombokinase.

The results indicate that agglutination of thrombocytes is independent of fibrin formation. Only secondarily is there activation of thrombokinase, which leads to fibrin production and formation of a thrombus; it is this secondary process that can be prevented by heparin. Formation of thrombi is thus favored by increased clotting tendency (increase of fibrinogen, prothrombin, thrombocytes or decreased heparin tolerance) but is not caused by it, as the process is initiated by platelet agglutination and simultaneous vascular damage which is due to endogenous or exogenous noxious substances (histamine, tumors, bacterial toxins and anesthesia).

"Fibrin Embolism" (Disseminated Intravascular Coagulation) with Defibrination as One of the End Results during Placenta Abruptio. Charles L. Schneider[1] (Wayne Univ.) describes a pathologic process, fibrin embolism, which occurs in late pregnancy, particularly with abruptio placentae. It is accompanied by low fibrinogen plasma levels, which may lead to severe hemorrhage. The distinctive feature of the process is the selective deposition of elements of fibrin culminating in massive deposition of fibrin intravascularly.

Three multiparas presented certain manifestations in common during the last trimester. Abruptio placentae with retroplacental hemorrhage and severe obstetric shock out of proportion to blood loss made emergency cesarean section necessary. All had extremely low fibrinogen blood levels, prolonged clotting and bleeding times and a pronounced tendency to hemorrhage, which complicated surgery. Blood fibrinogen was restored to adequate levels by the third postpartum day.

---

1 Sur. Gynec. & Obst. 92:27-34, January, 1951.

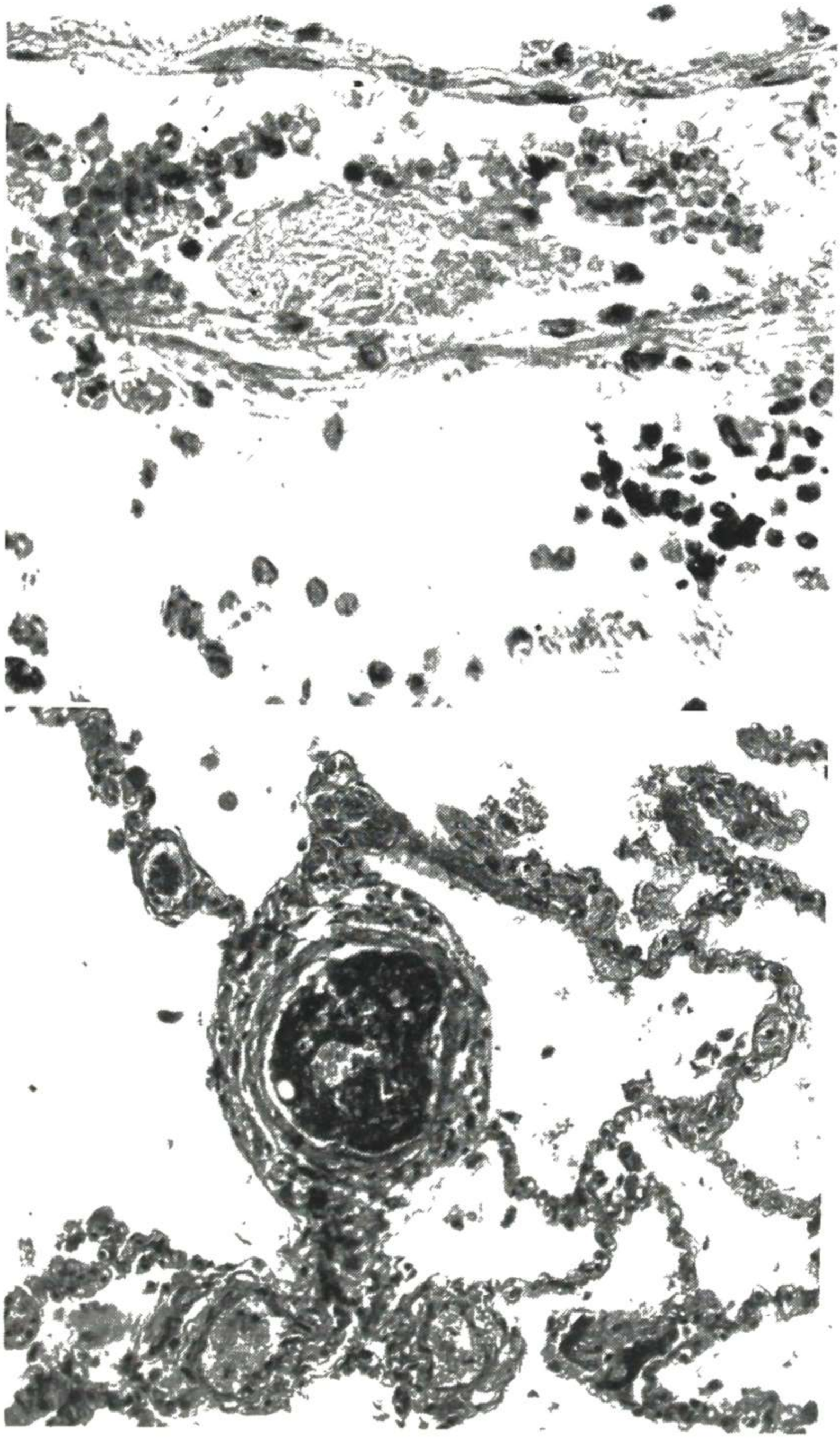


Fig. 36 (top).—Fibrin deposit in very small pulmonary artery of woman who died five days after abruptio placentae. If deposit was present from time of utero-placental accident, its form is no longer retained and orientation of its strands in relation to axis of vessel has been largely lost during five days between formation and patient's death.

Fig. 37 (bottom).—Cross-section of fibrin deposit in small pulmonary artery of woman who died a few hours after abruptio placentae. There is no lamination; at higher magnification, individual strands of fibrin can be seen in cross-section. Only central core contains clotted blood; bulk of vascular plug is made up of "coagulated protein," i.e., coagulated fibrinogen. Several arterioles are occluded also. Veins are not involved. (Courtesy of Bartholomew *et al.*)

(Courtesy of Schneider, C. L.: Surg., Gynec. & Obst. 92:27-34, January, 1951.)

One patient died of eclampsia five days after cesarean section. Autopsy showed pulmonary congestion and edema. Study of lung sections revealed no cause for edema. One remnant of intravascular fibrin deposit was found within a small artery in the lung (Fig. 36). Changes in the kidneys pointed to lower nephron nephrosis. The other two patients recovered.

Intravascular coagulation presumably develops along the usual chemical lines of fibrin formation from fibrinogen, under the influence of thrombin. The ultimate causative agent is believed to be thromboplastin. Symptoms may arise in the first stage, or coagulative phase. Autopsy on another patient who apparently died early after intravascular coagulation showed fibrin deposits disseminated throughout various organs but best seen in the lung (Fig. 37). Study of several sections showed fibrin to be the chief component occluding the vessel. Few erythrocytes were incorporated within the fibrin bands. In cross-section of occluded vessels the deposit was not laminated. In longitudinal section the fibrin strands were arranged parallel to the vessel wall, and the nuclei of the entrapped leukocytes were somewhat distorted longitudinally, as though laid down under tension. This fibrin deposit resembled those seen in longitudinal section in animals that have died as a result of thrombin injection or of thromboplastin injection or in a pregnant rabbit that has died of intravascular coagulation following placental trauma. Extensive intravascular coagulation may be the underlying cause of early death in cases of abruptio placentae or of eclampsia.

In patients who survive the first stage of intravascular coagulation, complications due to defibrination may develop. The fibrinogen levels in all three patients had apparently been adequate before development of the syndrome, as coagulation had taken place in the retroplacental hemorrhage. Fibrinopenia apparently developed acutely. In the first patient there was some evidence that this was actually defibrination resulting from intravascular fibrin coagulation. From comparison with experimental results, it is postulated that the intravascular coagulation became sufficiently extensive to deplete the circulating fibrinogen and cause the manifestation of hemorrhagic diathesis of pregnancy.

[In his address at the Ciba Symposium in London, January, 1950, Schneider indicated that evidence supports the view that autoextraction of thromboplastin from the decidua into the maternal circulation occurs spontaneously and becomes the chemical mediator of eclampsia. This is

further developed in another article [Fibrin embolism (disseminated intravascular coagulation) and the aetiology of eclampsia, J. Obst. & Gynaec. Brit. Emp. 58:538-554, August, 1950]. This interesting work requires confirmation. Although there is no doubt that thrombosis has been demonstrated, evidence of embolism in the literal sense is wanting. —Ed.]

Some Basic Observations on Venous Thrombosis and Pulmonary Embolism made on material obtained at autopsies on 100 unselected males over age 40 are reported by John McLachlin and J. C. Paterson[2] (London, Ontario).

Special attention was given to the lungs and to the veins

Fig. 38.—Thrombus arising in valve pocket at upper end of superficial femoral vein. The lines of Zahn are clearly seen. Postmortem clot is shown for comparison. (Courtesy of McLachlin, J., and Paterson, J. C.: Surg., Gynec. & Obst. 93:1-8, July, 1951.)

of the lower extremities. The pulmonary arteries and their branches were carefully searched for pulmonary emboli, using the "open book" method. All suspected emboli were confirmed by microscopic examination, and an attempt was made to compare their ages with those of the primary thrombi in the leg veins.

(2) Surg., Gynec. & Obst. 93:1-8, July, 1951.

The veins were removed in continuity from the lower end of the vena cava to the posterior tibial vein at the level of the internal maleolus. The specimen included the common, external and internal iliac, the common, superficial and deep femoral, the long and short saphenous, the medial and lateral circumflex femoral and the posterior tibial veins to their very small branches. All suspected thrombi in the veins were sectioned and examined microscopically to prove their antemortem nature. Thrombosed segments of the veins were removed in toto and subjected to serial section, but these failed to show any underlying intimal changes which would act as a precipitating factor in thrombus formation.

Grossly demonstrable venous thrombi were noted in 34 per cent of the dissections, and 56 per cent of these resulted in pulmonary embolism. In each case of pulmonary embolus a gross antemortem thrombus was demonstrated in the veins of the pelvis or lower extremities. The large veins of the thigh are the most common site for thrombosis. Seventy-three per cent of the thrombi arose in the thigh and pelvic veins and 31 per cent arose in direct relation to a valve pocket (Fig. 38).

Because of the interest in superficial femoral vein ligation for either prophylaxis or therapy of pulmonary embolism, the number of thrombi which originated above and below this site of operative intervention was assessed and showed 37 thrombi arising above usual site of surgical ligation and 39 thrombi arising below this site. In the 34 cases of venous thrombosis, superficial femoral vein ligation would not have prevented pulmonary embolism in 21.

The observations fail to show that there is any distinct difference between thrombophlebitis and phlebothrombosis as a source of pulmonary emboli. The authors do not believe that ligation of the superficial femoral veins to prevent or treat pulmonary embolism is basically sound.—Ed.]

Fatal Myocardial Fat Embolism in Periodic Catatonia with Fatty Liver is reported by Jan Cammermeyer and Rolv Gjessing.[3]

Man, 53, had had periodic catatonia for about 30 years. During a relapse he had three successive seizures consisting of collapse, cyanosis and muscular twitchings. The third resulted in death. Such seizures had not been present in previous attacks. Autopsy disclosed conspicuous centrolobular fatty accumulations in the liver (Fig. 39). The myocardium showed no acute necrotic changes but in the connective tissue there were many fat cells. Fat emboli were

(3) Acta med. scandinav. 139:358-367, 1951.

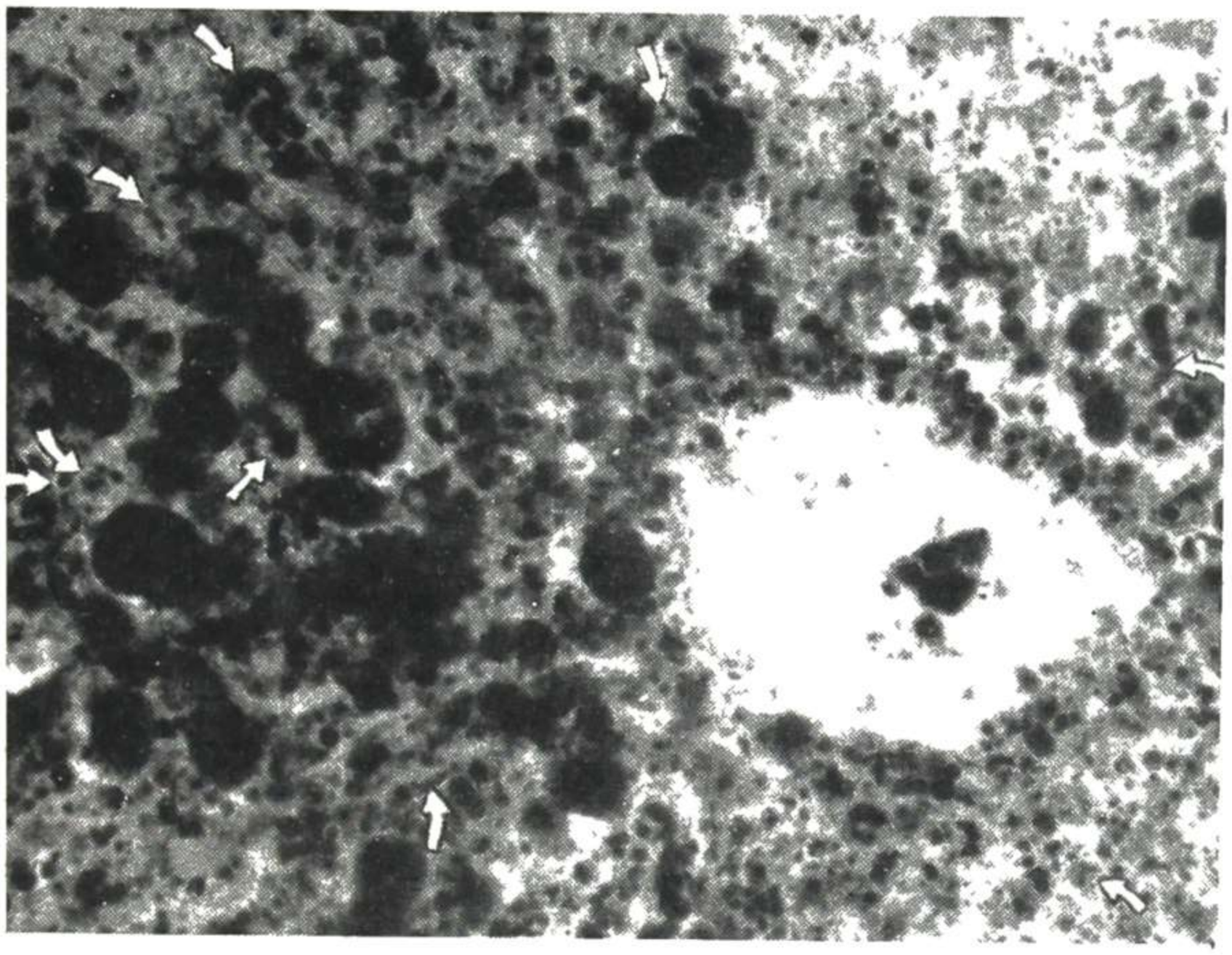


Fig. 39.—Fat accumulation in liver predominating in parenchymal cells adjacent to central hepatic vein, which encloses fat globules (emboli?). Kupffer cells filled with fat (arrows). Sudan gelatin-embedded frozen section; × 160. (Courtesy of Cammermeyer, J., and Gjessing, R.: Acta med. scandinav. 139:358-367, 1951.)

seen in the capillaries and a few in the small vessels of the lungs; there were none in the adrenals or brain.

It is suggested that the fat liberated from the liver passed through the lungs, occluding the capillaries of the myocardium, and caused death. If these acute terminal phenomena had been part of the pathophysiology of periodic catatonic disease, residua of old tissue damages so conspicuous in fat embolism should have been found but were not.

White Thromboembolism in Hamster Cheek Pouch after Trauma, Infection and Neoplasia. Brenton R. Lutz, George P. Fulton and Robert P. Akers[4] (Boston Univ.) produced platelet thrombosis and embolism in the distal blood vessels of transillumined cheek pouches of hamsters by vascular occlusion for 20-45 minutes, which resulted in trauma to the endothelium. They were demonstrated by cinephotomicrography.

After vascular occlusion, intubation of dicumarol® prevented formation of platelet thrombi and emboli. In animals which had not undergone vascular occlusion, it produced both leukocytic thrombosis and embolism. Heparin produced platelet emboli, but no platelet thrombi, and leukocytic coating (thrombosis), but no leukocytic emboli. Infection with Staphylococcus aureus produced mixed platelet and leukocytic

(4) Circulation 3:339-351, March, 1951.

coatings, together with emboli of a similar nature, as well as thrombopenia and leukocytosis. In the presence of cheek pouch transplants of methylcholanthrene-induced sarcoma, vessels showed white emboli composed largely of platelets. Mixed platelet and leukocytic coatings and leukocytosis were characteristic. Sludged blood was not produced by trauma, infection or malignant neoplasia.

Cardiovascular Responses to Air Embolism. G. R. Cameron, S. N. De and A. H. Sheikh[5] (London) believe that the most important factor in fatal pulmonary embolism is obstruction to pulmonary circulation. Air was introduced under controlled pressure and speed into ear veins of rabbits. Various other emboli were investigated, including those produced by injection of potato starch or mixture of olive oil and lecithin and direct introduction of rape seeds. There was a relation between the rate of air injection and time of death. As the rate increased, survival time decreased, but not in direct proportion to the amount of air introduced (table).

Injection of air was followed by fall in carotid arterial pressure and increase in right auricular pressure. This change

Representative Experiments of Air Embolism in Rabbits

Rate of Air Injection, Cc./Min.	Time of Death, Sec.	Total Air Injected, Cc.
1	520	8.6
1	475	7.9
2.5	225	9.4
3	295	14.9
8	80	10.6
13	40	8.6
2.5 (bilateral vagotomy)	270	11.2

was either prolonged or abrupt. At first the respiratory rate increased, becoming slow and irregular as embolism progressed. If bilateral vagotomy was done before air injection, respiration became deeper and slower. Vagotomy did not affect auricular or carotid pressure or the lethal amount of air.

As embolism progressed, the right auricle and ventricle, great veins, coronary veins and pulmonary artery became distended with frothy blood. The left auricle and ventricle, pulmonary veins and systemic arterial system were free from air bubbles and contained little blood. Air bubbles could never be demonstrated in the coronary arteries. In a few instances, when embolism was instituted during artificial respiration and

(5) J. Path. & Bact. 63:181-194, April, 1951.

the heart was exposed, bubbles were seen in the coronary veins before the right heart dilated and carotid pressure fell. All animals with air embolism showed definite ECG alterations. The principal changes were a deep S wave in lead I and a depressed RS-T segment in leads I and II. Ventricular fibrillation was not noted. Vagotomy did not affect the cardiac changes.

In experimental embolism, death is attributed to blocking of the pulmonary blood flow. The authors exclude as causative factors vagal inhibition of coronary flow, air embolism in either coronary veins or arteries and primary cerebral ischemia.

[The authority of the authors is unquestioned, and their technics are certainly of the best. Thus, credence must be given to their conclusion that with air embolism death is due to blocking of the pulmonary blood flow. This does not exclude, however, a possibility of gaseous emboli in brain and coronary arteries, which is observed in some instances of overexpansion of the lung in the accidents that may follow escape from considerable depths in the ocean. It is still possible that with solid emboli death may result from other mechanisms.—Ed.]

Edema and Capillary Anoxia. R. C. Nairn[6] (Univ. of Liverpool) reports effects of diminished oxygen supply to extremities of intact animals. In dogs, one hind limb was perfused via the femoral artery with blood flowing from the femoral vein of the other hind limb. Pressure of venous blood delivered to the opposite artery was increased to normal arterial level by a perfusion pump. Perfusion circulation was maintained as long as possible. After six to seven hours the animals usually showed signs of general circulatory failure and were killed. Hematocrit values, plasma protein concentrations and oxygen content were determined at intervals on blood from the femoral artery and vein of the donor limb and the femoral vein of the perfused limb. Edema was assessed by gross and microscopic manifestations and by the gravimetric method. Average oxygen saturation of the perfusing blood was about 50 per cent.

Throughout perfusion no detectable edema was found in the experimental limb or elsewhere. Percentage of water content in muscles after death was essentially the same in all limbs. Hematocrit readings and plasma protein estimations did not differ in perfused and control limbs. The donor limb and the upper extremities received almost completely oxygenated blood and extracted from it 5½ vol. oxygen/100 vol.

(6) J. Path. & Bact. 63:213-234, April, 1951.

blood. The perfused limb received one-half oxygen-saturated blood and extracted 1 vol./100 vol. blood.

Various modifications of the experiment were done to determine the possible influence of other factors. When the perfusing blood was diluted with saline, edema was produced. Slight generalized edema also developed because of the return of diluted blood to the systemic circulation. In four animals generalized edema was produced by intravenous injection of saline during perfusion. Extent of edema was the same in perfused and control limbs. Physiologic saline injected subcutaneously in perfused and opposite limbs was absorbed at the same rate from both sides. The effect of venous hyperemia was studied in four animals. Venous pressure was raised by inflation cuffs in the perfused and one or more control limbs. The same degree of edema developed in experimental and control limbs, the amount depending solely on extent of venous pressure increase. In biopsy and postmortem material histologic evidence of edema indicated that increased hydration chiefly affected the interfascicular spaces.

Hypoproteinemia was induced by plasmapheresis during one perfusing experiment. Ascites and edema developed. There was no difference in amount of edema of experimental and control limbs. Reactions of sensitized animals to horse serum were similar in perfused and control limbs. Exercise of the perfused limb of one animal for four hours during the experiment caused results no different from those seen in perfused limbs at rest.

Latent effects were investigated. Limbs were perfused for four hours as in the original experiment. All changes in circulation were returned to as nearly normal as possible. Two animals survived about four hours. Neither showed edema of the perfused or control limbs. Results suggest that capillary anoxia plays no part in production of edema.

Peroxidation of Human Adipose Tissue in Peripheral Venous Diseases. Vitamin E has been reported to exert a beneficial effect in cases of ulcus cruris, a condition accompanied by local changes in the adipose tissue, and in certain experimental diseases characterized by vitamin E deficiency, such as the yellow-brown fat in rats and chickens, peroxides of fatty acid can be demonstrated in the tissue by suitable chemical methods. These facts led Knud Ehlern Jessen, Johs. Glavind,

Svend Hartmann and Henrik Dam[7] (Polytechnic Inst., Copenhagen), during a study of trophic disturbances in the lower extremities of patients with venous disease, to examine subcutaneous fat for the presence of peroxides. Material was obtained at eight autopsies. Samples were taken from the affected subcutaneous tissue on the inside of the lower one third of the extremity. Control samples were taken from the corresponding location on the other extremity if the vessels were normal. The peroxide value, reported in milliequivalents/1,000 Gm. fat, was determined by photometric measurement of the color reaction produced in the chloroform-extracted material.

The peroxide values of the pathologic tissue of six patients were decidedly higher than those of the corresponding control sample. In one patient, the peroxide value of the pathologic tissue was as low as that of the control. This patient had a fresh, deep thrombosis originating from varices of the vena saphena magna. The patient had not been ambulatory for five days, and the effects of venous stasis may not have been fully developed. In another patient with pronounced edema from heart disease, peroxidation of the adipose tissue could not be demonstrated.

The positive peroxide values found in pathologically changed adipose tissue indicate that abnormal oxidation processes have taken place locally in the tissue. Peroxidation is thought to have occurred before death, possibly as a consequence of a local deficiency of vitamin E.

HEMOPOIETIC SYSTEM

New Inherited Abnormality of Hemoglobin and Its Interaction with Sickle Cell Hemoglobin. Eugene Kaplan, Wolf W. Zuelzer (Children's Hosp., Detroit) and James V. Neel[8] (Ann Arbor, Mich.) observed several patients with a hemolytic syndrome associated with erythrocytic sickling, the clinical, hematologic and genetic patterns of which did not fit those of sickle cell anemia. When blood from these patients and members of their families was analyzed electrophoretically, a new type of hemoglobin was clearly distinguishable from both normal and sickle cell hemoglobin. This hemoglobin compo-

(7) Acta path. et microbiol. scandinav. 29:73-76, 1951.
(8) Blood 6:1240-1259, December, 1951.

nent was designated hemoglobin III, as it is the third type of hemoglobin to be identified electrophoretically in adults. Combination of hemoglobin III and sickle cell hemoglobin was associated with a mild hemolytic syndrome, erythrocytic sickling and splenomegaly (Cases 1, 2 and 6). In combination with normal hemoglobin, hemoglobin III was associated with an asymptomatic carrier state without erythrocytic sickling (Cases 5, 7 and 10). The homozygous condition with respect to hemoglobin III has not been recognized. The parents and three children in each of two families of native-born American Negroes were studied.

CASE 1.—Girl, 12, showed normal weight and development. Erythrocytic sickling was found at age 4, when she had pneumonia. Since then she had been in good health. Hepatosplenomegaly had been present since age 2. Splenic enlargement was progressive; the spleen was smooth, firm and nontender. Mild normochromic anemia was present, with minimal reticulocytosis and no elevation of leukocytes or serum bilirubin value. Target cells were frequent in peripheral blood films, but the crescent sickle forms and iron-staining erythrocyte granules usually present in sickle cell anemia was not seen. In sealed moist blood films, erythrocytes showed rapid sickling. Fecal hemoglobin excretion was moderately increased. There was moderate erythroid hyperplasia of bone marrow. The patient's erythrocytes were eliminated more rapidly than normal cells after transfusion into a normal recipient, whereas normal erythrocytes transfused into the patient were eliminated at a normal rate. Electrophoretic studies revealed both the component characteristic of sickle cell hemoglobin and hemoglobin III.

CASE 2.—Boy, 10, sibling, showed normal development and weight. At 2½, he had an acute febrile illness which was followed by enlargement of the liver and spleen and severe anemia with many nucleated red cells and erythrocytic sickling. After that, he remained in good health. The liver and spleen were slightly enlarged, firm and nontender. Hematologic observations and electrophoretic pattern of hemoglobin were virtually identical with those in Case 1.

CASE 3.—Boy, 8, sibling, showed a normal clinical and hematologic status and normal hemoglobin electrophoretic pattern.

CASE 4.—Mother, 32, was in good health. Except for erythrocytic sickling, blood was normal. Electrophoretic study revealed the hemoglobin to be a mixture of normal and sickle cell hemoglobin.

CASE 5.—Father, 34, was in normal health. Except for increased erythrocyte resistance to hypotonic saline solution and for 18-25 per cent target forms of red cells, blood was normal. Erythrocytic sickling was absent. When transfused into a normal recipient, erythrocytes were eliminated at an abnormally rapid rate. Electrophoretic study revealed a mixture of normal and type III hemoglobin.

CASE 6.—Girl, 4, had a respiratory infection at age 2, when she

showed severe anemia, slight icterus and splenic enlargement. The icterus subsided and anemia improved. She developed normally. Liver and spleen were moderately enlarged. Skeleton was normal on x-ray examination. Blood showed moderate anemia, sickling of erythrocytes in vitro, mild reticulocytosis and frequent target cells in the films but no sickling forms or iron-staining erythrocyte granules. Fecal urobilinogen excretion was moderately increased. There was moderate erythroid hyperplasia of marrow. The patient's cells were rapidly eliminated when transfused into a normal recipient. Normal erythrocytes had normal survival time when transfused into the patient. Electrophoretic analysis revealed sickle cell hemoglobin and hemoglobin III, together with a very small proportion of normal hemoglobin.

Case 7.—Boy, 7, sibling, was well developed. Blood showed 3-5 per cent target cells, increased erythrocyte resistance to hypotonic saline solution and rapid disappearance of red cells transfused into a normal recipient. Mechanical fragility was normal. Hemoglobin was a mixture of normal and type III components.

Case 8.—Boy, 5, sibling, was entirely normal with respect to clinical and hematologic status. Electrophoretic studies revealed normal hemoglobin.

Case 9.—Mother, 29, had normal blood except for erythrocytic sickling.

Case 10.—Father, 30, was in good health. Peripheral blood levels of red cells, hemoglobin, reticulocytes and leukocytes were within normal limits. Blood films contained 8-10 per cent target cells. Slight hyperbilirubinemia was present on two occasions. Results of osmotic and mechanical erythrocyte fragility tests were normal. Electrophoretic study of hemoglobin showed a mixture of normal and type III components. When the patient's erythrocytes were transfused into a normal recipient, they were rapidly eliminated.

Presence of hemoglobin III is determined by a gene which appears to be transmitted as a simple mendelian dominant. The relation of this gene to the one responsible for sickle cell anemia which is transmitted similarly is not clear.

[The use of electrophoresis patterns is attaining increasing importance in clinical diagnosis of various disorders and gives great promise. The identification of a third type of hemoglobin, as correlated with clinical, hematologic and genetic observations, is an indication of what may be expected in the future.—Ed.]

Congenital Leukemia. William G. Bernhard, Ira Gore and Ralph A. Kilby[9] (Armed Forces Inst. of Pathology) present data on 14 acceptable cases from the literature and 4 new cases in which hematologic studies were conducted during life and autopsy was done. For a diagnosis of congenital leukemia there must be symptoms or signs at birth or shortly thereafter which can be correlated with the characteristic

(9) Blood 6:990-1001, November, 1951.

hematologic disturbance. Significant manifestations are spontaneous hemorrhages of the skin and mucous membrane, nodular skin infiltration, enlargement of liver and spleen, adenopathy, fever and pallor. The blood should reflect an alteration of the marrow by showing an undue proportion of poorly differentiated or undifferentiated cells, usually of the granulocyte series. In most cases white cell counts are elevated and red cells and platelets reduced. Nucleated red cells may be present in varying numbers. The pathologic changes often confused with congenital leukemia are congenital syphilis and erythroblastosis foetalis.

The authors' four patients lived from 19 hours to several weeks. The peripheral blood showed white cell counts varying between 5,600 and 246,000/cu. mm. A large percentage of immature or undifferentiated cells of the granulocyte series was present. There were multiple developmental anomalies in three cases. The bone marrow was hyperplastic and contained an increased percentage of poorly differentiated or primitive cells of the granulocyte series. One patient had multiple, red to purple subcutaneous skin lesions at birth. The liver, spleen, lungs and pancreas showed variable degrees of infiltration by immature cells of the granulocyte series. The liver was usually the most extensively infiltrated; frequently the normal histologic components were completely obliterated by the leukemic cells. In the case of subcutaneous involvement, leukemic infiltration formed the skin nodules. None of the mothers were leukemic.

The relative abundance of recognizable differentiation in the leukemic cells found in the tissues at autopsy in these four cases indicates that the process must have been present during an appreciable portion of fetal life. Histologically, the granulocytic leukemic process in most of the cases of the congenital variety resemble the chronic counterpart in the adult.

Effect of West Nile and Ilheus Viruses on Mouse Leukemias was studied by Chester M. Southam, Beverley Bronstein and Lorraine F. Webber[1] (Sloan-Kettering Inst.). Mice of the Akm strain were given inocula standardized to deliver 100,000 cells of leukemia Ak4 and Ak9421, with production of fatal leukemia in over 95 per cent. Blood counts were usually done three times weekly in the early stages of leukemia and daily after the leukocyte count began to rise.

(1) J. Cancer Res. 11:669-675, September, 1951.

In untreated Akm mice, Ak4 leukemia caused death in 4-16 days. No abnormality of the leukocyte count was apparent for about five days after inoculation. The count then rose rapidly to levels of 100,000-400,000 cells on the day of death. The increased leukocytes were predominantly very immature cells, probably lymphoblasts. At autopsy, the inguinal nodes, liver and spleen were enlarged. Histologically, there was widespread infiltration with leukemic cells, most obvious in the liver.

Untreated Ak9421 leukemia was less acute than Ak4, and the leukocyte count rarely exceeded 50,000. Death usually occurred 11-20 days after inoculation. The gross and microscopic pathologic pictures resembled those in Ak4 leukemia.

A 20 per cent emulsion of mouse brain infected by the West Nile virus or the Ilheus virus was used for intraperitoneal inoculation. For controls, a similar emulsion of normal mouse brain was injected. Nonleukemic Akm mice infected with the West Nile virus appeared well until the 3d day, when some animals exhibited paralysis and one died. By the 6th day, 8 of the 10 mice were dead, and all died by the 9th day. Only six of the 10 nonleukemic mice inoculated with the Ilheus virus died of the infection. Five died 9-13 days after inoculation. Both viruses caused slight leukopenia and lymphopenia around the 7th day.

West Nile virus was inoculated, in several experiments, from four hours to seven days after inoculation of Ak4 leukemic cells. In the untreated controls, leukocyte counts remained at normal or near normal levels for two or three days after the blood had become leukemic. There was no depression of granulocytes and only moderate depression of lymphocytes below normal levels during this period. The effect was a selective inhibition of leukemic blast cell proliferation. Since the virus usually kills in 5-9 days, studies of leukemia beyond 10 days were rarely possible. In the few mice that did survive to the 12th day, leukocytes and blast counts were elevated. This finding suggested that the antileukemic effect of the virus is merely suppressive. Treated leukemic mice did not show liver, spleen and lymph node enlargement. Results with the Ilheus virus in Ak4 leukemia paralleled those seen with the West Nile virus.

When the West Nile or Ilheus virus was inoculated in the early stages of Ak9421 leukemia, mice died of virus encepha-

litis before untreated leukemic controls showed any signs of leukemia. When the West Nile virus was inoculated seven days after inoculation with leukemia, blood counts remained essentially normal for two days after the controls showed leukemic counts, but there was no significant difference in the survival time. In this strain of leukemia, the inhibitory effect was against both mature and immature lymphoid cells.

When Ilheus virus was inoculated on the 11th day of Ak9421 leukemia, leukocytosis was partially suppressed. When the virus was given on the 7th day, no effect on leukemia was observed.

Mice with Ak4 leukemia had higher titers of West Nile virus in the spleen than in the blood. The brain contained no detectable virus at 48 hours but at 4 and 7 days showed higher titers than the blood or the spleen. The erythrocytes of Ak4 leukemia did not contain Ilheus virus, and the leukocytes showed higher titers of the virus than the blood plasma.

The antineoplastic effect of the neurotrophic viruses is manifested by a two to three day delay in development of leukemic leukocytosis and visceral infiltration of mouse leukemia. The interval represents 20-40 per cent of the total duration of the uninhibited neoplastic process. The virus may possibly enter the leukemic cell, destroying or preventing multiplication of the cell.

[It is to be hoped that the mechanism of inhibitory action of neurotrophic viruses in neoplasia will be clarified by further study. Until this is done, the use of such viruses clinically is something of an empiric procedure.—Ed.]

Diffuse Disseminated Platelet Thrombosis (Thrombotic Thrombocytopenic Purpura): Report of Two Cases is made by David C. Wallace[2] (Sydney).

Case 1.—Man, 22, was treated with procaine penicillin for secondary infection of a minor abrasion. Arthralgia and a purpuric rash developed a week later. Pain and swelling of the hands and ankles appeared. Urine contained albumin and blood cells. The rash and joint symptoms disappeared after a few days. During the second week, low grade fever developed. Blood studies showed leukocytosis and normochromic anemia. Variation in size and shape of the red cells, with numerous spherocytes, characterized the peripheral smear. Reticulocytes were increased. Red cell fragility was normal. Platelet counts were not done. Anuria developed and was followed by the manifestations of azotemia. Paralysis developed suddenly 14 days after the initial symptoms and he died.

Autopsy revealed punctate hemorrhages and blood in the renal

(2) M. J. Australia 2:9-13, July 7, 1951.

pelvis. Microscopically, there were lesions of the arterioles and capillaries in the pancreas, mesenteric lymph nodes and kidneys. Age of the lesions varied. The primary change appeared to be a circular accumulation of hyaline material beneath the endothelium. Further development produced occlusion of the lumen by platelet thrombi. Some vessels had no endothelial proliferation or surrounding cellular reaction. Other vessels, particularly in the kidney and lymph nodes, showed pronounced perivascular cellular infiltration associated with fibrinoid degeneration of arteriolar walls. Such a picture is typical of periarteritis nodosa. In addition the kidney showed proliferative glomerulitis.

CASE 2.—Man, 49, was treated with penicillin and a sulfonamide for sore throat. Oliguria appeared 11 days later. Elevated blood pressure, hematuria, albuminuria and anemia were followed by renal failure. The blood picture was normal. Platelet counts were not done. Paralysis developed suddenly and he died.

At autopsy a large hematoma was seen around the left kidney, the origin of which was not apparent. Microscopically, there was pronounced arteriosclerosis in all organs. Manifestation of a late stage of acute glomerulonephritis with typical crescent formation was seen in the kidneys. There was evidence of thrombosis of hyaline platelets in the small arterioles and capillaries of the pancreas and kidney.

Glomerulitis has not been previously recognized as a prominent feature of diffuse disseminated platelet thrombosis. In these two patients it was severe enough to cause renal failure. The bleeding tendency, so notable a symptom in other reports, was insignificant in them. Diffuse disseminated platelet thrombosis may be related to the collagen diseases, as suggested by the resemblance of lesions in Case 1 to those of periarteritis nodosa.

Influence of Stress Stimuli on Lymphatic Tissue of Adrenalectomized Mice. Acute lymphatic involution is known to develop after stress as a result of increased secretion of adrenocortical hormone. To determine if any other mechanism of stress exerts influence on lymphatic tissue, Thomas F. Dougherty and L. F. Kumagai[3] (Univ. of Utah) carried out experiments which eliminated the action of adrenocortical hormone.

METHOD.—Adrenalectomized mice were subjected to three types of stress: (1) fasting; (2) injection of histamine two hours after adrenalectomy; (3) anaphylactic shock induced by injection of horse serum two hours after adrenalectomy. Another group was subjected to the last type, with addition of splenectomy at the time of adrenalectomy. Control mice consisted of a nontreated intact group, nonstressed adrenalectomized animals and starved intact mice (controls for the fasted adrenalectomized group). Total blood and differential

(3) Endocrinology 48:691-699, June, 1951.

counts were done. Weights of lymph nodes, spleen and thymus were determined.

In nonstressed adrenalectomized animals, leukocytosis developed in 24 hours and was present for 5 days. This was due

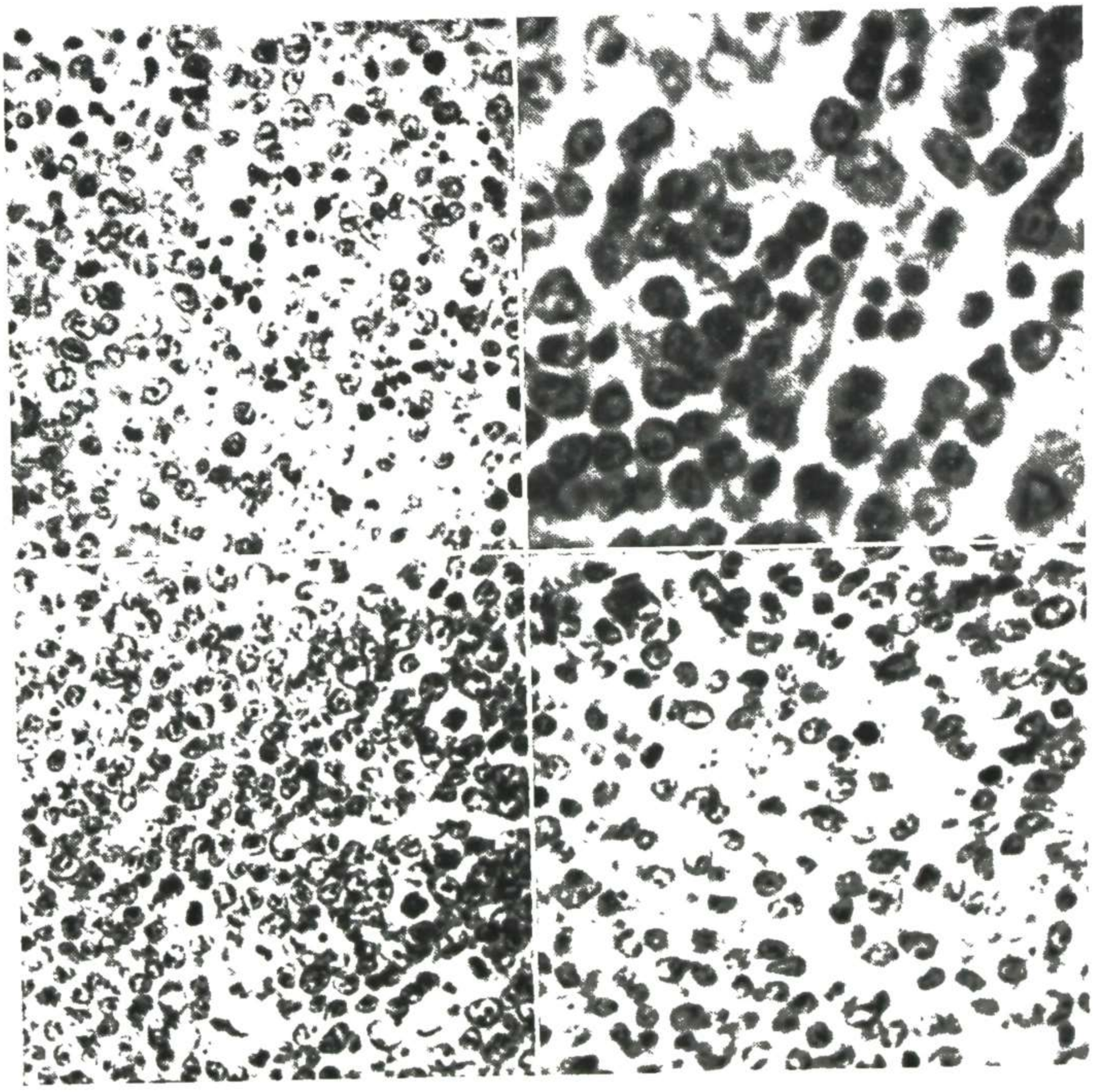


Fig. 40 (top left).—Mesenteric lymph node of sensitized intact mouse 45 minutes after administration of challenging dose of horse serum. Extensive lymphocytolysis, but little phagocytosis of nuclear debris; reduced from × 450.

Fig. 41 (top right).—Thymus of sensitized mouse treated as in Figure 40. Lymphocytolysis and edema present throughout cortex; reduced from × 900.

Fig. 42 (bottom left).—Mesenteric lymph node of adrenalectomized mouse in anaphylactic shock (45 minutes after challenging dose, 2 hours 45 minutes after adrenalectomy). Lymphocytolysis absent. Mitotic figures numerous throughout node; reduced from × 450.

Fig. 43 (bottom right).—Thymus of adrenalectomized mouse treated as in Figure 42. Complete absence of lymphocytolysis and edema. Numerous mitotic figures; reduced from × 450.

(Courtesy of Dougherty, T. F., and Kumagai, L. F.: Endocrinology 48:691-699, June, 1951.)

principally to absolute increase in lymphocytes. Intact fasted animals showed leukocytosis, eosinopenia and lymphopenia after 48 hours, at which time adrenalectomy was done. Leukocyte count remained high; eosinophil count began to approach normal 2 hours after surgery; and lymphocyte count reached

normal in 1 hour, passed its peak in 8 and remained above normal for 24. In animals receiving histamine, leukocyte count was elevated 2 hours after injection and remained high for 24. There was absolute increase in polymorphonuclear and eosinophilic leukocytes. The lymphocyte rise began at 2 hours, reached its peak at 12 and was back to normal in 24. After anaphylactic shock leukocytosis was more pronounced than after other forms of stress. Increase in polymorphonuclear leukocytes was apparent after four hours and reached its peak at eight. Eosinophilia was highest at eight hours. Increase of lymphocytes began within 2 hours, reached its peak at 12 and dropped to the normal characteristic of adrenalectomized nonstressed animals in 24. In the splenectomized animals of this group similar changes took place except the peak of lymphocytosis which occurred at four hours.

Weights of the lymph nodes and spleen did not change in nonstressed adrenalectomized animals. In adrenalectomized animals exposed to anaphylactic shock, their weights were increased at two and eight hours. Lymph nodes, spleen and thymuses were altered morphologically within 45 minutes after a challenging dose of horse serum in both sensitized intact and adrenalectomized animals exposed to anaphylactic shock. In sensitized intact animals, extensive lymphocytolysis was the outstanding change (Figs. 40 and 41). In sensitized adrenalectomized animals, no such change occurred. Instead, mitotic figures of the lymphocytes were increased (Figs. 42 and 43).

Apparently the three different types of stress used may produce changes in lymphatic tissue without relation to increase in adrenocortical hormone. In adrenalectomized animals the major stress response is greater and more rapid increase in lymphocytopoiesis. This is not due to release of lymphocytes from the spleen, but its cause is unknown.

[In the 1950 YEAR BOOK (pp. 7 ff.) Dr. Hans Selye explained his conception of reactions to stress.—Ed.]

Virus Scratch Lymphadenitis (Cat-Scratch Disease, Maladie des Griffes de Chat, Lymphoreticulosis Benigna), an epidemic disease new to Central Europe, causes acute regional lymphadenitis. The nodes may suppurate, but no organisms can be cultured. O. Gsell, R. Forster and E. Klaus[4] (St. Gallen) studied 10 patients (2 women), aged 6-44. The initial

(4) Schweiz. med. Wchnschr. 81:699-704, July 21, 1951.

diagnoses—lymphogranuloma inguinale, leukemia, Hodgkin's lymphogranuloma, tuberculosis, glandular fever and coccic infection with abscess—were not borne out by various tests, and glandular swellings subsided gradually within 3-12 weeks. Nine patients had contact with cats and two had a cat bite (Fig. 44). Definitive diagnosis was made by positive reaction to intradermal injection of Mollaret's antigen and by complement fixation reactions.

Virus scratch lymphadenitis, a lymphogenous infectious disease, has an external portal of entry and passes via the

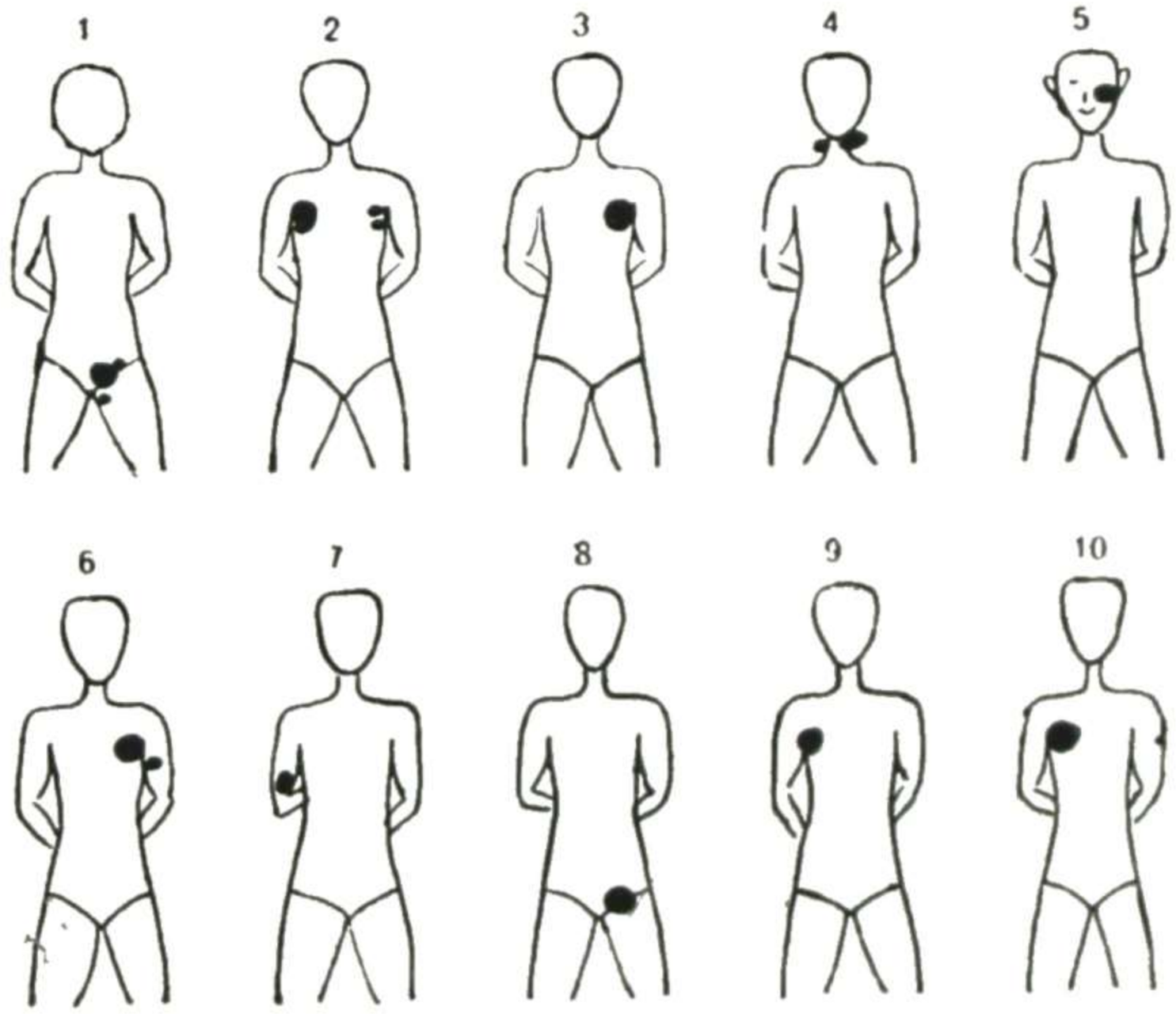


Fig. 44.—*1*, bite and scratch (cat hunter); *2*, *4*, scratch by house cat; *3*, *5*, *6*, *7*, *9*, contact with house cat; *8*, questionable cat contact; *10*, cat bite. (Courtesy of Gsell, O., *et al.*: Schweiz. med. Wchnschr. 81:699-704, July 21, 1951.)

lymphatics to the regional nodes. The first change is a small papule surrounded by a red area. The incubation period is 10-20 (occasionally up to 60) days. In this series the axillary nodes were involved most often and in some patients — but usually not in children — were spontaneously painful; palpation evoked pain. Suppuration occurred in two cases. Systemic signs of inflammation appeared oftener in adults than in children. Initially, some patients had neutrophilic leukopenia, but eventually the neutrophils increased. Eosinophil count was 2-9 per cent in some.

The etiology of scratch lymphadenitis is unknown but apparently involves an ultravirus which is related biologically to the agent producing lymphogranuloma inguinale, is carried

by cats and transmitted by close contact with these animals. Human-to-human transmission is unknown. The disease, reported since 1950 from Europe, Bombay and Cincinnati, is probably of world-wide incidence. Histologic study of the involved nodes shows nonspecific inflammation with proliferation of reticulum (hence benign lymphoreticulosis). Prognosis is good. Spontaneous recovery may be accelerated by aureomycin. Penicillin, streptomycin and sulfonamides are ineffective. Incision and drainage are indicated in suppurative cases.

Cat Scratch Disease: Nonbacterial Regional Lymphadenitis. Worth B. Daniels and Frank G. MacMurray[5] (Washington, D. C.) report studies on 12 patients. The patients were aged 10-73. All had more or less intimate contact with cats; seven had been scratched and one bitten. Five patients had lesions at the site of inoculation. In four with cervical lymph node involvement no primary lesion was found. The scratch usually presented a central raised papule or scab which occasionally oozed serum. Following the one cat bite, a severe necrotic lesion developed with foul-smelling exudate; anaerobic culture revealed a gram-negative rod.

As a rule systemic symptoms were either absent or represented by a mild fever which lasted less than a week. A few patients had fever and chills, general aching pains and malaise. Leukocyte counts, made in six patients, were normal. During the active stage, sedimentation rates were elevated. Serologic tests for syphilis, done in six instances, were negative in all but one patient with late latent syphilis. Skin test with antigen prepared by diluting pus from a suppurative lymph node with saline was found specific for cat scratch disease. A positive reaction 48 hours after intradermal injection of 0.1 ml. prepared antigen is represented as a raised indurated papule 0.5-1 cm. in diameter surrounded by an erythematous areola measuring 3-5 cm. Multiple antibody and agglutinin tests gave normal or negative results.

Painful swelling of the regional lymph nodes developed in two weeks to a month after the exposure in most. Axillary and epitrochlear nodes either together or separately were involved in five patients, the cervical or submental in four and the inguinal-femoral in three. Lymph nodes were usually notably enlarged; in some they were rubbery and insensitive, in others red and extremely tender. Suppuration to the point of

(5) A.M.A. Arch. Int. Med. 88:736-751, December, 1951.

necessary aspiration was present in two patients and in two others it was obvious at the time of biopsy. Average duration of lymph node enlargement was about two months.

In four instances, lymph nodes were studied 17, 36, 40 and 50 days after onset of disease; biopsy report was available on two other patients. Early changes consisted of reticuloendo-

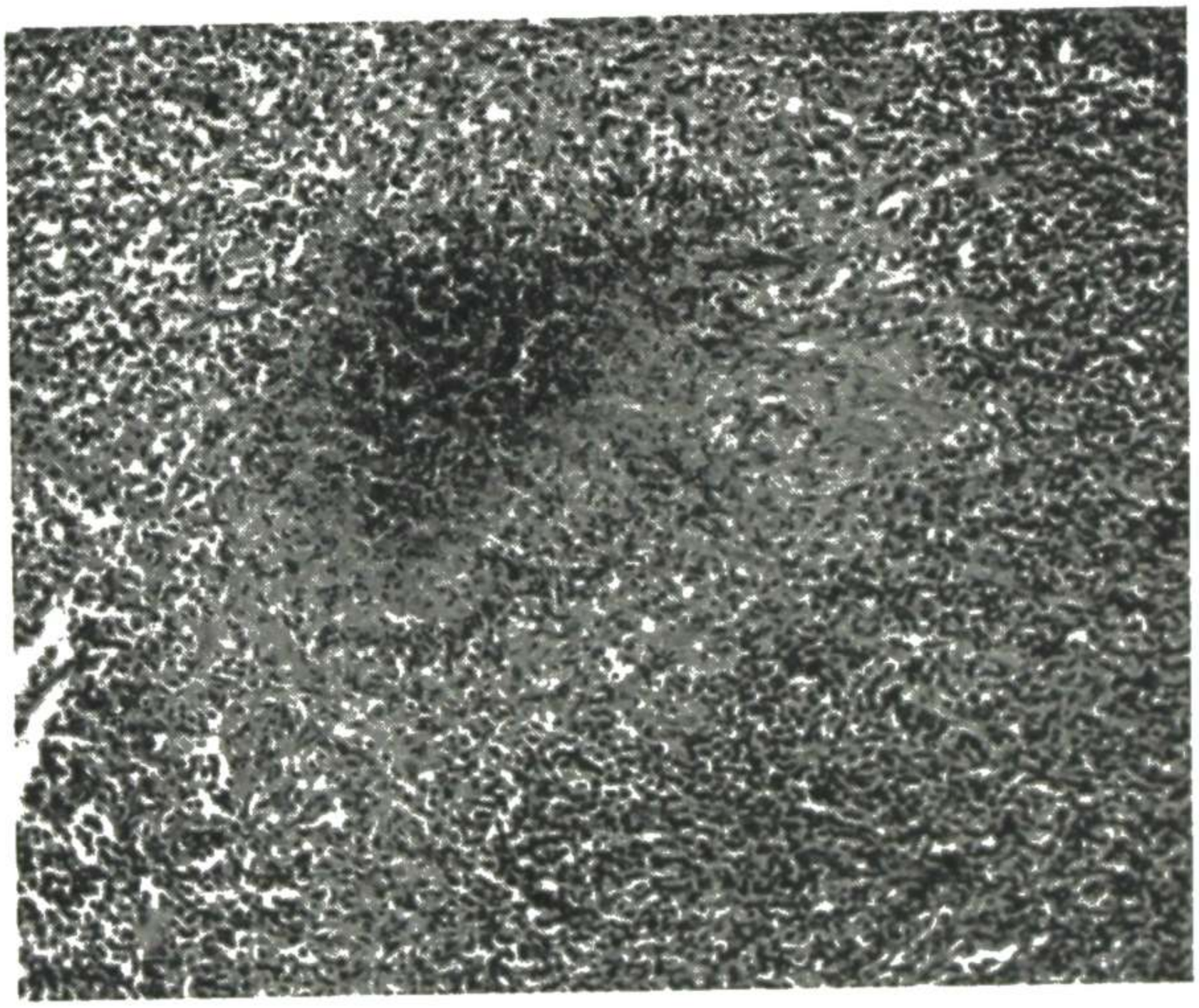


Fig. 45.—Later lymph node reaction. Focus of reticuloendothelial hyperplasia in medullary cord, with central necrosis and cellular debris. Numerous polymorphonuclear leukocytes are present in center of focus, and epithelioid cells form the wide peripheral band. Giant cells are absent. (Courtesy of Daniels, W. B., and MacMurray, F. G.: A.M.A. Arch. Int. Med. 88:736-751, December, 1951.)

thelial hyperplasia with lymphocytic and plasma cell infiltration of the capsule and pericapsular areolar tissue. Numerous polymorphonuclear leukocytes were present in the subcapsular sinus. Cortical follicles were infiltrated with polymorphonuclear leukocytes and contained numerous large reticuloendothelial cells, some of which coalesced to form giant cells. The medullary portion showed generalized hyperplasia of the lymphocytes in the cords and of reticuloendothelial cells in the sinuses. Later cortical involvement subsided and there was simple hyperplasia of secondary lymphoid follicles. Foci of acute inflammation and necrosis appeared in the medullary cords (Fig. 45), were varied in size and composed of polymorphonuclear leukocytes with much cellular disintegration and amorphous material in the center. They were surrounded

by a dense wide zone of elongated, slightly folded epithelioid cells. In the biopsy 50 days after onset of disease there was no distortion of general architecture of the node. Fibrosis developed in and around the capsule and portions of the peripheral sinus. The secondary cortical centers showed follicular hyperplasia but no necrosis. Various sized discrete foci of reticulum cell hyperplasia were present in the medulla. The cells had large vesicular nuclei and indistinct cytoplasmic boundaries. The latter factor resulted in syncytial-like clusters of the epithelioid cells. All attempts to demonstrate organisms were unsuccessful.

[This and the preceding article and publications from other countries indicate that the disease is widespread. More exact terminology might well be found for "cat scratch disease." Although the disease is benign in the sense that it is self-limiting, it is disturbing to the patient and especially to the pathologist confronted with a biopsy specimen of the lymph nodes. As Daniels and MacMurray say, the microscopic picture is "suggestive but not diagnostic." The cause is unknown, but skin tests with material from the nodes indicated that the disease in Washington and New York is the same. According to an editorial in the *Journal of the American Medical Association* (148:746, Mar. 1, 1952), Mollaret *et al.* (La découverte du virus de la lymphoréticulose bénigne d'inoculation: Inoculation expérimentale au singe et colorations, Presse méd. 59:701-704, May 23, 1951) studied four human volunteers and several monkeys and maintain that a virus is the cause, but confirmation and identification of the virus are much to be desired.—Ed.]

Problems Concerned with Histologic Diagnosis of Tuberculosis of Lymph Nodes. John R. McDonald and Lyle A. Weed[6] (Mayo Clinic) describe illustrative cases to show that errors are frequently made when the diagnosis of tuberculosis is based on histopathologic study alone. Too often a specimen is weighed, measured and described, a portion being prepared for histologic study and the rest being placed in Formalin. When the diagnosis 24 hours later is "granuloma, type indeterminate," no tissue is available for bacteriologic examination. In fairness to the patient, procedures should be carried out in order to arrive at a specific diagnosis.

It is desirable to have the bacteriologist review the history, examine the patient and indicate what material is desirable for study. Removed tissue should be handled with aseptic precautions to prevent contamination. Fluctuant areas may be aspirated by means of a needle and syringe. It is desirable to collect material before the patient has received extensive chemotherapy.

An emulsion should be made of removed tissue by grind-

(6) Am. J. Clin. Path. 21:223-233, March, 1951.

ing it to a paste in a sterile mortar; then sterile saline solution or broth is added. If the specimen has been contaminated, the contaminating organisms should be removed by treatment of the surface. The quick-heating small cautery blades used in routine gynecologic work are preferable for this purpose. Regardless of the patient's history, the specimen should be examined for the common organisms easily grown on blood agar, in brain broth or in thioglycollate; tubercle bacilli; brucella, and fungi. In the examination for tubercle bacilli, culture and inoculation of guinea pigs (two) should be carried out. Of the two procedures, inoculation is preferable. For routine isolation (not identification), ordinary blood agar is a satisfactory medium for isolating many strains of fungi, some of which cannot be detected on the so-called special mediums for fungi. To culture for brucella, trypticase-soy broth under 8-10 per cent carbon dioxide and hormone blood agar plates under carbon dioxide are used. These are kept three weeks before being discarded as negative.

Lipoprotein of Gaucher's Disease. L. Lahut Uzman[7] (Harvard Univ.) describes the isolation and properties of a lipoprotein fraction from two spleens removed from patients with Gaucher's disease. Kerasin was the sole lipid moiety of the complex.

The lipid and protein moieties of the lyophilized lipoprotein fraction were separated by extracting the dry material for 6½ hours with a boiling mixture of chloroform and methanol. The lipid content was 62 per cent in one case and 63.8 per cent in the other. Analyses of the lipid moieties showed 1.9 per cent nitrogen, 19.6-21.4 per cent galactose and no phosphorus or free amino nitrogen. Baryta hydrolysis of the lipid moiety yielded the crystalline sulfate ester of sphingosyl galactose; it contained 2.78 per cent nitrogen, 2.72 per cent amino nitrogen and 33.7 per cent galactose. The fatty acid component was isolated as the methyl ester; it melted at 57 C., which corresponds to the value for the ester of lignoceric acid. These data indicate that the lipid fraction of the lipoprotein complex consisted solely of the cerebroside kerasin.

The protein moiety made up 38 per cent of the lipoprotein fraction. It contained 14.7 per cent total nitrogen, 1.2 per cent amide nitrogen and no phosphorus. There was no significant

(7) A.M.A. Arch. Path. 51:329-339, March, 1951.

feature in its amino acid composition except for absence of valine.

At neutral pH, solubility of the lipoprotein fraction increased with increasing salt concentration. The lipoprotein was more soluble in alkaline solutions with an ionic strength below 0.5. As determined by osmometry, its average molecular weight was about 320,000. Although 6½ hours of boiling of the lyophilized protein in a chloroform-methanol mixture was necessary before the kerasin could be extracted completely, if the lipoprotein was in a partially hydrated state, complete extraction was possible in two hours. Treatment of the lipoprotein with the protein denaturant guanidine hydrochloride at room temperature resulted in extraction of the kerasin in 24 hours. Dialysis equilibrium experiments, in which methyl orange was used, disclosed that the lipoprotein fraction had an organic ion-binding power; this indicates that a major part of the peptide coils of the protein moiety are available at the surface of the lipoprotein molecule. Resistance of the molecule to proteolytic enzymes, such as trypsin, pepsin, papain and cathepsin, is probably due to the large cerebroside component rather than to any structural characteristic of the protein moiety.

The fact that kerasin can be isolated in the form of a lipoprotein from spleens of persons with Gaucher's disease by a relatively mild procedure and without use of organic solvents indicates that the cerebroside in the Gaucher cell is present in the form of a lipoprotein. That Gaucher's disease is a biochemical entity is indicated by the facts that the lipoprotein fraction has a single lipid component and a large average molecular weight, that it presents special solubility characteristics, that it can be taken through numerous salt and isoelectric precipitations without change in composition and that the lipid-protein bond has remarkable tenacity.

There is no explanation for the formation of a Gaucher lipoprotein. Since kerasin is a normal constituent of splenic and other tissue, the disease may result from an inherent genetic defect of the protein-synthesizing matrix of the cells of the reticuloendothelial system. The evidence that kerasin is firmly embedded in a mesh of peptide coils does not support the concept that the disease may be a defect in specifically active gluco- or galactocerebrosidase systems.

Experimental Studies on Reticulosarcoma. Akira Sakamoto[8] (Nagoya Univ.) transmitted five human lymphatic and myeloid reticulosarcomas to fowls in series. The supernatant fluid from a 1 per cent saline emulsion of tumors or enlarged lymph nodes was injected intravenously or intramuscularly. In subsequent generations, Chamberland L_2 filtrates of liver emulsion from birds dying of the inoculation were used.

Manifest disease occurred in about half the fowls tested when high concentrations of the emulsion were used. The changes produced in the fowls consisted of proliferation of reticuloendothelial or immature myeloid cells. The forms occurred alternately in subsequent generations or simultaneously in the same bird. Neither erythroleukosis nor lymphatic leukosis was encountered. Proliferation of primitive cells was sometimes found perivascularly, often with formation of nodules. Filtration of the test materials resulted in reduction of pathogenicity of the agents just as in the experiments on Rous sarcoma.

The blood picture of treated fowls was consistently aleukemic, either with striking leukopenia or slight leukocytosis. There was no evidence of proliferation of lymphatic cells, and spleens showed follicular atrophy.

It was concluded that leukemic reticuloendotheliosis (Downey), a type of the human leukemia, or a mixed form of reticulosarcoma with myelosis (Lubbers), was produced in the fowls by injection of the human material.

[If confirmed, this is a manifestation of heterologus transfer of neoplasms. Other articles on this general topic appear in the chapter on General Pathology (pp. 69-71).—Ed.]

RESPIRATORY SYSTEM

Role of Hyaline Membranes, Blood, Exudate, Edema Fluid and Amniotic Sac Contents in Preventing Expansion of Lungs of Newborn Infants was investigated by Franklin C. Behrle, David M. Gibson and Herbert C. Miller[9] (Univ. of Kansas). Lungs were obtained at autopsy from 43 infants who were divided into four groups: (1) liveborn weighing over 1,200 Gm. at birth and with no hyaline membranes; (2) stillborn weighing over 1,200 Gm.; (3) liveborn weighing less than 1,200

---

(8) Blood 6:314-329, April, 1951.
(9) Pediatrics 7:782-792, June, 1951.

Gm. and with no hyaline membranes; (4) liveborn with hyaline membranes. Amount of negative pressure required for both initial and complete expansion of the lungs was determined. Degree of expansion was judged on the basis of the average thickness of the alveolar walls.

In a few instances a negative pressure equal to a column of water 35 cm. high was necessary to overcome the initial resistance of the lungs. The four groups did not differ significantly in the pressure required. Lungs of group 3 and 4 infants could not be satisfactorily expanded. In these, average thickness of the alveolar wall was practically the same before and after expansion. In groups 1 and 2, expansion was manifested by greatly diminished thickness of the alveolar wall. The amounts of pressure required to initiate expansion and to bring about apparent complete expansion could not be correlated with the final degree of expansion that was obtained as measured by the thickness of the alveolar wall. The amount of negative pressure is approximately that which the infant could exert.

The presence of amniotic sac contents, blood, exudate and edema fluid in alveoli and air passages, even in large amounts, did not mechanically prevent what appeared to be satisfactory expansion of the lungs. Use of increased positive intrapulmonary pressure or negative intrapleural pressure offers little hope in overcoming the persistent atelectasis in a lung containing extensive hyaline membranes. How hyaline membranes prevent expansion is not clear, but they probably do not act as mechanical barriers, nor is the cause of the hyaline membranes ascertained. Apparently, bronchial obstruction is not responsible for the persistent atelectasis in the hyaline-containing lungs.

Essential Pulmonary Hemosiderosis, which presents a characteristic disease picture, is reported by B. Jonsson, B. Vahlquist and K. Agner[1] (Stockholm), who followed a typical case to fatal termination and made chemical analysis of the iron deposits in the lung.

Boy had been normal until age 2, when anorexia developed. No organic disease or anemia was found. At age 4½ hypochromic anemia (hemoglobin 3.7 Gm. per cent) with increased reticulocyte values was present; iron, liver extract and folic acid therapy had no effect. His general condition varied and at times seemed improved. At age 5, fever, cough and severe dyspnea and anemia developed.

(1) Blood 6:665-671, July, 1951.

X-rays of the lungs revealed cloudy, small, patchy shadows which improved in several weeks. The anemia was of a blood-loss type. Relapses occurred at one to two month intervals accompanied by hemoptysis up to 100 cc. The condition improved with blood transfusion but remained poor. At age 5½ the final relapse occurred.

Autopsy revealed no organ changes except in the lungs, which were large and firm, with generalized increased consistency. The pleural surface was thin, dark red and unevenly colored by many

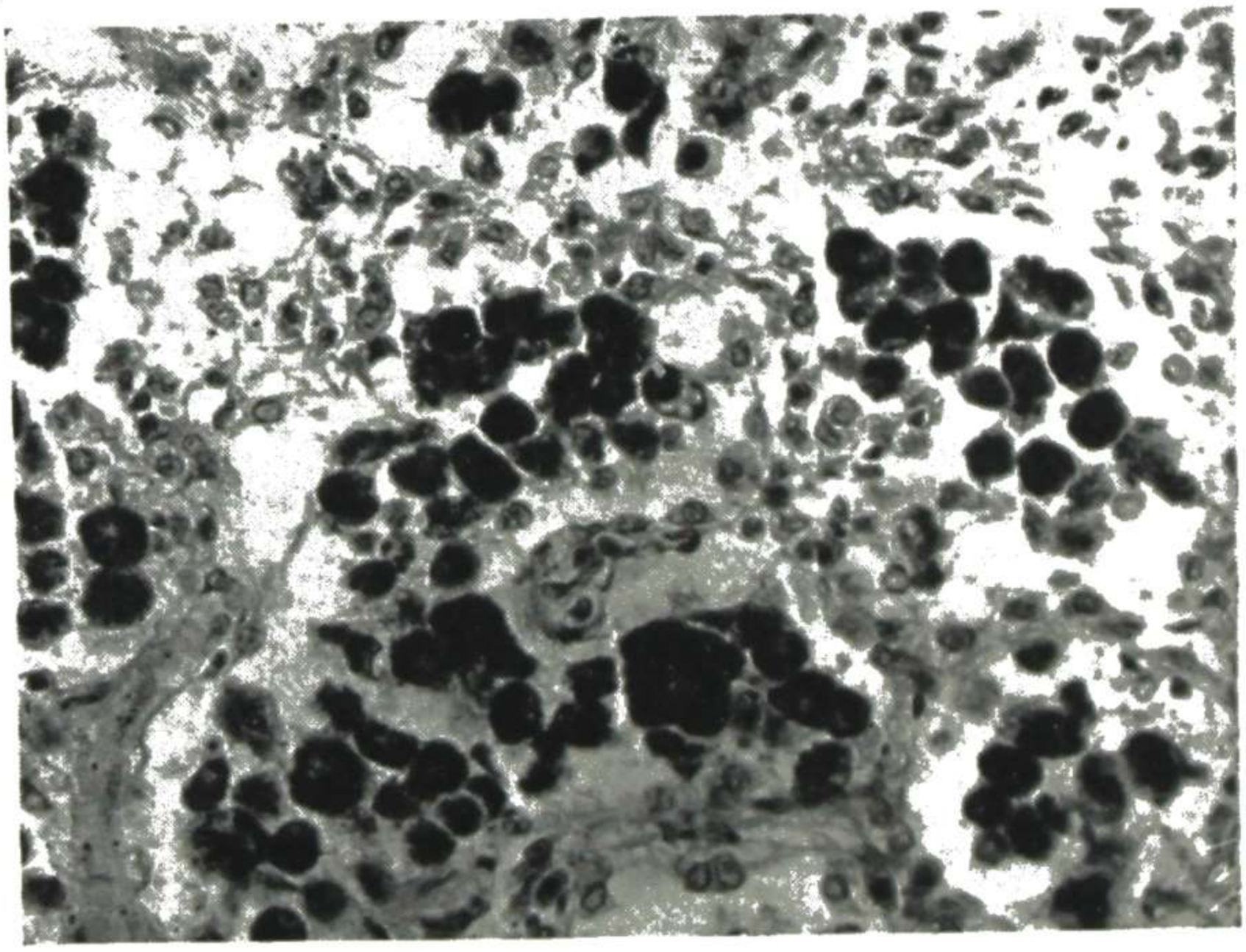


Fig. 46.—Lung tissue showing hemosiderin macrophages; Perthes-Berliner reaction. (Courtesy of Jonsson, B., *et al.*: Blood 6:665-671, July, 1951.)

petechiae. The surface was hardened but smooth and dark red-brown. Large amounts of clear brown fluid were expressed. Microscopic examination revealed diffuse "diapedesic" bleeding, massive hemosiderosis and striking changes in the elastic tissue of the pulmonary arteries. Numerous hemosiderin macrophages (Fig. 46) were present in the thickened walls between the alveoli.

Chemical analysis of lung tissue revealed 1.97 mg. hydrolyzable iron/Gm. tissue as compared with 0.03 mg. from lung tissue of five patients who died as a result of accidents without evidence of pulmonary or cardiac disease.

Essential pulmonary hemosiderosis occurs in childhood, has a prolonged course and is often fatal. It is characterized by relapsing attacks of hemoptysis and a simulation of pulmonary edema and eventually causes pulmonary insufficiency.

[E. K. Ahvenainen and J. D. Call, of Children's Medical Center and Harvard Medical School, reported on pulmonary hemorrhage in infants (Am. J. Path. 28:1-18, Jan.-Feb., 1952). Massive pulmonary hemorrhage may be alveolar or septal or both and is usually secondary to infections of various kinds and to blood dyscrasias. Presumably there are structural defects of intra ulmonary veins which play a part in the septal hemor-

rhages, but alveolar hemorrhages are largely of capillary origin. In their material, hemosiderosis was neither frequent nor extensive. Yet there were instances of minor hemorrhages which played little or no part in death. These studies may perhaps be interpreted to suggest a background for extensive hemosiderosis, such as that reported here.—Ed.]

Interstitial Plasma Cell Pneumonia: Report of Two Cases is presented by Theodor Walther[2] (Copenhagen). Both cases occurred in premature infants; this concurs with reports in the literature that about 80-90 per cent of all plasma cell pneumonias are in infants born before term. The disease starts when the infant has overcome the difficulties of the first weeks of life and begins to gain weight. The nature of the disease is still obscure but an infectious origin is generally accepted.

Common to both cases were a tendency to loose stools, transient edema, normal temperature and noncatarrhal condition throughout the course, sudden and unexpected attacks of dyspnea accompanied by cyanosis seven to eight days before death, lack of focal symptoms, and then vague and noncharacteristic findings in the lungs shortly before death and death with symptoms similar to those of suffocation at about the same age, 13 and 14 weeks.

Diagnosis cannot yet be exact without histologic examination. Typically, throughout the lungs the alveoli are filled with granular or thready masses and there is complete lack of inflammatory cells. The alveolar wall covering is well preserved and alveolar lining cells are often large. Interstitial spaces are heavily thickened and contain numerous cells; these are partly plasma cells but mostly larger and smaller cells resembling lymphocytes. There are practically no granulocytes.

Mononuclear Pneumonia in Sudden Death or Rapidly Fatal Illness in Infants. Peter Gruenwald and Mendel Jacobi[3] (State Univ. of New York, Brooklyn) report autopsy findings in 76 infants who presented certain clinical and pathologic manifestations of an obscure disease of unknown origin. Among 52 sudden deaths in infants older than a week, referred by the medical examiner's office during 1948-49, 47 infants had the condition and 2 had it in addition to other lesions. The infants died either suddenly or after a brief period of prodromal symptoms. A few patients died shortly after hospitalization with acute symptoms of respiratory distress or cyanosis.

---

(2) Acta paediat. 39:545-553, 1950.
(3) J. Pediat. 39:650-662, December, 1951.

At autopsy frothy fluid exuded from the mouth and nose. Petechiae, often found in the epicardium and pleura, were sometimes numerous. The heart was dilated in some cases. Most viscera were pale. The lungs, which grossly showed pulmonary edema, were voluminous and moderately firm with few or no completely airless areas; they were purplish gray with paler emphysematous anterior borders. Interstitial emphysema was occasionally seen. Purple depressed areas of atelectasis sometimes occurred in the posterior regions. On section, the lung surface was red, moist and exuded frothy fluid. Similar fluid often filled the respiratory passages. Microscopically the unaffected lung tissue was scant or absent. The diseased tissue was sharply demarcated and within it, areas of different degrees of expansion and aeration were also well demarcated. Strikingly thickened alveolar walls and exudate within the alveoli occurred in the affected areas. A few alveoli were aerated but most were expanded with fluid. Occasionally areas of atelectasis were seen. In the thickened alveolar walls connective tissue was increased and there was mild infiltration with lymphocytes and occasionally mononuclear cells. The alveolar exudate stained homogeneously and contained varying numbers of polygonal or oval cells, somewhat larger or smaller than macrophages. In most cells the cytoplasm stained homogeneously and deeply without inclusions. Bronchial walls were usually intact. In a few patients with complications, focal or spreading banal bronchopneumonia was seen.

The spleen was moderately soft and the pulp often pale with conspicuously enlarged follicles. Microscopically in some cases there was a center of homogeneous material, presumably necrotic, within the follicle. Lymphoid tissue of the body showed a characteristic pattern. The follicles and Peyer's patches of the intestine were enlarged and hyperemic. The mesenteric and peripancreatic lymph nodes were conspicuously larger than normal, pale and fairly firm. The retroperitoneal and pelvic lymph nodes and those in the mediastinum were usually small and presented no characteristic microscopic change. Within the sinuses of the peripancreatic nodes were often found large cells with an indented nucleus resembling those found in the pulmonary alveoli. The liver was pale. Hepatic cells showed moderate and uncharacteristic cytoplasmic degeneration such as cloudy swelling, fat-free vacuolation and fatty metamorphosis. About half the kidneys

showed peculiar spotty hyperemia of the cortex. This was due to greatly dilated venules, occasionally surrounded by hemorrhage in the stroma.

Gram stains on the lungs were negative in most and few bacteria could be demonstrated in the absence of polymorphonuclear leukocytes.

No one pathologic change alone is considered pathognomonic for the condition. Apparently significant is association of all findings with the typical clinical history. The mononuclear pneumonia is not a specific change but rather one occurring in a disease entity in which no bacteria or other source of infection has consistently been demonstrated as the cause.

Interstitial Monocytic Pneumonia: Thoughts on So-called Interstitial Plasmocellular Pneumonia of Premature Infants. Until recently, it was believed (on the basis of histologic sections) that the cellular infiltrate in the pulmonary interstitial tissue in premature babies dying of viral pneumonia was composed of plasma cells. In an autopsy 45 minutes after death on a premature infant, P. Loustalot[4] (Univ. of Basel) made impression preparations as well as histologic sections of various organs, including the lungs. The sections indicated the usual plasma cell infiltration. In the impression preparations, however, monoblasts, promonocytes and mature monocytes as well as a few true plasma cells could be identified. The artefacts of preparation of histologic sections are easily recognized by comparing the monocytes thought to be plasma cells with the true plasma cells of a plasmacytoma. The latter are smaller and their cytoplasm flows more readily, to merge into the tissue juices. They are much less resistant to mechanical pressure, and naked nuclei are often found. These investigations have also shown that the Unna-Pappenheim reaction is not specific for plasma cells. It is found not only in the basophilic cytoplasm of plasma cells but in the cytoplasm of blast cells of any variety of blood cell series. Granulations of mature blood elements may also give a strongly positive Unna-Pappenheim reaction. Loustalot suggests that impression preparations be made as soon as possible after death from interstitial pneumonia in premature infants.

[The pathogenesis and cause of this peculiar pneumonia of infants are not yet explained, so preventive measures cannot be prescribed. Whether

(4) Ann. paediat. 176:372-378, June, 1951.

morphologic details will help is uncertain, but impression preparations may well be as useful here as with bone marrow and spleen.—Ed.]

Effect of Adrenocorticotrophic Hormone (ACTH) on Pneumonia Induced with Tuberculin in Lungs of Sensitized Rabbits was studied by Oscar M. Reinmuth and David T. Smith[5] (Duke Univ.). The animals were sensitized to tuberculin by subcutaneous injection of a suspension of living avirulent tubercle bacilli (R1v). Thirty to 40 days were allowed for development of sensitivity. Old tuberculin in doses of 100-250 mg. was introduced into the trachea and allowed to flow into the lungs. Half the animals were treated with ACTH. Rabbits were killed at intervals of 1-17 days after introduction of OT. Nonsensitized animals were given an intratracheal injection of OT and killed at 24 and 48 hours.

The lungs of the nonsensitized rabbits showed a few areas of erythema 24 hours after injection. No gross reaction was found after 48 hours. The lungs of sensitized animals not treated with ACTH showed definite red consolidated areas 24 hours after introduction of OT into the lungs. Those of ACTH-treated animals had only spots of brownish discoloration. Microscopically, the quality of the reaction was the same in both groups of animals and consisted of intra-alveolar hemorrhage, a highly cellular inflammatory exudate and thickening of the alveolar septa. The reaction became more severe on subsequent days, reaching a maximum on the fourth day after introduction of OT. It was estimated to be only 10-40 per cent as extensive in the ACTH-treated animals as in the untreated sensitized rabbits. Microscopically, on the fourth day the untreated sensitized rabbits showed sharply demarcated areas of necrosis with underlying, dense cellular consolidation and complete obliteration of normal lung architecture. The treated animals showed a qualitatively similar but less severe reaction. In untreated sensitized animals killed on the seventh day, no gross lesion was seen; the pneumonic reaction had resolved. Sensitized rabbits treated with ACTH for four days after introduction of OT and killed three days later showed fresh red consolidation of the lungs which was similar to the initial reaction in the untreated sensitized animals. Microscopically, there were intra-alveolar cellular exudate and hemorrhage with thickening of the alveolar septa. The lungs of animals killed 13 and 17 days after introduction of OT,

(5) Am. Rev. Tuberc. 64:508-515, November, 1951.

with ACTH given until 3 days before death, showed areas of fresh consolidation which were not as extensive as the initial reaction in the sensitized untreated animals.

Sensitized rabbits treated with ACTH showed less extensive reaction after introduction of OT into the lungs than untreated controls. ACTH reduced the amount of the pulmonary reaction to OT about 60-90 per cent. When rabbits were killed three days after cessation of ACTH therapy, delayed reactions had developed in the lungs.

[Other discussions related to this general topic of sensitivity and resistance appear in the chapter on General Pathology (pp. 34, 35 and 40).—Ed.]

Role of Bronchi in Pulmonary Tuberculosis: Review Based on Study of 305 Cases is presented by Russell S. Jones and Frank H. Alley[6] (Univ. of Tennessee). The material studied was obtained at 105 autopsies and 200 resections of lungs or portions of lungs.

In the large bronchi the earliest and mildest of the lesions consists of scattered tubercles in the submucosa. Ulcerations may or may not be present. In the severe stages all of the bronchial wall may be replaced by tuberculous granulation tissue. Partial or complete healing is accompanied by fibrosis, and the area of scarring may range from a narrow band to a long section of the wall. There are several concepts of the pathogenesis of tuberculous bronchitis: implantation of tubercle bacilli in the bronchial mucosa; spread along a lymphatic vessel of the bronchial wall; continuous submucosal extension, and extension from contiguous lymph node or tuberculous pneumonia via lymphatic vessels. The present study indicated that submucosal extension is the commonest mode of origin of tuberculosis of the larger bronchi. This condition occurs most often in association with cavitation and sputum containing tubercle bacilli, but may occasionally be found without detectable parenchymal lesions.

Lesions of the smaller bronchi are often more numerous and more severe than those of the larger. Figure 47 illustrates that pulmonary tuberculosis often appears as nodular "tubers" connected to both proximal and distal bronchial "roots." Proximal or larger bronchi are frequently stenosed; smaller bronchi are occasionally dilated but more often destroyed by tuberculous disease. Accompanying this peripheral

(6) Am. Rev. Tuberc. 63:381-398, April, 1951.

bronchial disease are atelectasis and varying degrees of fibrosis, plasma exudation and alveolar macrophage accumulation, and scattered tubercles. Contrary to reports, pyogenic nontuberculous responses are unusual and nontuberculous bronchopneumonia is rare. Proximal obstruction of the bronchial tree, either by a caseonodular lesion or by ostial or mural

Fig. 47.—Caseonodular "tubers" along proximal and distal bronchial "roots" are beginning to excavate; there is caseous destruction of peripheral bronchi, although one is distended and filled with mucopurulent exudate. Note focal ectasia in a patent peripheral bronchus. Larger or proximal bronchi have thickened walls and narrowed lumens. (Courtesy of Jones, R. S., and Alley, F. H.: Am. Rev. Tuberc. 63:381-398, April, 1951.)

stenosis, plays a prominent role in development of peripheral bronchial disease. The obstructive and infective processes tend to aggravate the segmental or lobar bronchiectasis.

Both large and small bronchi play a most important role in pulmonary tuberculosis since their walls and lumens serve as major avenues for spread of the disease, not only in a lobe or segment but to other sites also.

Persistence of Beryllium Oxide in Lungs after Inhalation of Dust was studied by Frank R. Dutra, Edward J. Largent, Jacob Cholak, Donald M. Hubbard and James L. Roth[7] (Univ. of Cincinnati). Two groups of rats were exposed daily to beryllium oxide powder equivalent to 39.57 μg. beryllium/L., particle size 0.11-1.25 μ. One group, exposed for 1-25 hours, were killed immediately after last exposure; the other, exposed for 5 hours daily for 7 days, were killed at once or observed as long as 582 days.

After seven days of exposure, lungs showed numerous visible granules of highly refractile dust in the lung. Most particles were in large mononuclear phagocytes or swollen septal cells. Lining cells of septa appeared to be transformed into these phagocytes congregating in small clumps within alveoli. After 35 days the septal cells were flattened and all phagocytes were now clumped in scattered alveoli with visible ingested particles. In animals killed 582 days after exposure the lungs still contained appreciable concentrations of beryllium oxide.

During exposure of rats to beryllium oxide the concentration of dust in the lungs tended to be gradually progressive. When exposure was discontinued, the concentration remained fairly constant for a number of months. Inhalation of beryllium oxide in rats caused no granulomatous inflammation of the lungs. The minimal response did not resemble chronic pulmonary berylliosis in man even though the concentrations represent several times those of beryllium found in the lungs of persons who died of chronic pulmonary berylliosis.

Coal Workers' Pneumoconiosis: Pathologic and Etiologic Considerations. A. G. Heppleston[8] (Cardiff, Wales) describes two distinct forms and differentiates them from classic silicosis. In 50 American coal miners who had worked in anthracite and bituminous mines for an over-all average of 22 years, pulmonary changes resembled those in 8 Scottish and 4 other European coal workers. Tissue from 15 persons with silicosis and 25 unexposed town dwellers served as controls. In simple pneumoconiosis the essential pathologic change—black macules, 1-4 mm. in diameter, smaller and less numerous toward the base of the lung—developed during the early stages of

(7) A.M.A. Arch. Indust. Hyg. 4:65-71, July, 1951.
(8) Ibid., pp. 270-288, September, 1951.

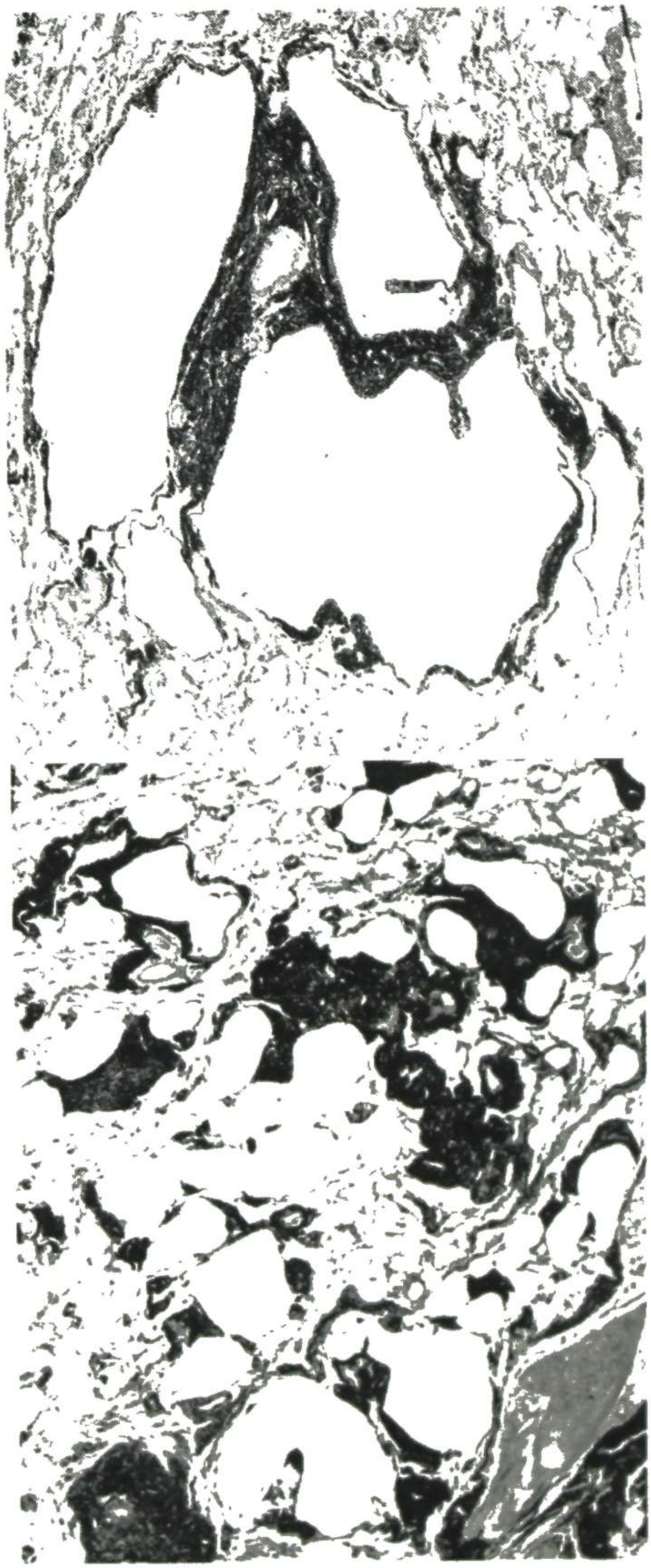


Fig. 48 (top).—Dust macule with moderately severe focal emphysema. Hemalum-eosin; reduced from × 20.

Fig. 49 (bottom).—Dust macules with focal emphysema, showing confluence of lesions. Hemalum-eosin; reduced from × 10.

(Courtesy of Heppleston, A. G.: A.M.A. Arch. Indust. Hyg. 4:270-288, September, 1951.)

exposure and was unrelated to the type of coal mined. [The term "macule" is not clear but appears to refer to a plane in a microscopic section.—Ed.] The total amount of dust within the lesion increased after prolonged contact. Little fibrosis was associated with the macules and they were just perceptible to palpation. Occasionally a ring of emphysematous air spaces, 1-3 mm. in diameter, surrounded the macules. In some instances air spaces were present within the pigmented lesion.

Microscopically the macular lesion began as a 1-2 mm. aggregation of dust, largely contained within macrophages and usually located near the division of the respiratory bronchioles and their arterioles. The adjacent interstitial tissue, alveoli and alveolar walls became pigmented. No dust was seen in the peribronchial or periarterial lymphatic vessels. The focal lesion became compact and devoid of air spaces. A delicate network of reticulin fibers was mixed with the coal particles and these fibers later were collected into small collagen bundles. Elastic fibers apparently degenerated or disappeared. Emphysematous spaces appeared in the vicinity of the accumulated dust. Vesicles were irregular and apparently enlarged slowly so that the advanced stage was represented by the confluence of the focal lesions (Figs. 48 and 49). Only a small proportion of the dust particles in the macules was doubly refractile.

The other type of lesion in pneumoconiosis of coal workers was manifested grossly as black masses of rubbery consolidation, often several centimeters in diameter, generally in the upper two thirds of the lungs. Usually only one massive lesion was found in the lung. On section the black solid nodule presented faint silvery filigree markings. Bullous emphysema was common in the adjacent pulmonary parenchyma. Smaller lesions of identical appearance were located near the margin of the nodule. Scattered throughout the entire lung were numerous black macules. Microscopically the massive nodules contained coarse hyalinized collagen fibers arranged in bundles. The fibrous tissue pattern was irregular and never showed the whorling characteristics of silicosis. Black dust particles lying free and in small aggregates were scattered throughout the lesion between, rather than within, the fibrous tissue. Small foci of chronic inflammatory cells, as well as arteritis, were associated with some of these nodules. Necrosis

in the form of inky black fluid sometimes containing cholesterol crystals occupied spaces with irregular edges but did not have a definite wall. Occasionally a cavity with a well defined gray wall was incorporated in a nodule. These cavities showed evidence of inflammation suggestive of tuberculosis.

It appears that the macular lesion of coal miners' pneumoconiosis is produced by the action of coal dust and is not related to the action of any distinct nodule of silicosis. Infection is not a factor in its development but probably influences the formation of the massive nodules. As in silicosis, ischemic and infective cavities can be distinguished in coal workers' pneumoconiosis. Pulmonary lesions in coal workers are unrelated to the type of coal. It is recommended that the term anthracosilicosis be replaced by the nonspecific designation coal workers' pneumoconiosis.

[Although the term "anthracosis" is widely used, there is a tendency among British workers to substitute "coal workers' pneumoconiosis." This does not seem to cover moderate degrees of anthracosis in persons who have never been near a coal mine or worked with coal except as an enforced exercise in the basement.—Ed.]

Lymphangitic Carcinomatosis of Lungs: Six Case Reports and Review of Literature. Theodore E. Hauser and Arthur Steer[9] (Fitzsimons Gen'l Hosp.) report data on six men, aged 46-71. Type and location of the primary tumors were: (1) adenocarcinoma of proximal rectum; (2) carcinoma of stomach (incompletely resected); (3) adenocarcinoma of cardioesophageal junction of stomach; (4) poorly differentiated bronchogenic adenocarcinoma of left lower bronchus; (5) scirrhous adenocarcinoma of stomach, and (6) alveolar cell carcinoma of lung. Significant symptoms pointing to the primary extrapulmonary site of the neoplasm were present for 17 months in the case of rectal carcinoma, for 8 months in the case of carcinoma of the stomach and for 1 year in the case of scirrhous adenocarcinoma of the stomach. Pulmonary symptoms were present in all cases, for one to eight months, and were the outstanding terminal manifestations. In the case of carcinoma of the cardioesophageal junction, all symptoms were referable to the lungs. Cough and dyspnea were present in most cases, the most constant finding being dyspnea, usually brought on or made worse by exertion. Cyanosis was occasionally prominent. Chest x-rays were often diagnostic,

(9) Ann. Int. Med. 34:881-898, April, 1951.

showing thin stringy lines with frequent interweaving which radiated out from both hilar regions.

At autopsy both lungs were involved. The subpleural lymphatics were prominent owing to distention by the tumor. Gross metastatic nodules were present in the lungs in some cases, whereas in others nodules were not demonstrated. The cut surface showed prominent fibrous septa with many minute, barely visible foci of tumor. In the case of scirrhous adenocarcinoma of the stomach no grossly recognizable tumor metastasis could be found in the lungs. Microscopically, in all cases the tumor was widely disseminated in the lungs. Lymphatic vessels everywhere contained tumor. Nests of tumor cells were scattered diffusely throughout the lung in the lymphatics, alveoli and blood vessels. Fibrosis often accompanied invasion of the lymphatics by tumor, particularly when the perivascular vessels were affected. Some vessels showed endothelial proliferation with thrombosed and occluded lumens. Occasionally tumor cells filled the alveoli with preservation of the architectural pattern.

Circulatory Failure in Metastatic Carcinoma of Lung: Physiologic and Pathologic Study of Its Pathogenesis. Ole Storstein[1] (Univ. of Bergen) reports two cases in women with metastasis from breast carcinoma and two in men with metastasis from gastric adenocarcinoma. In this condition it is important to distinguish between extensive destruction of lung tissue leading to anoxia and invasion of lung vessels by cancer cells leading to pulmonary arterial hypertension and later failure of the right ventricle.

At autopsy the right ventricle was slightly hypertrophic in two cases and normal in two. There were gross nodules on the pleural surface and on cut section of the lung in all four cases, as well as multiple metastatic lesions in other organs. Microscopically, the lungs in both cases of breast carcinoma showed diffuse neoplastic infiltration with large nodules, particularly in the pleura. Carcinoma cells were disseminated along the lymphatic channels. Groups of atypical epithelial cells were present in the adventitia of the arteries. In one of these cases there were no pulmonary vascular changes. In the other a few moderately large vessels were infiltrated by tumor, and some of the pulmonary vessels were filled with tumor thrombi. Vessel

(1) Circulation 4:913-919, December, 1951.

changes were not extensive enough to provoke any definite pulmonary hypertension. In both cases of gastric adenocarcinoma, pulmonary arterial changes were present. In one there were a few medium-sized vessels with atheromatous thickening of the intima, and some smaller arteries showed perivascular lymphatic infiltration by tumor with proliferation of the intima and closure of the blood vessels. Although the primary neoplasm was about 2 cm. in diameter, in the other case there was considerable tumor cell infiltration of the arteries, veins and small blood vessels in the lungs. The tumor infiltrated the perivascular lymphatic spaces, adventitia and media of the pulmonary blood vessels. In the small arteries extensive endarteritis and thrombosis often narrowed or occluded the lumen. Some of the small arteries showed invasion of the wall and obstruction with carcinoma cell emboli. During life this patient had considerable pulmonary hypertension and signs of failure of the right ventricle with enlargement of liver.

[Although I have no supporting statistics, my recollection of autopsies in comparable cases indicates a higher incidence of chronic cor pulmonale than was noted in this small series. Oxygen saturation of the arterial blood was normal in one and reduced in three cases, but this observation is too limited to have conclusive bearing. Since the condition can be identified during life, the catheterization technic might be useful if correlated with autopsy studies.—Ed.]

Health Hazards in Production and Handling of Vanadium Pentoxide. Sven-Gosta Sjöberg[2] (Eskilstuna, Sweden) observed 36 workers in a vanadium pentoxide factory for three years. Concentrations of the dust varied from 6 to 140 particles/ml., with 22 per cent of the particles less than 8 μ in size. Precautions were not taken at first, and the subjects had symptoms of severe irritation of the respiratory tract. A few had smarting of the eyes and papular eruption of the face and extremities. Bronchial disorder was the essential feature, and the workers periodically presented dyspnea, wheezing and cough with or without sputum. One subject had a grayish green coating of the tongue and sputum of similar color. All symptoms were acute and all subsided in dust-free environment. Pneumonia developed in five instances, in three after heavy dust exposure, suggesting a mixed chemical and bacterial origin.

Rabbits experimentally exposed to high concentrations of smaller particles than factory dust had conjunctivitis, acute laryngeal bronchitis and acute bronchopneumonic patches

(2) A.M.A. Arch. Indust. Hyg. 3:631-646, June, 1951.

containing vanadium particles. Animals killed later occasionally presented chronic tracheitis, mild pulmonary atelectasis and alveolar dilatation. Intraperitoneal injection of vanadium particles did not cause fibrosis.

Solitary (Localized) Mesothelioma of Pleura. Arthur Purdy Stout (Columbia Univ.) and George M. Himadi[3] (Presbyterian Hosp., New York City) report eight cases. Appearance and behavior of these tumors is sufficiently different

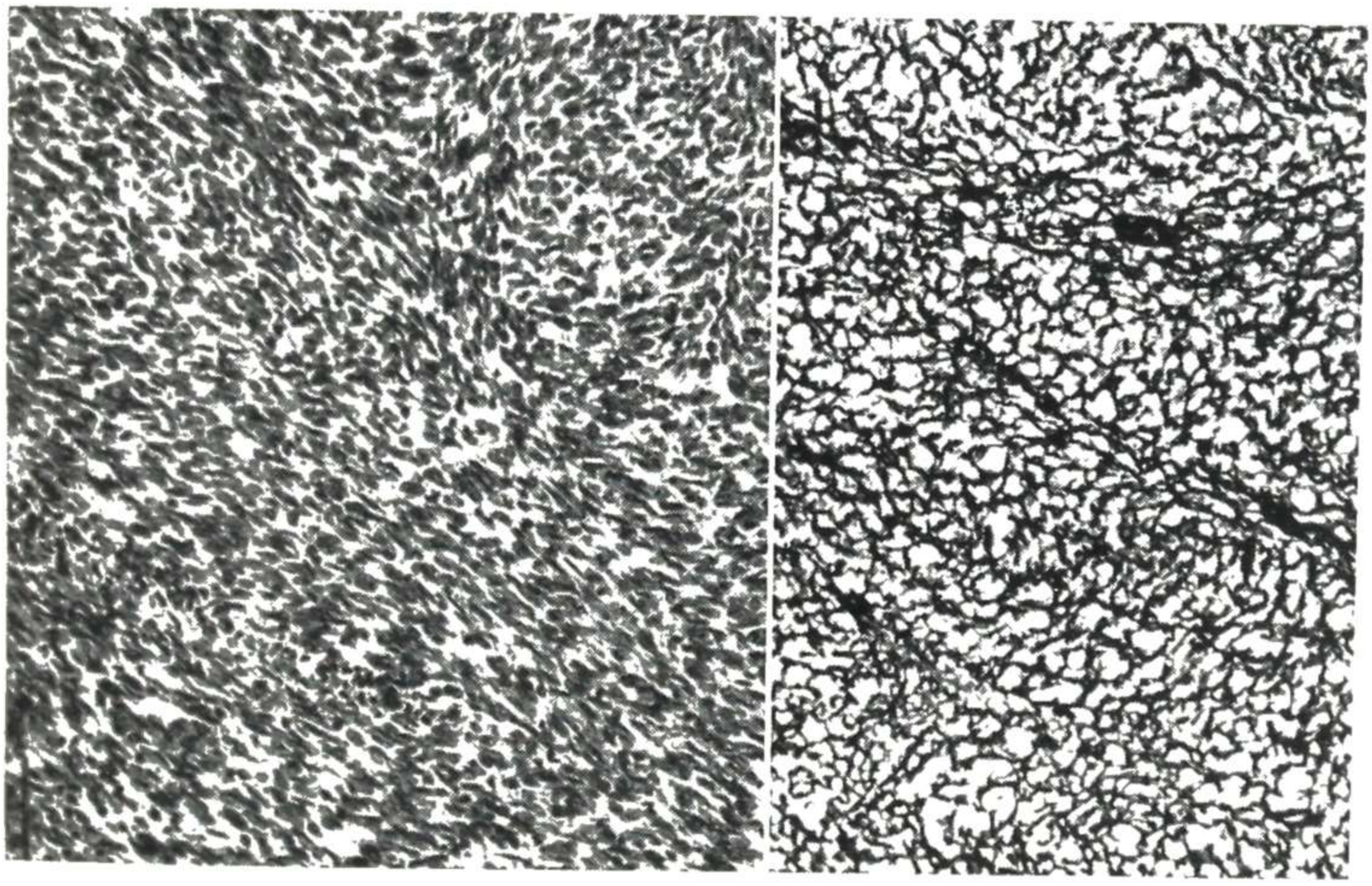


Fig. 50.—Tumor with Laidlaw silver recticulin impregnation at right. Tumor cells more numerous and closely placed and connective tissue fibers, although numerous, thinner and more delicate; reduced from × 160. (Courtesy of Stout, A. P., and Himadi, G. M.: Ann. Surg. 133:50-64, January, 1951.)

from those of diffuse mesotheliomas to qualify the name by the adjective solitary. X-ray features are striking and the entity is often amenable to surgery, with a good prognosis if the tumor is benign and some chance of cure if it is malignant. The tumors can be divided roughly into two groups.

The first group included three cases of encapsulated, pedunculated intrapleural growths which histologically were well differentiated. The microscopic picture consisted of elongated and spindle-shaped tumor cells, associated with collagen and reticulin fibers. Sometimes the cells and fibers ran in bundles but often their arrangement was completely confused and without definite pattern. In some areas blood

(3) Ann. Surg. 133:50-64, January, 1951.

vessels were numerous. A thin, fibrous capsule generally separated the tumor from the pleural mesothelium, although sometimes this was missing.

In the second group the five tumors, instead of projecting outward into the pleural cavity, were buried in lung tissue or subpleural tissues beneath the parietal pleura, but in either case were closely adherent to overlying pleura. Although the cells were spindle shaped, they had a more anaplastic appearance, which suggested malignancy (Fig. 50). The tumors were circumscribed but usually not truly encapsulated. On section they were much softer than those of the first group, with a reddish gray cut surface and sometimes areas of necrosis. Mitotic division of cells was common. There were no collagen fibers and only extremely delicate reticulin fibers between the individual cells. Three patients in the second group died of recurrence, one was still well five years after operation and the other was seen initially too recently for evaluation.

The tumors in both groups have considerable resemblance. Their nature is obscure. A mesothelial origin is suggested because in one case tumor explants produced cells which imitated the behavior of mesothelial cells in vitro.

ALIMENTARY TRACT AND ASSOCIATED GLANDS

Pathology of Experimentally Produced Lye Burns and Strictures of the Esophagus was studied by Lewis H. Bosher, Jr., Thomas H. Burford and Lauren Ackerman[4] (Washington Univ.). A 10 per cent lye solution was introduced into the lower esophagus of dogs suspended in a vertical position. After a 60 second exposure the lye was neutralized with dilute hydrochloric acid. In 24 hours epithelial destruction and submucosal edema were noted in the lower esophagus. Leukocytic infiltration, vascular thrombosis and necrosis of the submucosa appeared in 48 hours; this led to sloughing by the fifth day. Muscle necrosis and degeneration varied and depended on the severity of the edema, vascular damage and bacterial invasion in the superficial levels as well as on the initial chemical injury. Granulation tissue replaced the slough, forming a temporary false lining membrane. Strictures developed in the third to fourth week. When the destruction involved the inter-

(4) J. Thoracic Surg. 21:483-489, May, 1951.

nal layers, re-epithelization was not complete before the sixth week. At first the epithelium was very thin and very slowly approached normal. There was no regeneration of the esophageal submucosal glands.

Early dilation, before the tenth day, would be illogical, as it would only intensify the damage present at that stage.

Multiple Erosions and Acute Perforations of Esophagus, Stomach and Duodenum in Relation to Disorders of Nervous System have been investigated by Joseph H. Globus and Bruce L. Ralston.[5] Usually these lesions are shallow, small ulcerations of the mucosa and submucosa, found most frequently in the stomach and upper part of the duodenum. There are vascular congestion, dilatation and sometimes thrombosis and hemorrhage with a cellular reaction at their periphery. Acute perforations of the gut wall may occur.

The role of the nervous system in production of these ulcerations is widely recognized. Experimental work has shown that similar changes can be produced by lesions in various parts of the central or peripheral nervous system. The erosions are not the result of any specific neurologic disease and may be encountered following trauma, infection, hemorrhage, tumors, toxic factors or congenital malformations of the nervous system. The central nervous system lesions may be diffuse or discrete; there is no selective point in the central or peripheral nervous systems which must be involved before the erosions will occur. There is no evidence from previously reported cases and the 34 studied by the authors that the hypothalamus is the site of predilection for the cause of the erosions.

Incidence of erosions was about 8 per cent in general autopsy material. Such gastrointestinal erosions should indicate possible central or peripheral nervous system involvement.

Morphologic Consequences of Acute Exogenous (Staphylococcic) Gastroenteritis on Gastric Mucosa. Eddy D. Palmer[6] (Walter Reed Army Hosp.) studied 42 patients at various intervals during and after an attack of acute staphylococcic food poisoning. In all, gastroscopy was done and in 24 a biopsy specimen of the mucosa was taken. In six patients biopsy and gastroscopy were done in the early stage of the

(5) J. Mt. Sinai Hosp. 17:817-842, Mar.-Apr., 1951.
(6) Gastroenterology 19:462-475, November, 1951.

illness. The rest were examined at later intervals after vomiting had ceased. Duration of illness was measured from onset of the first symptom.

Acute exogenous gastritis was observed in 13 patients. In the acute stage, hyperemia, edema, muscular irritability, erosion, petechiae and purulent exudate were found in seven and varying combinations in the rest. The hard, fiery hyperemia was patchy in distribution, with intervening areas of pale, succulent edema. Muscular irritability was reflected by frequent segmental spasms across the pars media and, in all patients, absence of rhythmic peristalsis in the antrum. Erosions and petechiae were common, usually seen as small groups in the pars media. They were rare in the antrum and absent in the fundus. The abundant purulent exudate was thin and gray, running between the rugae. It was composed of leukocytes, surface mucous cells, sheets of mucous epithelium and erythrocytes.

Biopsy five hours after onset in one patient revealed normal gastric mucosa. In another, eight hours after onset, the mucosa was intact but the foveolar layer was packed with extruded glandular cells. Changes found in other patients during the first day of illness were desquamation of glandular cells into the foveolae, an occasional focus of subacute inflammation about the neck region and early necrobiosis at the junction of gland and foveolae. Masses of glandular cells were extruded from the foveolar lumen onto the surface. The separation of the foveolar layer was associated with subserosal edema and hyperemia. On the second day, exfoliation was more advanced and resulted in disruption of surface integrity. Superficial erosions, acute and chronic inflammatory infiltration, and edema were present, Biopsy specimens from three patients on the third day were normal, but three others showed some degree of necrobiosis and inflammation. The depths of the glands and the regional interstitial tissue were not changed at any time and the muscularis mucosa was normal in all specimens.

After 80 hours, gastroscopic examinations showed normal stomachs except for antral irritability or isolated patches of edema. It was concluded that the sudden severe damage which is secondary to acute staphylococcic food poisoning produces no permanent morphologic abnormality in the gastric mucosa.

Preinvasive Adenocarcinoma of Appendix: Report of 16 Cases. William McCollum and Edgar R. Pund[7] (Univ. of Georgia) define preinvasive carcinoma as carcinoma confined to natural surfaces without penetration of the basement membrane of the epithelium. In absence of invasion, diagnosis de-

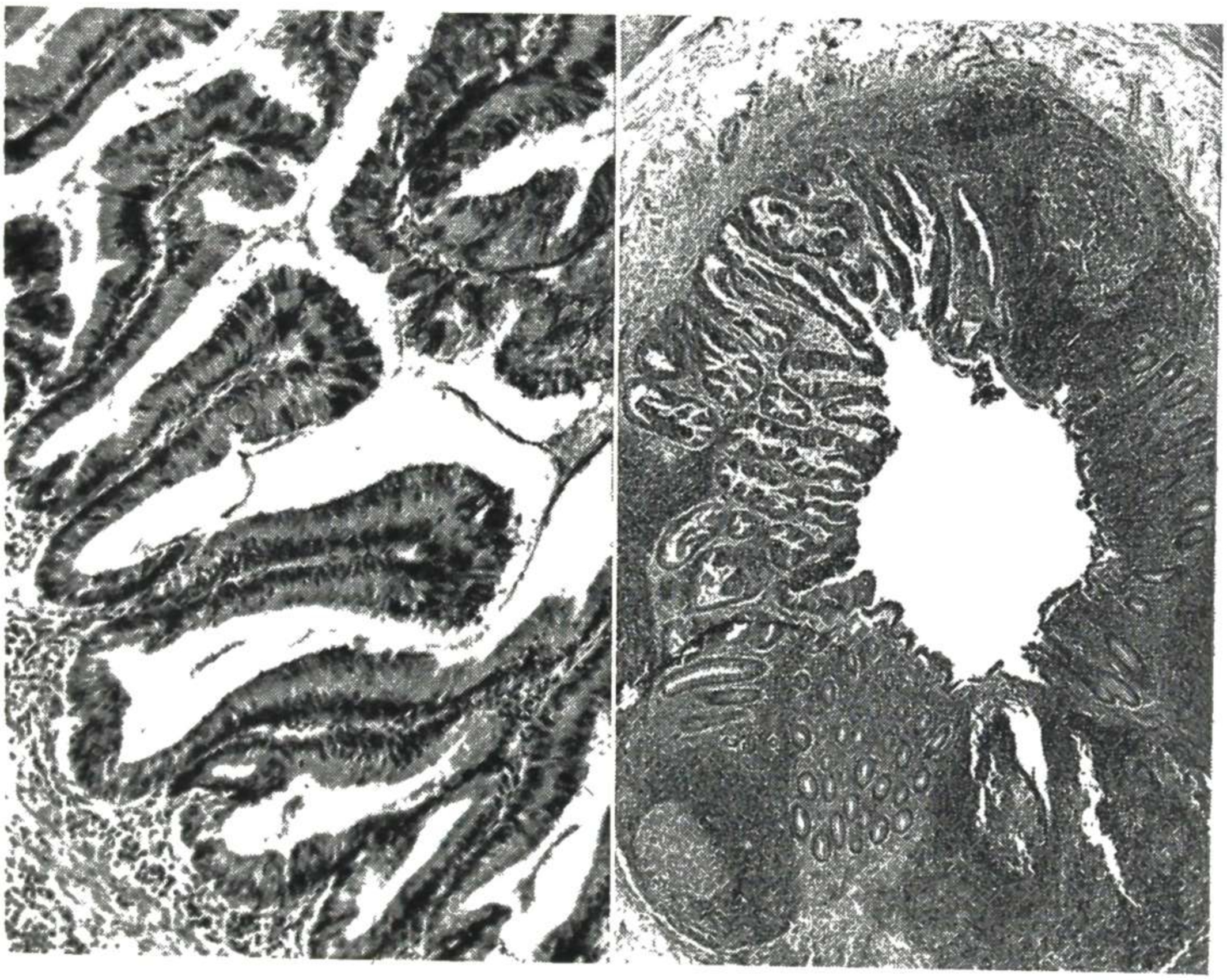


Fig. 51 (left).—Preinvasive carcinoma of entire mucosa. Irregular branching of glands, stratification of hyperchromic nuclei, active chronic inflammatory changes and pronounced hypertrophy of muscularis were found; reduced from × 100.

Fig. 52 (right).—Appendix removed at time of hysterosalpingectomy. Preinvasive carcinoma was found in one small area of the mucosa; reduced from × 30.

(Courtesy of McCollum, W., and Pund, E. R.: Cancer 4:261-264, March, 1951.)

pends on the cytologic alterations and lack of uniformity of the glandular structure. The microscopic characteristics on which diagnosis was based in the 16 cases included irregular branching and bizarre structure of the mucosal glands, pronounced excess secretion of mucus and hyperchromic vesicular nuclei which at times varied considerably in size and shape and frequently tended to stratification (Fig. 51). No gland formation was evident in some areas, the lining mucosa consisting of either a single or stratified layer of anaplastic cells. In five cases the carcinomatous epithelium was found through-

(7) Cancer 4:261-264, March, 1951.

out the appendix, either diffusely replacing the mucosa or occurring in focal areas in various segments. In the rest neoplasia was limited to one segment of the appendix or even to a solitary focus (Fig. 52). None of the carcinomas appeared to arise on a pre-existing polyp. Inflammatory changes or their residua were present in 14 cases.

Although available records were scant, symptoms and physical findings usually suggested or definitely indicated appendicitis. Presence of carcinoma is apparently conducive to development of superimposed acute or chronic inflammatory changes. Obstructive lesions of the appendix with retention of mucus and formation of a mucocele are probably a predisposing cause of the cancer and may lead to pseudomyxoma peritonei.

[There is question in the minds of other competent pathologists and oncologists that carcinoma in situ or intraepithelial carcinoma inevitably progresses to invasive carcinoma. This is as true in the uterine cervix as in other situations. That it may so progress seems established, but many years of follow-up will be required to settle the question. This seems to be especially true of the appendix, which is so infrequently the seat of carcinoma.—Ed.]

Lymphoid Polyps (Benign Lymphoma) and Malignant Lymphoma of Rectum and Anus. Elson B. Helwig and James Hansen[8] (Armed Forces Inst. of Pathology) studied specimens from 70 patients with benign lymphoid polyps. In general the polyps had a broad base with little or no stalk, but occasionally a pedunculated lesion with a long stalk was encountered. In most instances they were covered with a smooth, gray mucous membrane. The cut surface of smaller lesions tended to be gray and homogeneous; larger lesions showed incomplete connective tissue septa dividing the surface into nodules. Microscopically there were lobules of lymphoid tissue which exhibited a pattern of follicle formation with reaction centers. Follicles as well as reaction centers were often large. Each lobule might be comprised of one or several follicles. In some instances the follicles seemed to be fused into a continuous mass of lymphoid tissue. Because of this and the not always obvious reaction centers, diagnosis should be attempted only on the entire lesion, not on a small biopsy specimen. Silver stains show a moderate amount of rèticulum between the nodules but only sparse distribution within them. Lymphoid cells sometimes replaced portions of normal glandular mucosa but neither infiltrated diffusely nor

(8) Surg., Gynec. & Obst. 92:233-243, February, 1951.

obscured the normal glandular pattern to any extent. These cells do not extend into the muscularis propria. A few eosinophils but no cells suggesting Reed-Sternberg cells were seen. The cells comprising the follicles of lymphoid tissue appeared normal. Large histiocytic cells which had phagocytized debris were commonly seen in the reaction centers.

In contrast, microscopic study of material from the rectum of 17 patients with generalized lymphoma, showed diffuse infiltration of neoplastic cells without follicle formation or reaction centers. There was little or no tendency toward phagocytosis. Mitotic figures occurred indiscriminately throughout the tumor. There were no phagocytic histiocytes in the reaction centers. In several examples the tumor cells invaded the muscularis propria. Stains for reticulum showed either a diffuse pattern or an absence of this substance. In most cases nodules had been noted elsewhere in the body before rectal examination.

[This study furnishes aid to the practicing pathologist, but it is at least possible that complcte autopsies might temper the conclusions.—Ed.]

Primary Linitis Plastica Type of Carcinoma of Colon. Harold Laufman and Otto Saphir[9] (Michael Reese Hosp.) report four cases. All presented the characteristic anatomic features of the linitis plastica type of carcinoma usually seen in the stomach and rarely encountered in the gallbladder or breast. Grossly, it is characterized by an insignificant primary site, rapid spread along the submucosa involving large portions of the affected organ and spread into the muscularis of the gastrointestinal tract (Fig. 53). Microscopically the combination of inflammatory changes with much fibrosis and carcinoma is typical. The carcinoma is composed of diffusely infiltrating, darkly stained epithelial cells, the signet ring cell type and the glandular elements often present in miniature form. All patients had peritoneal involvement. In all, spaces filled with a mucinous material clearly indicated that the carcinoma was principally a mucin-secreting adenocarcinoma.

In contrast with other types of primary carcinoma of the colon, the liver was not involved in any patient. Outstanding were metastases to the ovaries in the three female patients. Such metastases were classified as a Krukenberg type because of the presence of the signet ring-shaped tumor cells in the ovaries.

---

(9) A.M.A. Arch. Surg. 62:79-91, January, 1951.

No case was diagnosed as carcinoma before operation or death. Prognosis is poor because the tumor is not recognized early when the patient is still operable. Since the tumor spreads principally along the mucosa and muscularis, it does not lead to early obstruction. For the same reason it is not easily recognizable on x-ray examination. All patients had

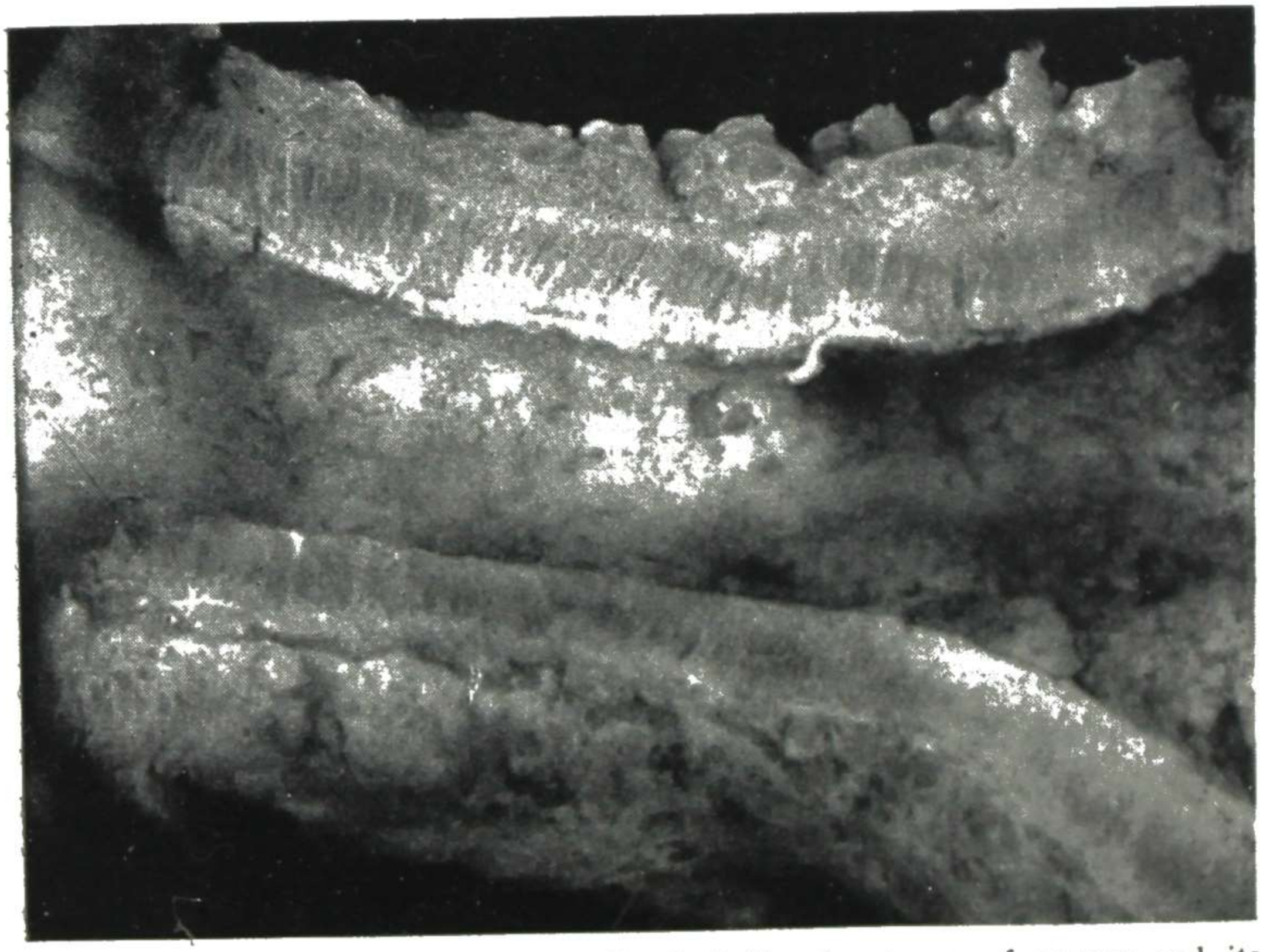


Fig. 53.—Lumen of colon. Note diffusely infiltrating tumor of mucosa and its extension through muscularis to peritoneum. (Courtesy of Laufman, H., and Saphir, O.: A.M.A. Arch. Surg. 62:79-91, January, 1951.)

occult blood in the feces, which emphasizes its presence and indicates diligent investigation. Because of the peritoneal spread, ascites occurs often; it was present in three patients, although the cause was misinterpreted clinically.

[This lesion is to be distinguished from the still more rare tubular carcinoma of the rectum, in which the wall is greatly thickened by encircling, extensive, massive carcinoma without fibrosis.—Ed.]

Infarcts of Liver. Kenneth R. Woolling, Archie H. Baggenstoss and James F. Weir[1] (Mayo Clinic and Found.) review 54 cases. The primary disease was varied; of the total number, it affected the gastrointestinal tract in 31 instances. In 13 cases the primary disease was cardiovascular, and in 3 others it involved the spleen.

In 10 patients occlusion of only the hepatic artery or one

(1) Gastroenterology 17:479-493, April, 1951.

of its subdivisions was found; in 11, of both the hepatic artery and portal veins or of their subdivisions, and in 11, of the portal vein alone or one of its subdivisions. There was occlusion of the portal and hepatic veins in three patients, of the branches of all three hepatic vessels in one and of a branch of the hepatic vein in one. In 17, vascular occlusion was not demonstrable.

In 46 patients infarcts were anemic and appeared yellow; in 4, hemorrhagic and red; in 4, partly anemic and partly hemorrhagic. Infarcts were more than 5 cm. in diameter in 15, 1-5 cm. in 17 and less than 1 cm. in 13. Twenty-three patients had multiple infarcts.

Microscopically the infarcts showed a central region of necrosis surrounded by a rather definite zone of reaction. Peripheral to the latter in 30 cases was a variable-sized zone of partial necrosis. In 19, proliferation of the bile ducts was seen in the zone of partial necrosis. In 13, numerous bacterial colonies could be demonstrated at the periphery of the central necrotic region.

In four patients over half of the right lobe of the liver was the seat of infarct. Prominent symptoms were coma, fever, ileus, oliguria, jaundice and azotemia, a picture which resembled that of "the hepatorenal syndrome."

Role of Shock in Production of Central Liver Cell Necrosis is reported by Max Ellenberg and Kermit E. Osserman[2] (Mount Sinai Hosp., New York City). In 200 routine autopsies, central liver cell necrosis was well defined in 34. All showed: (1) hyperemia of central veins and distention of sinusoids; (2) eosinophilic staining of involved area; (3) nuclear disintegration and degeneration; (4) leukocytic infiltration, and (5) architectural disruption. In all but two, findings were associated with shock preceding death but were not consistently related to any other factor. Shock was also present in 61 patients with no central liver cell necrosis. Duration of shock was the most significant factor in these two groups. Shock was present for at least 24 hours before death in 26 patients with liver necrosis. All but 2 of the 61 patients without liver changes were in shock for less than 24 hours. A wide range of conditions precipitated shock. The varied initial diseases did not influence presence or absence or the pathologic picture of central necrosis.

---

(2) Am. J. Med. 11:170-178, August, 1951.

Liver necrosis was found at autopsy on two patients who did not have terminal shock. One died of congestive failure from rheumatic heart disease and the other had bronchogenic carcinoma with extensive metastases. Congestive heart failure played no part in the production of acute central liver cell necrosis unless shock was superimposed.

Of the 200 patients, 20 did not have all the criteria for the diagnosis of central liver cell necrosis but did present suggestive changes in the liver. In all morphologic respects these lesions appeared to be an early stage of central liver cell necrosis. All patients had shock, in 16 for 10-24 hours.

Central liver cell necrosis is probably due to the anoxia and acute circulatory insufficiency present in prolonged shock. The lesion is not specific for shock, a similar picture appearing in poisoning with chlorinated hydrocarbons.

Liver in Heart Failure: Relation of Anatomic, Functional and Circulatory Changes in patients with congestive failure from a variety of causes is reported by Sheila Sherlock[3] (Postgraduate Med. School, London). Sections of liver obtained by aspiration biopsy and occasionally at autopsy on 50 patients with heart failure were studied histologically and correlated with biochemical manifestations of liver function and altered circulatory dynamics.

In early stages of congestive failure the histologic architecture of the liver lobule was retained. Central veins were dilated and adjacent sinusoids engorged. Disappearance of liver cells progressed outward from the central vein. Degeneration occurred in the more peripheral hepatic cells. Fatty change was significant in only 15 of 41 livers seen in early stages. The fat was in scattered droplets, frequently in the peripheral zone. Diffuse loss of glycogen was present only in agonal stages. There was always an increase of brown pigment in liver cells at the center of the lobule. Sometimes large pigment granules filled the central degenerating cells. On disintegration of cells, pigment was freed into the amorphous substance. The pigment failed to give the prussian blue reaction and was negative to tests for hemofuscin. It stained richly brown with sudan III both in frozen and formol-fixed sections. Pigment stained green with methylene blue, suggesting a relation to bile pigment. Excess of bile pigment in the minute bile channels was especially common in the peri-

---

. 13:273-293 ul , 1951.

portal region. Iron was not increased in liver cells or Kupffer's cells. The portal tracts were essentially normal and surrounded by a variable zone of relatively normal liver cells.

In patients with long-standing congestive failure and those who did not respond to treatment the process in the liver became more severe. Loss of central liver cells resulted in collapse and condensation of reticular stroma in the center of the lobule. Phlebosclerosis was apparent in the central vein. Connective tissue around one central vein became joined to the fibrous tissue of another in late stages and portal areas were then surrounded by a ring of fibrous tissue. Such change produced a reverse picture of the usual lobular pattern. In advanced cardiac cirrhosis proliferation of bile ducts and fibroblasts with mononuclear infiltration increased the architectural confusion.

Hepatic cell necrosis occurred in all forms of heart failure but was most severe in mitral stenosis. In the entire group there was no correlation between right auricular pressure and extent of hepatic necrosis. Jaundice was rare but frequently there was correlation between degree of elevated serum bilirubin and extent of central hepatic necrosis. Urine urobilinogen was increased; bilirubin was often detected in the urine. Exact cause of the jaundice was not apparent. With increased severity of liver cell necrosis bromsulphalein® excretion was diminished. No significant change was found in serum alkaline phosphatase and total protein.

Integrity of liver cells depends on adequate oxygen supply. Diminished cardiac output is associated with anoxia. Structural changes in the liver are related to circulatory changes, namely, reduction of cardiac output, diminished arterial oxygen saturation, height of hepatic venous pressure and duration of heart failure.

[The advantage of Dr. Sherlock's study is the examination of fresh tissue, but the disadvantage is the small amount of material to be examined. Her wide experience with this method warrants confidence insofar as its limitations permit. Evidently her material did not include cases of chronic constructive pericarditis, a notable cause. Her interpretation of central necrosis in the liver will meet with more accord by pathologists than is true of the preceding article.—Ed.]

Pathogenesis of Cirrhosis Produced by Choline Deficiency: Escape of Lipid from Fatty Hepatic Cysts into Biliary and Vascular Systems. W. Stanley Hartroft and Jessie H. Ridout[4] (Univ. of Toronto) describe the formation of fatty cysts

(4) Am. J. Path. 27:951-989, Nov.-Dec., 1951.

in the liver of choline-deficient rats. They believe that the subsequent escape of the fat with collapse of the cyst results in condensation of reticulum, a major factor in production of cirrhosis.

Young rats were killed after 6-18 months on diets low in choline and its precursors. Early in choline deficiency, fat droplets appeared in the cytoplasm of the hepatic cells, particularly those in the centrolobular regions. As intracellular fat accumulated, one or two large spherules were formed

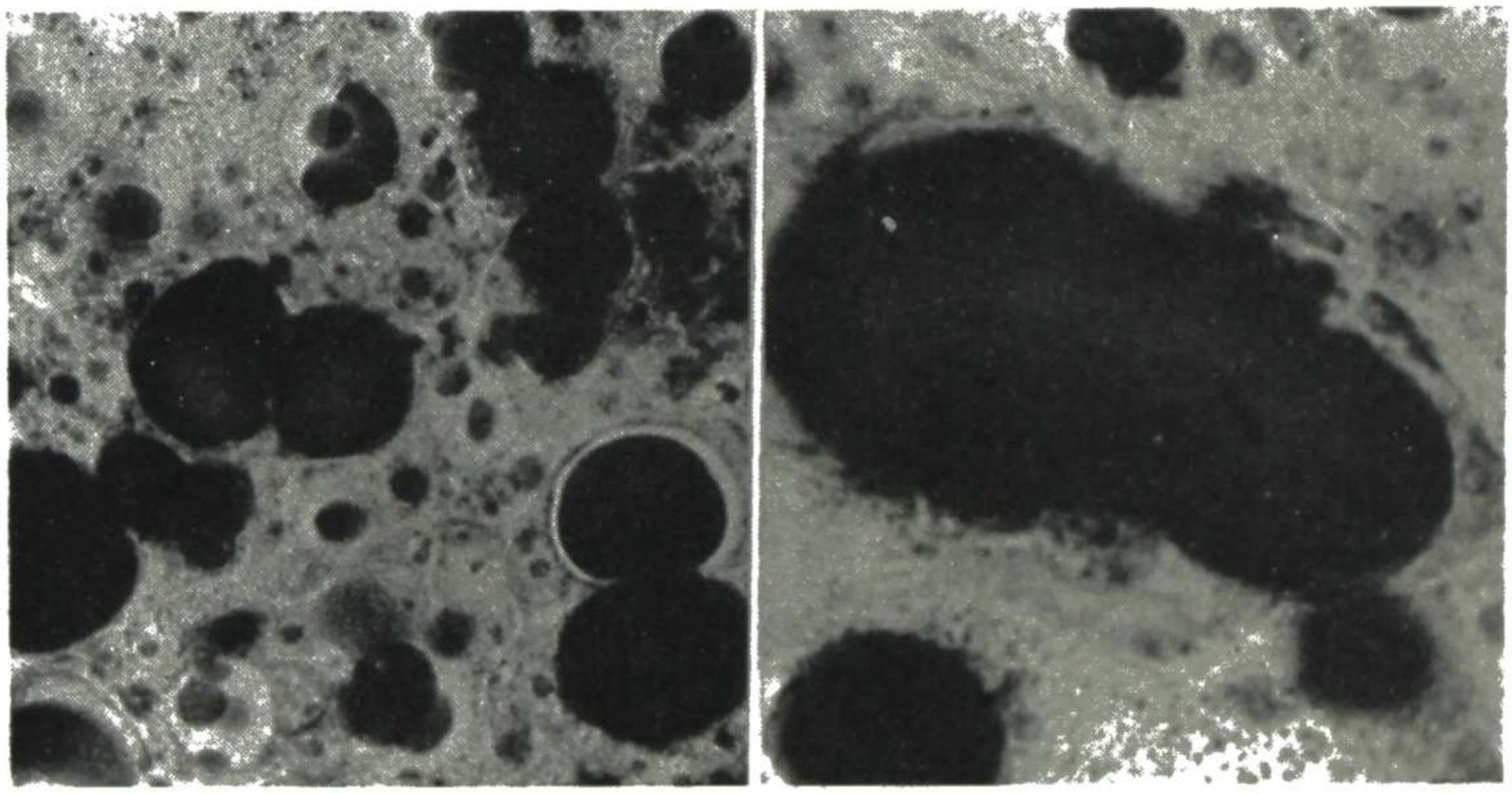


Fig. 54 (left).—Four pairs of fatty cysts, either in process of fusing to form larger ones or at stage just preceding fusion. Frozen section; Wilson's stain; reduced from × 300.

Fig. 55 (right).—Oil immersion view of fatty cyst just after membrane between two smaller ones has ruptured. Hourglass shape of newly formed or newly enlarged cysts is characteristic. Note surrounding nuclei in cyst wall. Frozen section; Wilson's stain; reduced from × 500.

(Courtesy of Hartroft, W. S., and Ridout, J. H.: Am. J. Path. 27:951-989, Nov.-Dec., 1951.)

which displaced the nuclei, distended the cell and thinned the limiting membrane between adjacent cells. Sinusoids or bile canaliculi between the membranes of the two distended cells were usually pushed to one side. The thinned septa between fat-distended cells eventually ruptured. Repeated intercellular septal breaks accumulated in the formation of cysts of a multicellular nature. Their unilocular lumens were completely filled with fat (Figs. 54 and 55). Septal defects between cysts produced larger cysts. Stretching and displacement of bile canaliculi and sinusoids increased in proportion to cyst formation until the thinned wall of the canaliculi or sinusoid ruptured, producing a communication between the ruptured canaliculi

or sinusoid and the cyst. In frozen sections fat droplets were demonstrated passing through breaks in the septa and entering canaliculi. When India ink under low pressure was introduced into the biliary tree of cirrhotic livers, many fatty cysts were partially or completely filled with ink. In some instances bile canaliculi filled with ink could be followed to the cyst.

Communication between fatty cyst and sinusoid developed in a manner similar to that involving rupture of the biliary canaliculi. Frozen section revealed fat passing from the cyst into the sinusoid through rupture. Erythrocytes and plasma entered the cyst, replacing the escaped fat. Plugs of fat sometimes blocked sinusoids.

In the cardiac muscle of some of the cirrhotic rats small elongated fat emboli were found in the capillaries. These sometimes were associated with small foci of necrotic muscle cells surrounded by fibrous tissue in which calcium salts were deposited. They resembled small infarcts. In frozen sections of lungs, lipid droplets were found in relatively large numbers, lying in arterioles and capillaries. Fat was also present within macrophages in the alveolar lumens and appeared to collect in the peribronchial lymphoid tissue. The most striking demonstration of the cumulative effects of small intermittent showers of fat emboli were found in the kidneys. Glomerular loops were obstructed by the fat emboli. Focal necrosis and hyalinization of the glomerular tufts were present, and hyalin masses were seen in and between the glomerular capillaries. Stainable fat was found in the space of Bowman and in capillary tufts. Lipid casts appeared in the tubules.

There were abundant deposits of ceroid in the regions after the hemorrhagic cyst had shrunk. Evidence from in vitro and in vivo investigation indicated that erythrocytes which entered and disintegrated in ruptured fatty cysts were converted into ceroid rather than hemosiderin. Areas of nonportal fatty cysts became replaced by fibrous tissue in the forms of trabeculae which extended from one central vein to another. A well marked pattern of annular fibrosis developed in this manner in the livers of the experimental rats. The amount of fat in livers of comparable animals decreased as fibrosis increased. Only a relatively small fraction of the components of the so-called fibrous trabeculae gave the characteristic staining reaction of connective tissue. Strands of reticulin and collagen were widely separated by interlacing channels lined

by simple epithelial cells and aggregates of ceroid pigment in atrophic cyst remnants.

Results of the experiment support the view that in choline-deficient cirrhosis of rats the fibrous tissue in the trabeculae represents a consolidation (without proliferation) of the reticular stroma. Reticulin in the form of single fine strands which originally surrounded each liver cell became incorporated in the wall of the cyst. With involution of the cyst, reticulin surrounding the cell groups was concentrated to a fraction of the volume. There was no direct evidence that fibrous tissue proliferation occurred in the trabeculae and histologic observation suggested that the connective tissue developed by stromal condensation only. Increase in the total amount of fibrous tissue in cirrhotic livers is probably due to formation of new reticulin in the regions of periportal hyperplasia along with simultaneous persistence of condensed reticulin which surrounded cysts before they shrank or disappeared.

[Earlier studies of the depancreatized dog's liver were interpreted in much the same fashion as to development of cirrhosis, but no such fat cysts were reported. That disintegrated erythrocytes lead to production of ceroid must be supported by additional evidence. The fusion of fat cysts and entry of the material into the circulation seems well documented. That such degrees of fat infiltration occur in the human liver has not been shown, even when fat infiltration is massive.—Ed.]

The Liver in Sarcoidosis. Harry Shay, J. Edward Berk, Maurice Sones, Ernest E. Aegerter, Jean Kendrick Weston and Andrew B. Adams[5] (Philadelphia) studied the functional and morphologic changes in the liver in sarcoidosis. Liver function was investigated in 24 patients with proved or suspected sarcoidosis. Serum bilirubin was above 1.5 mg./100 cc. in only one patient and was below 1 mg./100 cc. in all but five others. Most frequent abnormalities were in flocculation tests with positive results for cephalin cholesterol in 10 patients, colloidal gold in 16, thymol turbidity in 13, 18 hour turbidity ratio in 10, and gamma globulin flocculation in 21 patients. Patients with active sarcoidosis showed a significant increase in total serum protein and globulin and reduction of albumin with reversal of the albumin-globulin ratio. Electrophoretic analysis substantiated the striking difference between active and "cured" cases. Patients in whom healing had taken place and who were free from clinical signs of activity showed almost normal serum protein patterns.

Bromsulphalein® retention in the serum at the end of 30

(5) Gastroenterology 19:441-461, November, 1951.

minutes was demonstrated in 10 patients. Serum alkaline phosphatase values were abnormally high in four patients, three of whom showed the greatest bromsulphalein® retention. Serum lipid fractions were essentially within normal limits.

Granulomas compatible with sarcoidosis were found on liver biopsy in 16 of 21 patients. Variations of the accepted, typical sarcoid granuloma, found in biopsy material of all 21 patients, probably were manifestations of the same lesions in different stages of the developmental cycle. The earliest

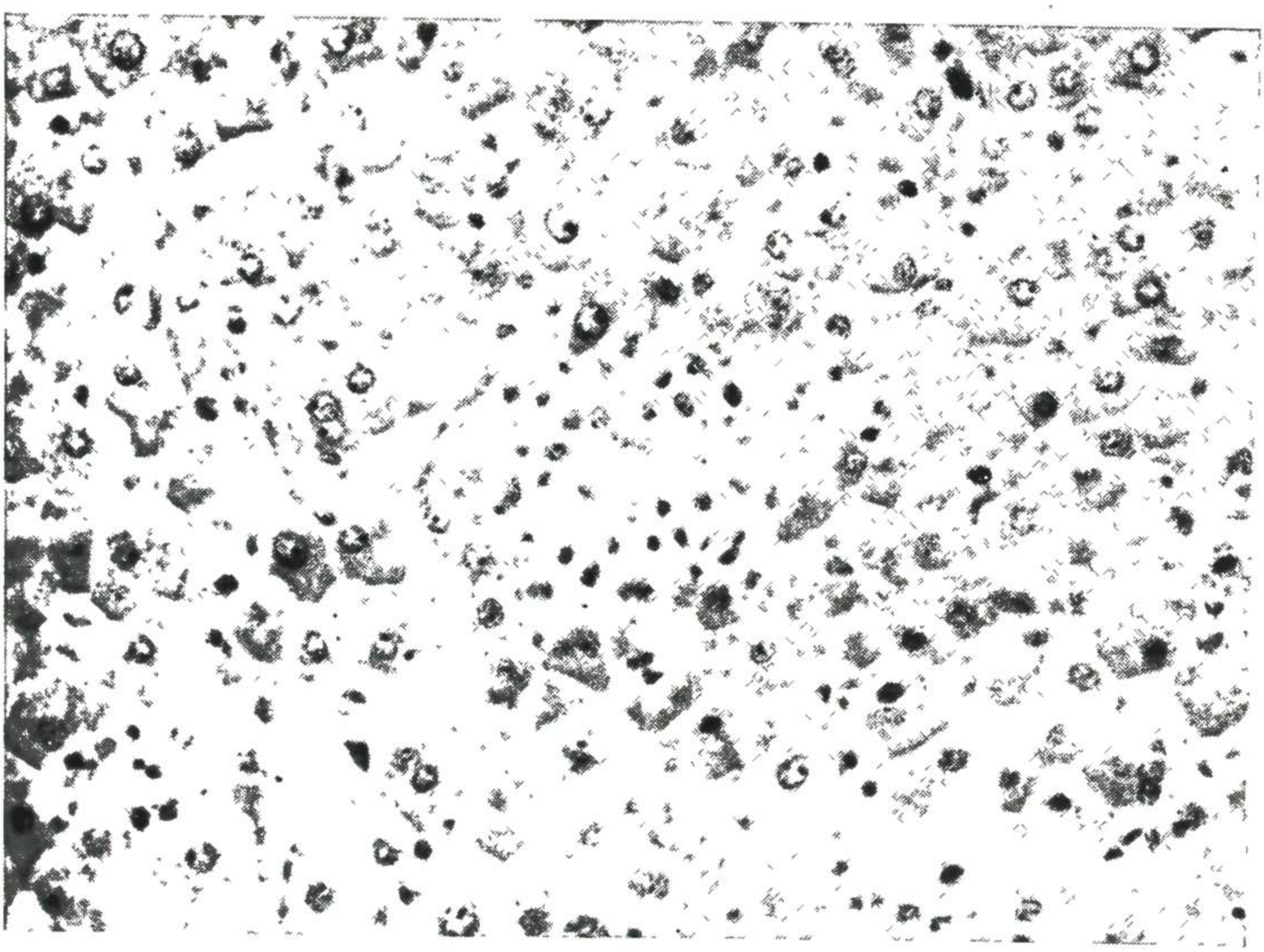


Fig. 56.—Very early lesion. Liver cells have undergone necrosis. Viable cells are difficult to identify but are probably reticulum derivatives; × 440. (Courtesy of Shay, H., *et al.*: Gastroenterology 19:441-461, November, 1951.)

lesion appears as a rather well delineated area of degeneration less than 2 mm. in diameter (Fig. 56). At first there is practically no exudative reaction but later the area may contain lymphocytes. Histiocytes appear and a rather homogeneous pink-staining material resembling paramyloid is found within the surrounding lesion. Liver cells between individual lesions are destroyed, and masses 1-3 mm. in diameter of contiguous granulomas are seen but may be kept distinct by a capsule of acellular pink-staining material. Multinucleated giant cells with nuclei indistinguishable from those of surrounding histio-

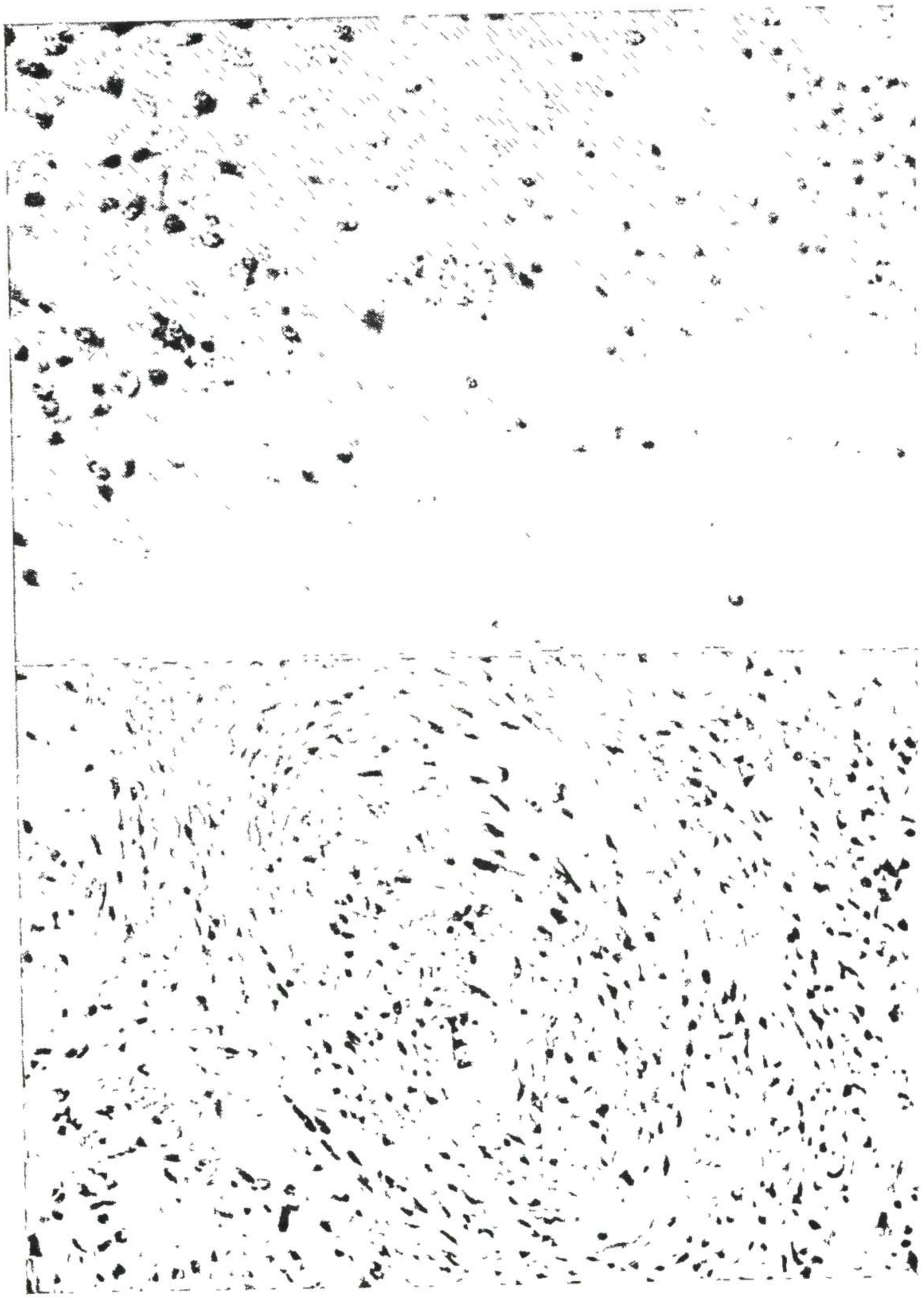


Fig. 57 (top).—Typical multinucleated giant cell containing an asteroid body; reduced from × 440.

Fig. 58 (bottom).—Old lesion undergoing conversion to fibrous tissue; reduced from × 374.

(Courtesy of Shay, H., *et al.*: Gastroenterology 19:443 461, November, 1951.)

cytes then appear. An asteroid body was found in the cytoplasm of one such cell (Fig. 57). Eventually fibroblasts make their appearance (Fig. 58) among the histiocytes and about the periphery of the lesion. They increase in number and later become smaller, accompanied by some distortion of microscopic pattern. Irregular scars which are occasionally seen probably represent healed granulomas.

Schaumann bodies, fungi and bacteria were not found. The granulomas were located both in the liver lobule and in the triads. Severely involved specimens contained abundant fibrous tissue with little recognizable liver tissue. The scarring seemed more irregular and patchy than that seen in portal cirrhosis.

Liver biopsy material from nine patients was stained for alkaline phosphatase. In four there was an increase in enzyme content in the vascular endothelium about the granulomas; in these four patients serum alkaline phosphatase was elevated. In eight of the nine there was an increase of alkaline phosphatase in the infiltrating cells (lymphocytes) about the granuloma. In those cases in which granulomas occupied a large proportion of the biopsy specimen, there seemed to be a compression effect and an increased phosphatase reaction in the sinusoidal endothelium and the perisinusoidal and/or liver parenchyma.

[A study of morphology may be found in the chapter on General Pathology (p. 51). The report here is concerned with functional disorders, some of which might possibly be the result of associated hepatic disease.—Ed.]

Hormone Excretion in Liver Disease and Gynecomastia was studied by J. Rupp, A. Cantarow, A. E. Rakoff and K. E. Paschkis[6] (Jefferson Med. College). Free and total urinary estrogen, gonadotrophin and urinary neutral 17-ketosteroids were determined in two groups of patients: (1) 22 males, aged 7-62, with gynecomastia without liver disease; (2) 25, aged 14-62, with liver disease, 6 of whom had gynecomastia. Liver function tests were done on all to discover latent or subclinical hepatic disease.

Abnormally large amounts of total urinary estrogen were excreted by 12 of 17 patients with cirrhosis; 5 of these had gynecomastia. Varying amounts of free estrogen were excreted by nine patients. Large amounts of urinary estrogen were excreted by two of four patients with metastatic carcinoma of

(6) J. Clin. Endocrinol. 11:688-699, July, 1951.

the liver. Low urinary values of 17-ketosteroid were obtained in all cases of liver disease.

Of the 22 males with gynecomastia but no liver disease, 13 had large breasts during puberty; 5 of these had abnormally high estrogen excretion. Semen analyses made on some of these patients gave normal results. Increased urinary estrogen values were recorded in nine instances. Gynecomastia developed after puberty in six patients. One of these had acromegaly, with normal hormone excretion. Another had severe thyrotoxicosis and excreted increased amounts of estrogen; fluctuations in size of his breasts and urinary estrogen values were in direct proportion to each other. When the thyrotoxicosis was controlled by iodine^{131} the gynecomastia disappeared.

In most instances there was no correlation between clinical findings in liver disease and hormonal patterns concerning excretion of estrogen. In liver disease, gynecomastia may be absent in the presence of high urinary estrogen titers or present in association with normal urinary estrogen values. An intrinsic difference in tissue response may explain some instances of absence of gynecomastia in the presence of high estrogen excretion. Of the patients with gynecomastia, 53 per cent had normal urinary estrogen values at the time of study. This may indicate that excessive estrogenic stimulus was previously present, since gynecomastia incident to estrogen therapy sometimes persists after cessation of therapy.

[Whether to include this article here or in the chapter on Breast has been a problem of classification. However, it is important with regard to the action of liver on estrogens. It is one of few studies in which assays of estrogens have been made in cases of gynecomastia without neoplasms of the testis. The lack of correlation between estrogen excretion and presence of gynecomastia leads to the vague assertion of the endocrinologists that there are differences in sensitivity of the receptor tissue.—Ed.]

Cirrhosis and Primary Carcinoma of Liver in African Negro are discussed by Frédéric C. Roulet[7] (Univ. of Basel). A survey in a Dakar hospital showed that 5.4 per cent of male and 3.5 per cent of female hospitalized natives had cirrhosis or cancer of the liver, an incidence far greater than that found in European institutions. This is attributed to the native diet which is low in proteins and high in fat (peanut oil is the only fat used by most natives); the diet is taken from childhood on. The results take a long time to develop, but sometimes manifest themselves in the second decade. Of 15 patients with cirrhosis and cancer, 4 were under 30 and 10

(7) Schweiz. Ztschr. allg. Path. 14:237-260, June, 1951.

under 40, an age distribution that is not found in the Negroes of Europe or the United States. Such cirrhosis is rarely rich in fat; there was some steatosis in only 2 of 50 cases. On the other hand, diffuse fat infiltration is common in the native children; this may represent an initial stage which goes on to fibrosis and discrete epithelial destruction, cirrhosis with change of hepatic architecture, and epithelial regeneration of cells, so that fat can no longer be absorbed. Hepatomas, or areas of hyperplasia, have no excess of fat, and fat vacuoles are seen only in areas where cells are still more or less normal. Thus, composition of the diet and length of time it is taken are the determining factors in these liver changes.

Prevention and Reversal Despite Hyperglycemia of Glycogen Infiltration ("Hydropic Degeneration") in Pancreas in Alloxan Diabetes in Rabbit were achieved by G. Lyman Duff and W. E. Toreson[8] (McGill Univ.). In 17 untreated rabbits

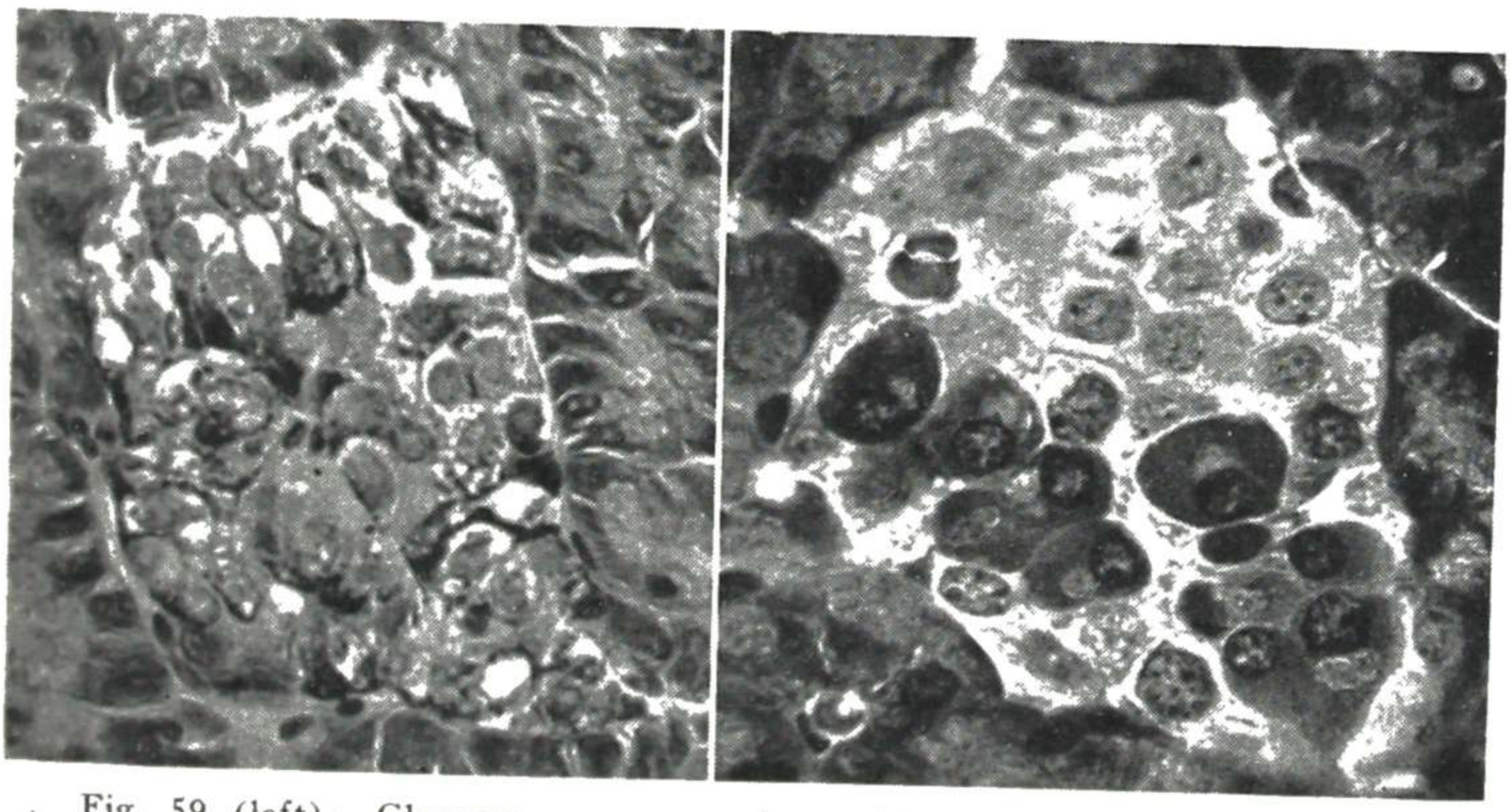


Fig. 59 (left).—Glycogen appears as heavy black linear or crescentic deposits near cell membranes. Best's carmine. Helly's fluid; reduced from × 530.

Fig. 60 (right).—Large dark cells are alpha cells. The rest are beta cells which have full complements of cytoplasmic granules. Zenker-Formol fixation; Gomori's stain; oil immersion; reduced from × 1,100.

(Courtesy of Duff, G. L., and Toreson, W. E.: Endocrinology 48:298-312, March, 1951.)

with alloxan diabetes, glycogen infiltration was found in the pancreatic islets and ductules in biopsy specimens or at autopsy (Fig. 59). After pancreatic biopsy, three were given small doses of insulin for one or two days; none showed appreciable differences in extent or degree of glycogen infiltration. When hyperglycemia and glucosuria were controlled in

(8) Endocrinology 48:298-312, March, 1951.

three rabbits by administration of sufficient insulin, cells of the pancreatic islets and ductules had normal structural appearances. In each animal the restored pancreatic islets of Langerhans contained numerous granular, beta type cells (Fig. 60). Insufficient insulin to control the diabetes was administered to four rabbits for 10-49 days. Biopsy showed persistence of traces of glycogen in the cytoplasm of a few islet cells, and some of the ductular epithelial cells of two animals contained conspicuous accumulations of glycogen. Glycogen infiltration was prevented in five rabbits by administration of small doses of insulin, insufficient to control hyperglycemia, for 5-16 weeks, which was begun immediately after injection of alloxan.

Results suggested that hypoinsulinemia plays a more important role than hyperglycemia in pathogenesis of glycogen infiltration into the cells of the islets of Langerhans and pancreatic ducts. Hyperglycemia per se has no more than the slightest direct effect. Insulin therapy, even though inadequate to control symptoms, may be partly responsible for the reported rarity of "hydropic degeneration" in the human diabetic subject.

[But on the other hand, the low incidence of hydropic degeneration in the islets of the human pancreas may be due to inadequacy of present methods with autopsy material.—Ed.]

URINARY SYSTEM AND MALE GENITALIA

Microscopic Observations of Living Mammalian Kidney: Effect of Crush Injuries, Shock and Adrenalin® on Cortical Blood Flow of rabbits was investigated by J. F. Ross Fleming and W. G. Bigelow[9] (Univ. of Toronto). True crush syndrome has apparently never been produced experimentally in animals without supplementing the crush injury with some other factor, such as injection of muscle pigments. The difference between the clinical entity of crush syndrome and post-traumatic anuria is emphasized. Crush syndrome is a term applied to a clinical condition where crushing injury results in a state of shock which responds to transfusion and is followed by oliguria and uremia. The anuria of crush syndrome follows a latent period, which includes the period of shock, and exists for several days in the presence of a normal or elevated blood pressure. Patients usually die of renal failure in about a week.

---

(9) Surgery 30:994-1003, December, 1951.

A similar clinical course has been described in a variety of other disorders, all being associated with similar pathologic changes in the kidney. After severe trauma, widespread embolic occlusion by circulating clumps of red cells is observed in the small vessels of both man and animals.

By transilluminating the kidney cortex of rabbits, blood flow was well visualized. The vessels observed were the interlobular or radiate arteries and veins surrounded by intricate capillary networks. The venules leading to interlobular veins were smaller and more numerous than the arterioles. Under normal conditions blood flow was rapid and smooth. Some intermittence of blood flow in the renal cortex was often seen and some vessels were filled and a few empty at the same time. Reversal of direction of blood flow was common.

After crushing injury to the legs of rabbits, blood flow through the cortex was not completely stopped immediately following and for several days. It was slower than normal and there were frequent areas of stasis in capillaries, arterioles, venules and occasionally in an interlobular vein. There appeared to be vasoconstriction, especially during the first 24-48 hours. Agglutinations of red cells were apparent as clumps in the 20-30 μ vessels. In the capillaries these clumps were seen intermittently obstructing the lumen after causing reversal of the direction of flow or complete stasis. In the kidneys of animals after burn, similar changes were found, except that clumping was the most notable abnormality. Constriction of capillaries and arterioles was less prominent. After removal of tourniquets from extremities, renal cortical blood flow appeared slower than normal and there was a moderate amount of vasoconstriction. After 24 hours, red cell clumping was more apparent. Low blood pressure due to hemorrhage was associated with generalized constriction of arterioles and capillaries in the renal cortex. Rate of blood flow through the vessels was decreased. The intermittence of flow increased and as the blood pressure reached 20-40 mm. Hg, stasis and vasodilatation were seen.

Rabbits anesthetized with nembutal® showed variation in the vascular response to injection of epinephrine. Changes appeared in the renal cortex almost immediately. There was striking vasoconstriction, especially of the arterioles and capillaries, associated with slowing of blood flow and in many vessels complete cessation of flow. There appeared to be some

dilatation of the larger interlobular venules. Some of the capillaries in which blood flow had stopped were filled with static red cells and others were completely empty of blood. A few capillaries showed intermittence of flow and occasionally reversal in its direction. The changes lasted as long as epinephrine affected the arterial blood pressure. After large doses, there was complete cessation of flow in all vessels and many more capillaries appeared completely empty. The vasoconstriction was replaced by pronounced vasodilatation and rapid blood flow as the effect of epinephrine wore off. When it was given to animals with intravascular clumping of red cells or to post-traumatic rabbits, there was striking, immediate, complete stasis in all vessels under observation. By the direct observations of this sort of experiment, cortical flow was found to persist, contrary to the reports of Trueta and associates with an injection technic.

Renal Anoxia Syndrome: Review and Report of 22 Cases. Peter Gaberman, Donald H. Atlas, Erwin M. Kammerling, Lee Ehrlich and Julien Isaacs[1] (Chicago) studied selected patients with nonrenal conditions in whom acute renal insufficiency developed. The conditions included severe infection, shock, hemorrhage, electrolyte imbalance, dehydration, hepatitis, sulfonamide reactions, diabetic coma, cerebral hemorrhage, acute pancreatitis and hyponatremia from therapy of heart disease. Death occurred in 12 cases and autopsy was performed in 7.

The degree of azotemia did not parallel severity of the primary condition and had no prognostic value. Some patients survived despite findings considered indicative of terminal uremia. Shock was not always present. Hemoconcentration was present in some instances and absent in others. Urinary output and clinical appearance varied with the rate of onset and pathogenesis. Patients with sodium depletion had oliguria or excessive urinary output. Urine sometimes contained pigmented granular casts. Specific gravity varied from 1.017 to 1.023. Blood urea nitrogen and creatinine values were elevated to various levels in different patients.

There was no constant pathologic pattern in the seven autopsy cases. The kidneys were usually large and pale, with easily freed capsules. The cortex was swollen and over-all markings were obscured. Histologic changes ranged from no

(1) Ann. Int. Med. 35:148-168, July, 1951.

visible lesion to severe degeneration and necrosis of tubular epithelium. The distal segment of the tubule was the area most commonly damaged. True lower nephron nephrosis was often found when surgical shock had been present. When dehydration was the prominent clinical feature, the renal parenchyma often revealed no demonstrable change. Degeneration of tubular epithelium was usually found surrounding pigmented casts, irrespective of location in the tubule.

The term lower nephron nephrosis is not appropriate for all cases of nonrenal azotemia because the pathognomonic changes are frequently absent when the condition is caused by mechanisms other than shock or hemorrhage. The term renal anoxia syndrome seems a more suitable designation. Renal anoxia appears to be a common factor in all of these cases of nonrenal azotemia. The pathogenesis of renal anoxia syndrome includes (1) delayed shock (lower nephron nephrosis), (2) dehydration, (3) neurogenic and psychogenic anuria, (4) excessive protein catabolism, (5) toxic nephrosis, (6) the "hemoglobinuric kidney," (7) the "allergic kidney," and (8) renal circulatory failure (as in heart failure). More than one mechanism is operative in most cases.

[Even though renal anoxia is common to these various states, that is not proof of its causative significance. It may be ancillary to other factors which are known to participate.—Ed.]

Experimental Sucrose Storage in Mitochondria of Renal Tubules. Walter Zingg[2] (Univ. of Zurich) found that after injection of 0.2 cc. of 50 per cent sucrose in mice vacuolization took place in the cytoplasm of proximal convoluted tubules within ½ hour, was most striking in 8-10 hours, still observable 7 days later and had disappeared after a month. Special staining methods and the phase microscope showed that the sucrose is stored in the mitochondria, which fuse together forming larger bodies. The vacuolization seen in the sections is an artefact, due to absorption of water by the sugar-loaded hyperosmotic mitochondria during preparation of the section. Glucose is only quantitatively different in its effects; doses as high as 1 cc. of 50 per cent solution were required to produce similar changes.

Zingg suggests that sucrose is quickly eliminated from the blood by absorption in the mitochondria, which fuse and are eliminated in the lumen of the tubules. The mitochondria also affect the normal reabsorption of glucose from the lumen;

(2) Schweiz. Ztschr. allg. Path. 14:1-16, 1951.

however, as soon as the blood level exceeds a certain limit, the same process takes place. The question of formation of new mitochondria is unanswered.

[The morphologic features in the human kidney have been known for a long time, and interest attaches to this explanation of the mechanism.—Ed.]

Nephrosis-Like Renal Changes and Other Effects of Intraperitoneal Injection of Protein Hydrolysate were studied in rats by Jens Bing, Ivar Sperber and Gunnar Teilum.[3] Animals were divided into groups according to the substance injected. Materials used were (1) a combination of different alkaline hydrolysates from serums and casein; (2) a single alkaline hydrolysate from casein; (3) Formalin-treated protein hydrolysate with a pH of 7.4; (4) gelatin solution, and (5) dextran solution. Daily doses of 5-10 ml. were given for periods varying up to 120 days. Control rats did not receive injections. Methods of study included determination of serum proteins and blood urea, examination of fixed tissue sections, macerated kidney tissue and content of dry substance, nitrogen and phosphatase in the kidneys.

In all animals general health was uninfluenced by the intraperitoneal injections. There was no significant difference in the serum proteins and blood urea of experimental groups and controls. Rats receiving a combination of alkaline hydrolysates rapidly developed renal changes. The kidneys were large and pale. Microscopically, incipient vacuole formation in tubular epithelium was distinguished 24 hours after injections were started. After three days of treatment, vacuolation of cells was well established. When injection periods were longer the degree of alteration progressed. Pronounced vacuolation followed five days of injection. Maximal vacuolation of tubular cells was seen in animals treated for three months. In kidneys from animals injected for 15 days, vacuolation of cells was still evident three weeks after discontinuation of treatment; suggestive changes persisted four to eight months. The vacuoles were found only in the proximal convoluted tubules; the distal tubule was not involved. No glomerular lesions were detected. Following prolonged injection periods, vacuolation of tubular epithelium extended from Bowman's capsule to the beginning of the terminal segment of tubule. Vacuoles varied in size, usually being large in severely involved kidneys, and were

(3) Acta. path. et microbiol. scandinav. 29:57-71, 1951.

located in epithelial cell cytoplasm, resulting in increased thickness of tubular lining.

Kidneys from animals given a single alkaline hydrolysate of casein showed corresponding changes in the tubules with an additional process not apparent in the first group. Diffuse masses of yellowish brown precipitate, which occurred in the tubules of the inner cortex, stained yellow in van Gieson's preparation. Tubular degeneration was severe, with variable transitions from vacuolation into structureless coagulative necrosis and hyalinization of intertubular tissue.

Rats receiving injections of Formalin-treated protein hydrolysate had lesions located in the subglomerular zone. Tubular epithelial vacuolation was lower and approached the distal convoluted level. Kidneys were free from vacuoles in animals receiving gelatin. The epithelium of tubules throughout the cortex was swollen. Rats receiving dextran showed renal tubules with vacuolation of epithelial cells in the distal convoluted portion. The distal tubular lumen was filled with deposits of material appearing bright brown in van Gieson's stain. The thicker part of Henle's loop was also involved.

Chemical examination of kidneys showed changes in concentration of dry substance and of phosphatase but nothing could be concluded as to the content of the vacuoles. The omentum of the injected animals was thicker than normal. Microscopically there was massive infiltration of the fatty tissue by histiocytes. These cells varied in size. Some had abundant vacuolated cytoplasm and eccentric nuclei. Fibroblastic proliferation was present. Chemical analysis of the omentum showed increased nitrogen and phosphatase values. The spleens of experimental animals tended to be larger than normal and, microscopically, showed reticulosis in the pulp with numerous cells resembling those in the omentum. No distinct pathologic change was found in the liver of the experimental rats.

[The fact that this article comes from Teilum's laboratory makes it worthy of note. I see no reason why the condition should not be called nephrosis instead of nephrosis-like. The authors' observations on gelatin differ from those of Hartman (p. 79).—Ed.]

Thrombosis of Renal Veins with Massive Hemorrhagic Infarction of Kidneys in Childhood: Report of Four Cases of this rare condition is made by Sidney D. Kobernick, John R. Moore and F. W. Wiglesworth[4] (McGill Univ.) who think

(4) Am. J. Path. 27:435-453, May-June, 1951.

the condition may be significant in children with nonrenal infections which are accompanied by dehydration from diarrhea and vomiting.

The history suggested urinary tract involvement in only one patient. Most prominent presenting symptoms were diarrhea and vomiting. Abdominal masses were noted in two patients. Urinary findings may seem negligible but should not be overlooked. In all cases pathologic findings included infec-

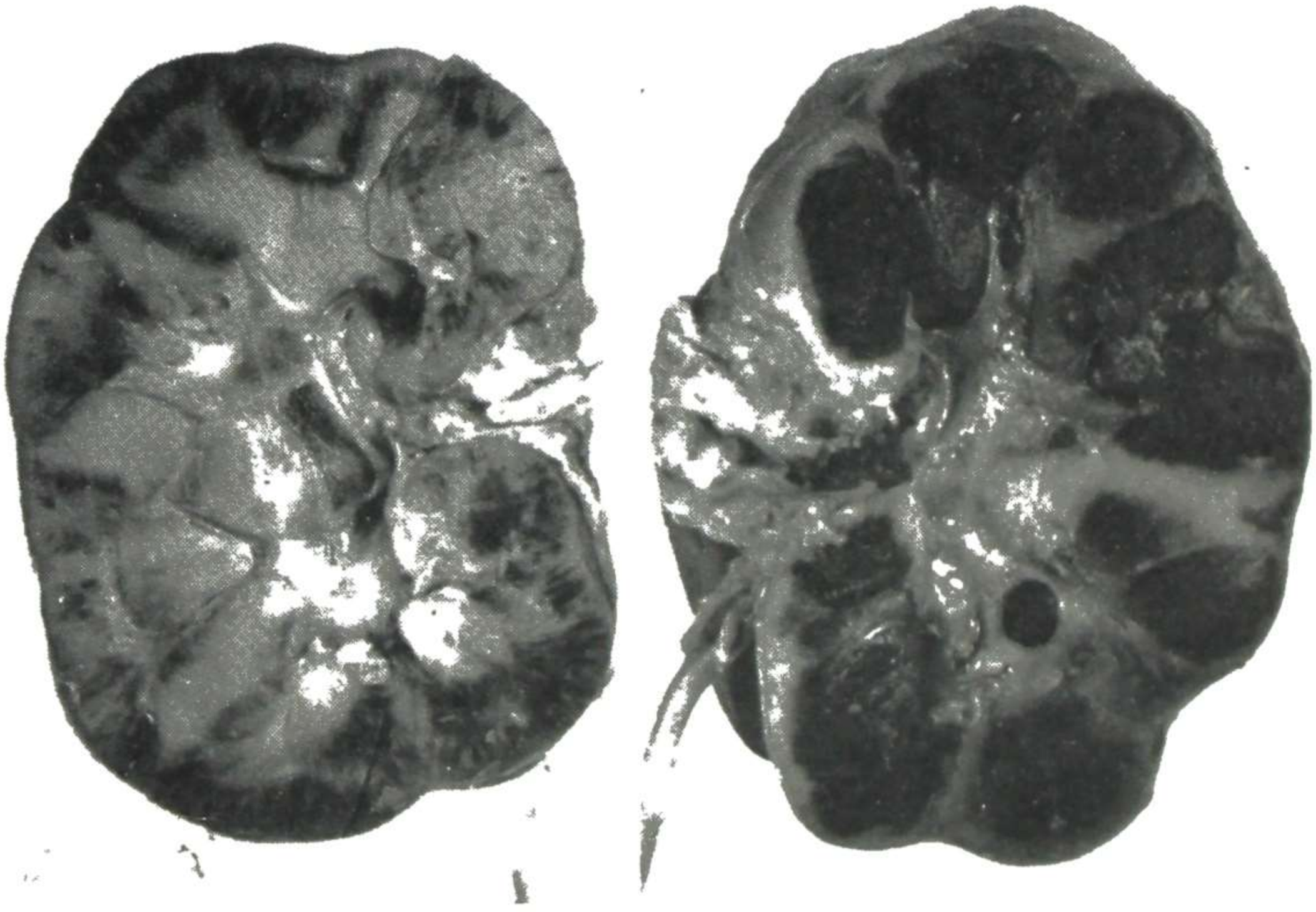


Fig. 61 (left).—Right kidney, showing patchy hemorrhage in corticomedullary junction and on either side of it; nonocclusive, yellowish white thrombus with tapered end is present in main renal vein.

Fig. 62 (right).—Left kidney, showing striking appearance of hemorrhagic pyramids and inner two thirds of cortex with strands of preserved cortical tissue. Pale thrombus occluding main renal vein is shown cut obliquely.

(Courtesy of Kobernick, S. D., *et al.*: Am. J. Path. *27*:435-453, May-June, 1951.)

tions in a site distant from the kidneys. Renal infarction, bilateral in two patients (Figs. 61 and 62) and present in only the right kidney in the other two, was hemorrhagic. In cases of short duration there was patchy capillary and venular hyperemia and hemorrhage in the region of the corticomedullary junction compressing and causing early necrotic and degenerative changes in the tubules. In later lesions the whole medulla and most of the inner cortical structure were obliterated by hemorrhage. The case with longest duration showed coagulative necrosis of almost the entire cortex; liquefaction

had occurred in focal areas of the cortex and near the tips of the pyramids. Thrombosis of the main renal veins and of their largest branches was seen grossly; microscopic examination showed similar involvement of almost all the smaller intrarenal veins. More advanced organization in the smaller than in the larger veins was a probable indication of origin in the former. Arteries were free from thrombi except in one case in which a large branch of the main renal artery contained a recent thrombus associated with peripelvic inflammation. In three, pulmonary vascular embolism or thrombosis was evident; in one the adrenal vein contained a recent thrombus, in another the right saphenous vein.

In all instances the vein walls were free from inflammatory changes; this suggests that local renal factors could not account for the thrombosis. The presence of thrombi in other organs tends to support the concept that systemic factors are important. Venous thrombosis in these patients may be related to increased coagulability of the blood under conditions of dehydration, infection and bed rest. The complex anatomic arrangement of veins at the corticomedullary junction, the site at which the earliest changes were noted, also may be an important etiologic factor.

Production of Malignant Nephrosclerosis by Simultaneous Treatment with Cortisone and Anterior Pituitary Preparation. Hans Selye[5] (Univ. of Montreal) studied the effect of lyophilized anterior pituitary (LAP) preparation, cortisone and lyophilized liver injections on rats sensitized by unilateral nephrectomy and substitution of 1 per cent sodium chloride solution for drinking water. Somatic growth was increased by LAP, the liver being particularly affected in all animals. Cortisone had the opposite effect, and, when administered simultaneously, inhibited the growth-promoting action of LAP. Lyophilized liver, serving as a control, produced no change in somatic growth. In rats treated with cortisone with or without lyophilized liver, the adrenals underwent atrophy; but if LAP was given with cortisone, atrophy was milder. The thymus of animals given cortisone, alone or with either lyophilized liver or LAP, showed intense involution. The thymus gland of rats given LAP injections enlarged slightly. Enlargement of the spleen when LAP and lyophilized liver were given separately was probably a reaction to a foreign protein.

(5) Acta endocrinol. 7:288-305, 1951.

Occasional granulomatous proliferations, found in the hearts of rats given cortisone and LAP simultaneously, appeared as hyaline degeneration of myocardial fibers and arterioles usually surrounded by inflammatory cells. Some aspects of these lesions resembled periarteritis nodosa and Aschoff nodules.

In animals given combined LAP and cortisone, increased fluid intake and pronounced diuresis were attributed to lessened tubular reabsorption of fluid by kidneys damaged by the combined treatment. All animals given both cortisone and LAP had nephrosclerosis. Bowman's capsule contained a protein precipitate. Casts were present in the convoluted tubules. The glomeruli and small arterioles underwent hyaline necrosis. The nephron changes were usually accompanied by inflammatory infiltration of interstitial tissue, often severe near the renal pelvis. The effect of the combination of the two hormones was out of proportion to the changes after either was given alone. Lyophilized anterior pituitary alone caused only mild dilatation of the glomerular capillaries. Two animals given cortisone and LAP had peculiar nuclear inclusion bodies in the epithelium of the renal tubules. Usually appearing as deeply basophilic, dense, round or amorphous, these inclusions resembled the bodies seen in various types of virus disease and inclusions of the tubular epithelium recently described in severe lead or bismuth intoxication.

Animals treated with LAP showed hypertrophy and hyperplasia of the adrenocortical zona fasciculata. Animals given cortisone had pronounced adrenocortical atrophy of all three layers. Cortisone alone or in combination with LAP or lyophilized liver caused diminution of thymocytes in the sections of thymus gland. There was atrophy of lymphoid elements of the spleen and involution of splenic megakaryocytes after cortisone, whereas LAP caused lymphoid hyperplasia and increase in splenic megakaryocytes.

In a few animals given cortisone alone or with the other two substances, abscesses developed in the lungs, usually surrounded by hemorrhagic halo. In the center of such lesions was a bronchus filled with purulent material. This picture suggested that the origin of the abscesses was based on decreased resistance to potentially pathogenic agents in the air passages.

[The observations are made with meticulous care, but the inferences

are based on earlier ideas regarding stress (see the 1950 YEAR BOOK, p. 7). What troubles me is the necessity for sensitization by unilateral nephrectomy. Regardless of interpretations, this is a way of producing chronic renal disease.—Ed.]

Inflammation and Repair of Glomerulus. David B. Jones[6] (State Univ. of New York, Syracuse) studied normal and pathologic glomeruli by means of various staining technics, using sections of 2 μ. Normal kidneys were obtained from persons under age 30 who had died suddenly. It was found that distinct epithelial and endothelial basement membranes are present in the glomerular tuft. The basement membrane of this tuft is continuous at the hilus with the basement membrane of the parietal layer of Bowman's capsule, and this, in turn, is continuous with the basement membrane of the tubule. The basement membrane of the glomerular tuft does not show the same continuation with the connective tissue around the afferent and efferent arterioles. Such a relation suggests that this membrane and the parietal layer of Bowman's capsule are epithelial basement membranes and are reflected over the glomerular capillaries in a manner similar to the peritoneal reflections over the bowel. In a capillary loop between the inner layers of this basement memrane there is a space, or potential space, which is continuous with the interstitial space at the hilus of the glomerulus. The space is not visible in the normal adult kidney, but in a child's glomerulus the interstitial material is prominent, forming a stalk of connective tissue surrounded by the capillary loop. In this stalk are found cells with small to moderately large vesicular nuclei and a small amount of pale cytoplasm—interstitial cells. They appear to be of mesenchymal origin, with the ability to lay down connective tissue scar as in healing glomerular injury. They are comparable to the cells of the undifferentiated perivascular connective tissue seen throughout the body. During early life the average number of epithelial cells per glomerular tuft is higher than the average number of endothelial cells, and the interstitial cells are the least numerous. The cell incidence changes gradually with age until at the end of the third decade the three types of cells are present in equal number.

Kidneys from 30 patients were studied: 9 with acute proliferative glomerulonephritis, 6 with exudative and proliferative glomerulonephritis and 15 with various degrees of acute glomerulitis. It was found that in the glomerulus inflam-

(6) Am. J. Path. 27:991-1009, Nov.-Dec., 1951.