PART I
INFECTIONS

SOME HAZARDS OF CONTEMPORARY THERAPY

Superinfection: Complication of Antimicrobial Therapy and Prophylaxis is discussed by Louis Weinstein[1] (Tufts Univ.). Antibiotic administration in therapeutic doses always produces a profound change in the composition of the bacterial population normally inhabiting certain tissues and organs. The so-called broad-spectrum antibiotics or combinations of antimicrobial compounds produce the most intense changes and may provoke overgrowth of drug-resistant strains of Staphylococcus aureus, proteus and pseudomonas, as well as of Fungi Imperfecti such as candida, or true fungi such as aspergillus and mucor.

The over all incidence of superinfection is about 2%. A study of 3,093 patients treated with various antibiotics suggested that age of the patient, the presence of acute or chronic infectious or noninfectious disease of the respiratory tract and the type of drug used appear to be the most important determinants of susceptibility. The complication occurs most often in patients under age 3 and over 50 and those with pneumonia, emphysema, atelectasis, pulmonary fibrosis, measles and pertussis. In general, the narrower the range of bacterial types susceptible to an agent, the lower is the incidence of superinfection. Superinfections tend to occur with greatest frequency 4 or 5 days after starting chemotherapy. They develop not only when antibiotics are given for therapeutic purposes but also when given prophylactically.

Changes in the bacterial population alone probably do not account entirely for the development of superinfection. Examples of host factors are the presence of leukemia, lymphoma and chronic disease, extremes of age and treatment with corticosteroids. There is little doubt that superinfection is largely responsible for the present increase in disease and

(1) Am. J. Surg. 107:704-709, May, 1964.

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death caused by drug-resistant staphylococci, enteric bacteria and fungi. Antimicrobial agents should not be given except in situations in which clinical experience indicates they will produce beneficial effects. In the field of surgery, this involves primarily the avoidance of their use for preventing infection, especially in "clean" or "elective" procedures. Another important measure is repeated study of the bacterial flora of the respiratory tract or intestine or of exudate in an infected local focus during the period of antibiotic administration.

► [It has been estimated that half of all prescriptions written are for antimicrobial drugs, and that one fourth of patients treated in American hospitals receive antimicrobials. If only 2% of them develop superinfections, it still follows that we are inducing a very substantial number of serious infections by our own therapy! — Ed.]

Clinical and Bacteriologic Study of Infections Associated with Venous Cutdowns. John M. Moran, Roger P. Atwood and Marc I. Rowe[2] (Boston City Hosp.) obtained data in a double-blind study of 89 cutdowns.

TECHNIC.—After shaving and preparing the skin with triple application of tincture of benzalkonium chloride, a polyvinyl catheter, usually 0.065 in. in internal diameter, was placed in a vein by means of an open surgical technic and the skin closed with 4-0 silk. A standard light dressing was applied. In 11 cases, no ointment was used. In 38, a topical antibiotic containing 5,000 units of polymyxin B sulfate, 400 units of zinc bacitracin and 5 mg. neomycin sulfate per Gm. was applied and in 40, placebo ointment with a light petrolatum base. Ointment was liberally applied to the wound and emerging catheter after skin closure and reapplied every 24 hours.

Significant numbers of organisms were found in 18% of the 38 wounds treated with antibiotic and 78% of the 40 treated with placebo. Not all bacteriologically positive wounds were clinically suppurative or phlebitic, and many that were phlebitic were sterile, especially in the treated group. Five cases of septicemia due to cutdown infection were noted, 2 in untreated and 3 in placebo-treated subjects.

It is recommended that a combined antibiotic ointment be applied daily to cutdowns and perhaps other percutaneous catheters, such as those used in regional perfusion chemotherapy for cancer, paracentesis for peritoneal dialysis and ascites drainage, ventriculostomy, indwelling spinal catheters and others.

► [We have all seen serious infection develop in patients who had been treated with venous catheters. The present study provides impressive information on the dimensions of the problem and, at the same time, offers a simple

(2) New England J. Med. 272:554-560, Mar. 18, 1965.

and effective measure to reduce the danger It seems deserving of general adoption —Ed]

Clostridial Myositis after Parenteral Injections. One unusual source of clostridial infection that carries a high mortality rate is parenteral injections; the reason for the high mortality seems most often to be delay in diagnosis. Ronald B. Berggren, Thomas D. Batterton, Gilbert McArdle and William H. Erb[3] (Philadelphia) report 5 cases, in 2 of which the patients survived.

In the first case, a man, 26, with glomerulonephritis received sodium amobarbital parenterally, and a painful left buttock developed. The area was aspirated 5 days after the last injection, and the aspirate yielded Clostridium welchii on culture. Wide incision and drainage was carried out with excision of necrotic muscle, and the patient was given potassium penicillin G and polyvalent antiserum. He died of the renal disease A diabetic woman, 48, had pemphigus and treated herself with parenteral corticotropin injections and insulin. Cellulitis of the left arm developed, and the arm had to be amputated after incision and drainage. Myoglobinuria and acute renal faulure developed, and the patient died after massive gastrointestinal bleeding; acute tubular necrosis and massive jejunal necrosis were found at autopsy.

A diabetic woman, 55, who had received insulin, atropine and meperidine hydrochloride, acquired acute intestinal obstruction and, after laparotomy and lysis of adhesions, crepitance in the left upper arm. Wide incision, debridement and drainage were carried out, and further treatment was given with hydrogen peroxide irrigation, penicillin, streptomycin and gas gangrene polyvalent antitoxin. Other systemic antibiotics were added when an overgrowth of klebsiella and pseudomonas developed, and the patient improved gradually A man, 67, with recurrent pleural effusion was treated for congestive heart failure with parenteral mercaptomerin and digoxin and responded well, but a sore left buttock developed, and Cl. perfringens was cultured Incision and debridement was carried out after treatment with tetanus toxoid and antitoxin, penicillin and streptomycin. Secondary closure of the wound was necessary; the wound healed well.

A man, 73, with an elevated fasting blood sugar level, un-

(3) J.A.M.A. 188:1044-1048, June 22, 1964.

derwent endarterectomy and was placed on NPH insulin A superficial wound infection developed in the thigh and, after being opened, healed by secondary intention The 5th toe became gangrenous, and an incision failed to heal Lumbar sympathectomy, amputation of the toe and debridement and graft of the ankle wound were planned, but the right shoulder became sore the day before surgery, and Cl perfringens later was cultured Wide incision and drainage was carried out, and penicillin, streptomycin and tetanus antitoxin were given, followed by hyperbaric oxygen therapy After aspiration of vomitus, the patient died

Whatever the precipitating cause, fatalities in untreated clostridial myositis occur quickly, 85% within 48 hours Needle aspiration can be helpful in confirming the diagnosis, and should be tried when there is a suspicion of this diagnosis Treatment should be immediate and aggressive once the diagnosis is made Hyperbaric therapy should be used when proper facilities and personnel are available

► [This is perhaps the gravest kind of infection resulting from intramuscular injections, but other pathogens may also cause suppuration and fever It is important to examine sites of intramuscular injections in febrile patients Surprisingly large gluteal abscesses can escape detection for days Ed]

Syndrome Resembling Infectious Mononucleosis after Open Heart Surgery. A clinical postperfusion syndrome of fever and splenomegaly with atypical lymphocytes in the peripheral blood was described by Seaman and Starr D R Smith[1] (Postgrad. Med School, London) reports 9 examples of this syndrome, encountered among 173 open heart operations performed during 1961-63, for an incidence of 5 2% Splenomegaly was noted 48 hours after onset of fever in 3 instances and after 7-21 days in the rest Fever occurred at a mean of 27 days after operation and was the presenting symptom in 7 cases. The mean duration of fever was 17 days. General well-being was apparent despite the fever. Hepatomegaly was noted only once Lymphadenopathy was found in 7 patients, concurrent with the splenomegaly and lasting 4-14 days; there was a discrete, shotty enlargement of the anterior and posterior cervical nodes A transient, nonpruritic maculopapular rash was seen in 4 patients concurrent with the appearance of splenomegaly, it lasted 3-5 days in 3. Atypical lymphocytes were present on the day of onset in 8 patients The total white cell count was above 10,000/cu. mm. in only

1) Brit. M J. 1 945-948, Apr. 11, 1964

2 patients The percentage of atypical lymphocytes varied considerably. Eosinophilia was absent in this series. Paul-Bunnell tests were negative in 7 cases

Perillie and Glenn suggested that an immune reaction might be a factor in the pathogenesis of this syndrome. No single drug has been incriminated. The only constant factor in previously reported cases appears to have been the use of cardiopulmonary bypass. A common denominator has been the use of large volumes of donor blood. It seems reasonable to suggest that virus disease may be transmitted to a susceptible recipient via donor blood. Cases tend to occur in sporadic outbreaks The relative constancy of the interval between operation and the development of symptoms is in keeping with either an infectious or an immune etiology.

► [The tendency of this syndrome to crop up sporadically seems strongly in favor of the thesis that an infectious agent is being transmitted in blood But if so, why is the syndrome so much more common in patients who have been treated with blood pumps than in others? See the next article - Ed]

Pyrexia after Heart Surgery Due to Virus Infection Transmitted by Blood Transfusion. B A Ross[5] (Guy's Hosp., London) reports a further cause of continuing disturbance other than the post-valvotomy syndrome or bacterial endocarditis This takes the form of pyrexia developing just before or after the 25th postoperative day It occurs after various open and closed operations involving transfusion of widely differing amounts of blood In most cases, the usual postoperative pyrexia had settled Generalized lymph node enlargement was noted in 10 of 11 patients, and there was a constant absolute lymphocytosis, many of the cells being typical of the abnormal lymphocytes seen in virus infections Two patients reported sore throat at the outset, but cervical lymphadenopathy was noted in most patients with or without oropharyngeal symptoms In 2 others, splenomegaly developed about 2 weeks after onset of the pyrexia

Man, 31, with coarctation of the aorta and an aneurysm, was admitted for resection and insertion of a homograft At operation, he received 10 pt. blood, and postoperative anemia was treated by further transfusion. When discharged about 1 month postoperatively, his cardiovascular state was excellent and he was afebrile The blood picture was normal. Six days after discharge, he was readmitted with a temperature of 100.4 F. and general malaise There was generalized lymphadenopathy. The hemoglobin content was 78% and the white blood cell count 30,000/cu mm., with 22% neutro-

(5) Thorax 19: 159-161, March, 1964.

phils, 77% lymphocytes and many atypical mononuclear cells of the "glandular fever" type Five days later the white blood cell count was 22,000/cu mm , with 8% neutrophils and 89% lymphocytes The Paul-Bunnell test was positive at a dilution of 1 32 The fever abated after 12 days and the patient recovered uneventfully The maximal temperature reached was 103 F

This case history is typical of those noted in the other 10 cases. At no time was any causative organism cultured It seems reasonable to suppose that a virus is transmitted by massive blood transfusion, since the illness has not been seen after major general operations in which smaller amounts of blood were transfused. The incubation period appears fairly constant at 25-28 days Of the 11 patients, 3 were operated on without the use of extracorporeal apparatus.

Infectious Diseases Associated with Renal Homotransplantation: I. Incidence, Types and Predisposing Factors; II. Differential Diagnosis and Management. David Rifkind, Thomas L. Marchioro, William R Waddell and Thomas E. Starzl[6] analyzed the infectious diseases occurring in the first 30 patients having renal homotransplantation at the University of Colorado Medical Center. The 25 males and 5 females were aged 6-49 years; 21 patients had chronic glomerulonephritis.

Homografts were from living volunteer donors in 28 cases and cadavers in 2. Thymectomy was performed before transplantation in 9 of the first 13 cases, and splenectomy was performed in 29 cases Earlier patients usually had thymectomy and splenectomy 2-4 weeks before bilateral nephrectomy and transplantation. Later patients usually had splenectomy, bilateral nephrectomy and renal homotransplanta tion done in a single operation

Just before operation, about 0.5 Gm neomycin sulfate and 50,000 units of bacitracin were instilled into the bladder; after renal implantation, the wounds and subphrenic spaces were irrigated with the same amounts. All patients were strictly isolated when immunosuppressive drug therapy was begun. Azathioprine was used as the primary drug, supplemented by total body irradiation in 1 case only. Corticosteroid therapy was begun at the first sign of graft rejection; 27 patients received actinomycin C at this time.

Infectious diseases occurred in 26 patients—after opera-

(6) J A M A 189 397-407, Aug 10, 1964

tion in 21, but in 6 of these one or more septic complications originated before the operation. There were 52 individual infections; of the 17 arising preoperatively, 11 were cured. Infectious diseases caused or contributed to 8 of the 12 deaths. In an addendum, the authors report that 4 other patients have died after 93-293 days; infection contributed to death of 2

Infections due to coagulase and mannitol-positive staphylococci developed in 18 patients, and these bacteria were present in 33 infections. Staphylococci were involved in all 8 cases in which infection contributed to death. Pseudomonas infections appeared 16 times. The enteric gram-negative bacilli were involved in 19 infections, primarily of the genitourinary tract. Non-group A streptococci occurred in mediastinal infections in 2 cases and in septicemia in 1. Candida albicans and Mycobacterium tuberculosis were each found in 1 pulmonary infection. Nineteen patients carried staphylococci in the nasopharynx or on the skin preoperatively; 17 of these developed significant staphylococcic infections, compared with only 1 of the 11 noncarriers

Septicemia occurred in 8 patients; the infection was suppressed in the 2 in whom it occurred preoperatively and in 1 other. Pneumonia occurred 7 times in 5 patients and resulted in the death of 4. Wound infection occurred 13 times in 11 patients. Mediastinal sepsis occurred in 4 patients in whom thymectomy was done. Bacteriuria occurred in 15 patients. Paravertebral gutter abscess and pancreatic abscess occurred in 1 case each. Agranulocytic angina occurred in 2 patients. Most postoperative infections arose after appearance of the rejection phenomenon; only 3 developed during the average 12-day interval between transplantation and onset of the rejection crisis. Total leukocyte counts below 3,000/cu. mm. with granulocytopenia appeared in 12 patients, including 7 of the 8 in whom infection contributed to death. Steroid-induced diabetes occurred in 10 of 26 patients tested. Hypogammaglobulinemia was found in 6 of 22 patients studied.

Apparently, infections in this series were frequently caused by microorganisms carried by the patient and developed when the host's defense mechanisms were depressed. Infectious disease may prove important in transplantation of other organs as well as the kidney. If fever is due to sepsis,

immunosuppressant drugs will only further impair the already depressed host resistance, while if only antibiotic therapy is given in a rejection crisis, progressive damage to the transplant will ensue. Rejection crisis is characterized by malaise, vague uneasiness, fever, oliguria, hypertension and tenderness over the homograft site. Infectious diseases do not produce early and severe impairment of renal function. The white blood cell count is of little differential value

All staphylococcic carriers are now being treated with systemic antibiotics for several days before transplantation and until wound healing has occurred. Usually penicillinase-resistant penicillins are used. Bacteriuria should be treated before operation; if it persists after operation, antibiotic therapy is continued for 1-2 weeks or longer. When pyelonephritis is part of the end-stage renal disease, both ureters should be completely excised at the time of bilateral nephrectomy.

► [One of the by-products of the current intense interest in organ transplantation is increasing information on host resistance to infection Not unexpectedly, measures to suppress an immune rejection of the graft are likely to impair immunity to infection Especially noteworthy is the fact that the infections which develop in these patients are caused by their own bacterial flora; consequently little benefit is likely to be achieved by the most elaborate precautions to protect them from other sources of infection, e g , so-called reverse isolation – Ed]

Infectious Pulmonary Disease in Patients Receiving Immunosuppressive Therapy for Organ Transplantation. Rolla B. Hill, Jr., David T. Rowlands, Jr., and David Rifkind[7] (Univ. of Colorado) reviewed data on 32 fatalities after homo- or heterotransplantation, in 26 of which active pulmonary infection was found at autopsy. In general, azathioprine was used an average of 10 days before transplantation, and postoperatively the dose was raised to the maximum tolerated. Prednisone, 150-400 mg. daily, was given until rejection was suppressed. In some cases, 2-6 doses of actinomycin C, 200 μg. daily, were added. Specific antimicrobial agents were given at the appearance of clinical infection Many patients had multiple infections. Of the 45 infectious agents involved, 10 were common pyogenic bacteria or were unidentified, 7 were pseudomonas species, 15 were cytomegalovirus, 12 were fungi and 1 was pneumocystis. The incidence of infection with cytomegalovirus was greater in the patients with longer survival.

(7) New England J Med 271 1021-1027, Nov 12, 1964

A classic bronchopneumonia was seen in a few cases, but a characteristic pattern, most commonly seen with candida and pseudomonas infection, was that of widespread but sharply limited lesions. A few alveoli were filled with blood and proteinaceous fluid, usually near a small arteriole whose wall was massively invaded with bacilli or fungi. Polymorphonuclear leukocytic reaction was absent. A particularly violent necrotizing effect of fungous organisms was noted. Clinical evidence of biologic response to the infecting organisms was lacking in a high percentage of patients; half of those with pulmonary infection gave no evidence of this clinically. Survival and cumulative drug dosage correlated with the incidence and type of infection. All patients dying without demonstrable infection lived less than 24 days after transplantation. All those with triple infections lived more than 24 days

Seven more deaths occurring recently were all in patients with pulmonary infection, including 5 with cytomegalovirus, 2 with aspergillus, 2 with pneumocystis, 2 with candida, 2 with pseudomonas, 2 with Staphylococcus aureus and 1 with tiny gram-negative intracellular bacilli. Recently, a cytopathogenic agent, apparently cytomegalovirus, was isolated from the lungs of 2 patients in whom inclusion bodies were demonstrated histologically at autopsy

► [This study and the preceding one, by the Denver group are especially important because of the careful study of infections which develop in patients on steroids and immunosuppressive drugs. Cytomegalovirus is apparently widely distributed in man, and reports of its isolation in patients with debilitating disease especially those receiving "modern" drugs are springing up everywhere.—Ed.]

Course and Management of Varicella in Children Receiving Steroids for Intractable Asthma. Constantine J. Falliers (Denver), Elliot F. Ellis (Gainesville, Fla.) and Samuel C. Bukantz[8] (Bloomfield, N. J.) reviewed the experience of the past 6 years at the Children's Asthma Research Institute and Hospital in Denver where children aged 6-16 are admitted for an average of 18-24 months. Of the children admitted during this period, 90% had taken steroids and 55% were currently taking maintenance doses daily.

Steroid withdrawal was accomplished in slightly more than half of these children. Of 59 cases of varicella, 21 children were receiving prednisone or betamethasone when the

(8) South. M. J. 58:1054-1059, September, 1964.

diagnosis was made. No change was seen in the intensity of asthmatic symptoms during the acute phase of the disease in 24 patients, whereas 10 had some increase in symptoms (mainly in the pre-eruptive period and 1st day of illness), and 21 showed a decrease in severity of the symptoms during the disease. A bacterial infection became superimposed on the skin of 2 patients, and pneumonitis of bacterial origin developed in 2 others. In many, the remission of asthma appeared to be directly related to the height and duration of the febrile response. The degree and duration of fever in children receiving steroids did not differ significantly from that of children not receiving steroids. Steroid doses were maintained at previous levels in practically all of the 21 children receiving these drugs when varicella supervened.

In asthmatic patients having varicella, steroid therapy is continued at maintenance levels (25-50 mg. cortisone, 5-10 mg. prednisone, 0.3-0.6 betamethasone, or two to nine dexamethasone inhalations daily). Abrupt discontinuance of therapy before or during varicella not only is unnecessary but may result disastrously. A prompt increase in the steroid dosage (doubling the daily dose or adding an equivalent of 50-100 mg. cortisone daily) may be indicated to control the stress associated with severe forms of the illness or in the presence of complications responsive to steroids.

► [The experience here reported is much more favorable than that by some other clinics where varicella has been thought to follow an unusually severe course in children receiving steroids – Ed.]

Nephrotoxicity of Amphotericin B: Early and Late Effects in 81 Patients were studied by William T. Butler, John E. Bennett, David W. Alling, Paul T. Wertlake, John P. Utz and George J. Hill, II[9] (Nat'l Inst. of Health). Amphotericin B is the only available drug effective in preventing death from a number of systemic fungal infections, and so is widely used despite toxic properties that otherwise would make it unacceptable. Recently, evidence has accumulated that persistent abnormalities of renal function are not uncommon. During treatment, elevated blood urea nitrogen values were found in 93% and elevated serum creatinine levels in 83% of the patients for whom adequate data were available. The maximal rise in blood urea nitrogen was directly related to the total drug dose. At most recent follow-up, blood urea nitrogen levels were higher after treatment than before

(9) Ann Int Med. 61:175-187, August, 1964

treatment in 74% of the patients, and serum creatinine levels were higher in 85%. The net rise in serum creatinine was significantly correlated with the total drug dose. Abnormalities of renal function persisted in 7 (44%) of the 16 patients who received over 4,000 mg. amphotericin B and in 6 (17%) of the 36 who received less than 4,000 mg.

Histopathologic changes, especially tubular leisons associated with calcium deposit, were noted in the kidneys of 24 of 26 patients studied. Renal biopsies performed before and after treatment in 1 patient showed that calcium deposit and tubular damage had occurred during treatment. In another patient, calcium deposit was demonstrated 5 years after treatment. A decreased ability to promptly excrete a water load occurred during treatment in 2 patients. One was unable to conserve sodium during treatment, but 1 year later this ability had returned to normal.

It is concluded that amphotericin B should be used only when specifically indicated and with the full understanding that impaired renal function and damaged renal structure occur in most patients.

► [Amphotericin B can save lives and shorten the course of serious illnesses, but only at a price. The diagnosis must be right to justify acceptance of risk of serious renal injury.—Ed.]

Paralytic Disease Associated with Oral Polio Vaccines. Donald A. Henderson, John J. Witte, Leo Morris and Alexander D. Langmuir[1] (Atlanta) summarize the basic epidemiologic data considered by a committee of the Public Health Service convened by the Surgeon General to reassess the problem of vaccine-associated cases of polio. In the United States, the incidence of paralytic poliomyelitis has declined precipitously in recent years, but 123 vaccine-associated cases have been reported since December, 1961. Of the cases, 36 which occurred along with vaccine-control programs in epidemic areas were considered to have been in the incubation period of a naturally acquired infection at the time of feeding. Of the 87 cases from nonepidemic areas, 57 were clinically indistinguishable from paralytic poliomyelitis. All had significant residual paralysis. Onset was 4-30 days after feeding, and laboratory data were not inconsistent with respect to multiplication of the vaccine fed.

The Committee concluded that at least some of these cases were caused by the vaccine, although it is not possible to

(1) J.A.M.A. 190:41-48, Oct. 5, 1964.

prove that any individual case was so caused The rate per 1,000,000 doses fed was 0 17 for type I, and 0 02 for type II and 0 40 for type III The risk with type III vaccine was significantly greater for adults than for children. The number of cases following type III in adults was considerably greater among males than females There appeared to be more cases among persons in the rural areas and in the upper socioeconomic groups.

The Committee recommended "changes in emphasis" of the national poliomyelitis program stressing continuing intensive immunization of infants and preschool-age children.

► [From the standpoint of the whole population, the oral polio vaccine program has been a smashing success and must be maintained Nevertheless the occasional paralytic disease following ingestion of the oral vaccine is catastrophic for the patient and his family —Ed.]

ANTIMICROBIAL THERAPY

Cephalothin: Activity In Vitro, Absorption and Excretion in Normal Subjects and Clinical Observations in 40 Patients are reported by Jerome O Klein, Theodore C. Eickhoff, Jeremiah G Tilles and Maxwell Finland[2] (Harvard Med School) In vitro tests of 1,254 strains of various bacteria indicated that cephalothin is highly active against penicillinase-producing staphylococci, although less effective than penicillin G, against other susceptible gram-positive cocci It appears to be bactericidal, and it is bound to an appreciable extent to serum protein Cephalothin has little or no activity against most gram-negative bacilli, especially klebsiella-aerobacter, proteus, pseudomonas and herellea.

Only minimal antibacterial activity was present in the serum of normal young men after single oral doses of 1 Gm. given either fasting or after a standard breakfast, with or without concurrent probenecid. After intramuscular doses, peak serum levels were attained ½-1 hour after administration and lasted about 4 hours. Probenecid more than doubled the peak levels and prolonged duration of serum activity. About two thirds of the amount given intramuscularly was

(2) Am J M Sc 248:640-656, December 1964

recovered in the urine, over 95% of this in the first 6 hours.

The over-all mortality in 38 patients with severe staphylococcic disease treated with parenteral cephalothin was 32%. Nearly half of these patients were over age 60 years, and most had other medical and surgical diseases and had acquired their infection in the hospital. Most deaths were in elderly patients with acute lower respiratory infection. The mortality rate compared favorably with that in previous studies at the same hospital in comparable patients treated with penicillinase-resistant semisynthetic penicillins (methicillin, oxacillin and diphenicillin) Except for a maculopapular rash in 1 patient, no drug toxicity was noted

If further experience confirms absence of cross-sensitization with penicillins, cephalothin or other cephalosporin C derivatives may prove of great value in patients with severe staphylococcic disease who are sensitive to various penicillins

Treatment of Infections in Man with Cephalothin is reported by Louis Weinstein, Kenneth Kaplan and Te-Wen Chang (Tufts Univ.) The nucleus of cephalosporin C, one of the naturally occurring antibiotics produced by the fungus Cephalosporium, is 7-amino-cephalosporanic acid. Cephalothin is a semisynthetic derivative of this substance, which is insensitive to penicillinase. Cephalothin inhibits the growth of various bacteria

Eighty patients, aged 10 days to 81 years, received no other antibacterial agent while cephalothin was given. About 75% received most or all of the drug intramuscularly, the rest were treated intravenously The dose in children was 40-120 mg./kg. daily, given in equal amounts every 6 hours. Adults received 2-12 Gm daily. Treatment was given for 5-7 days in fairly mild cases and 4-6 weeks in patients with bacteremia or severe localized disease.

Of the 80 patients, 77 were cured. All 50 infections due to Staphylococcus aureus were cured, as were 27 of the 30 due to other bacteria. Alpha and beta hemolytic streptococcus was involved in 11 cases, Streptococcus anaerobius in 1, Diplococcus pneumoniae in 7, Escherichia coli in 3, Clostridium perfringens in 1, Aerobacter aerogenes in 1, mixed Proteus mirabilis and Str. faecalis in 1 and mixed Staph aureus and beta hemolytic streptococcus in 2. Of 3 patients

(3) J.A.M.A. 189:829-834, Sept. 14, 1964.

who failed to respond to therapy, 1 had miliary tuberculosis, 1 had Hemophilus influenzae meningitis and 1 had vaccinia of the cheek

The in vivo activity of cephalothin appears to parallel its in vitro antibacterial spectrum. Many of the patients studied had alterations of host response or an underlying disease on which infection was superimposed. The incidence of adverse reactions was about 4%. The only side effects appeared to result from hypersensitization of mild to moderate degree. Many persons with known sensitivity to penicillin tolerated treatment with cephalothin without untoward effects.

► [Weinstein and his colleagues report better survival rates, but their cases seem, in general, to have had less threatening clinical problems than those reported by Finland's group in the preceding article. Cephalothin appears to be an effective agent, but not greatly superior to penicillinase resistant penicillins such as oxacillin. One advantage is that it can be given to patients allergic to penicillin.—Ed.]

Lincomycin Hydrochloride: Clinical and Laboratory Studies were undertaken by A. W. Geddes, R. A. Sleet and J. McC. Murdoch[4] (City Hosp., Edinburgh). Lincomycin was isolated from Streptomyces lincolnensis in 1955. In vitro, the antibiotic has comparable activity against the same range of gram-positive organisms as erythromycin. Oral doses are well absorbed from the upper small bowel, giving peak serum levels after 4 hours. Significant concentrations are present in most body tissues, but not in the cerebrospinal fluid. Bile may be an important route of excretion. From 1.1 to 6.6 μg./Gm. has been found in bone specimens.

Twenty-four patients, aged 12-77, with gram-positive infections were studied. A penicillin-resistant Staphylococcus aureus was obtained from 15 patients, Streptococcus pyogenes from 4 and no organism from 5. Four of the latter had "closed" osteomyelitis with sterile blood cultures, and the fifth had a cellulitis without sinus formation. Lincomycin hydrochloride was given orally in doses of 250 or 500 mg. every 6 hours.

Case 6.—Man, 77, fractured his left femur 40 years before admission and presented with a discharging sinus of the left hip, from which repeated cultures were sterile. There was x-ray evidence of widespread femoral destruction. A trial of antituberculosis therapy was unsuccessful. Lincomycin produced slow but definite improvement. The sinus closed and the sedimentation rate fell from 73 to 20 mm. per hour. He has received lincomycin for 120 days without evidence of toxicity.

(4) Brit. M. J. 2:670-672, Sept. 12, 1964

CASE 16.—In girl, 13, staphylococcic septicemia developed after aortic valvulotomy, which responded to cloxacillin. When she was readmitted 6 months later with fever, Staph. aureus was isolated from the blood, but there was no response to cloxacillin after 2 days, and lincomycin was given. Her condition improved gradually and she was afebrile after 6 days. Eleven months after discharge she had a second successful operation for repair of a false aortic aneurysm. Swabs from the endocardium and aneurysm were sterile. Lincomycin was discontinued after a total of 9 months' treatment.

Nineteen of the 24 patients showed complete clinical recovery. Bacteriologic cure was achieved in 14 with positive pretreatment cultures. In 2 cases, failure to respond was due to superinfection with gram-negative organisms; 1 patient had carcinoma; and 1 had inadequate drainage of an empyema. The minimal inhibitory concentration was usually 0.5 or 1 μg./ml., but in 2 patients it was 4 μg./ml. Of 160 serum level determinations, 80% were between 0.5 and 16 μg./ml. Of 184 strains of Staph. aureus isolated over 3 months, 70% were penicillin resistant but sensitive to methicillin, erythromycin and lincomycin. There were 46 erythromycin-resistant, 10 methicillin-resistant and 2 lincomycin-resistant strains. Mild diarrhea occurred transiently in 2 patients.

Lincomycin hydrochloride is acid stable and can be given orally for long periods without risk of serious toxicity. It is useful when a patient is infected with a penicillin-resistant staphylococcus and cannot be given one of the new penicillins because of drug sensitization or because resistance to one of the new penicillins has been demonstrated. The drug should also be considered in cases of infection with erythromycin-resistant staphylococci. It is particularly valuable in treating staphylococcic osteomyelitis.

➢ [This drug seems very much like erythromycin. The reports of unusually high concentrations in bone bring up the possibility that it may have some usefulness in treatment of osteomyelitis. Furthermore, it can be used as a substitute in patients allergic to penicillin.—Ed.]

Clinical Evaluation of Nafcillin in Patients with Severe Staphylococcic Disease is reported by Theodore C. Eickhoff, Jay Ward Kislak and Maxwell Finland[6] (Harvard Med. School). Nafcillin (6-[2-ethoxy-1-naphthamido] penicillin) is one of the semisynthetic, penicillinase-resistant penicillins that has been introduced since the isolation of 6-aminopenicillanic acid. The newer penicillins have relative acid stability, permitting absorption on oral administration, and greater

(6) New England J. Med. 272:689-709, Apr. 6, 1965.

in vitro activity against penicillinase-producing and other staphylococci than methicillin.

Nafcillin was given to 86 patients with serious staphylococcic infections. Many patients were elderly and most had serious underlying diseases. The over-all mortality was 38%. The mortality was 53% among 19 patients with well-authenticated infections of the lower respiratory tract who were given nafcillin alone, 25% in 24 patients with other authenticated staphylococcic infections similarly treated and 36% in 11 patients with bacteremia given only nafcillin. There were no substantial differences in mortality rates in comparable groups of patients given methicillin, oxacillin or nafcillin. Strains of staphylococci were uniformly sensitive to nafcillin. Serum levels of nafcillin were high and comparable to those found in normal young adults after parenteral administration. After oral administration, they were low and variable. In patients with impaired renal function, they were high and well sustained. Several serious superinfections occurred, but not oftener than in similar patients given other treatments. The drug was generally well tolerated. Rashes occurred in 4 patients (5%).

Nafcillin is an effective and well-tolerated antistaphylococcic agent. Results of therapy are entirely comparable to those previously observed with other penicillinase-resistant penicillins and cephalothin.

Activity of Ampicillin In Vitro Compared with Other Antibiotics was investigated by R. Sutherland and G. N. Rolinson[6] (Beecham Res. Lab., Ltd., Betchworth, England). Ampicillin is a penicillin with broad-spectrum activity. It is acid stable and gives satisfactory serum concentrations after oral administration. Study was made of 673 strains of bacteria obtained from three London hospitals; nearly all were associated with urinary tract infections. Minimum inhibitory concentrations were determined by serial dilution in agar.

Of 269 strains of Escherichia coli, 78% were inhibited by 5 μg. ml. ampicillin or less; the corresponding figures for chloramphenicol and tetracycline were 52 and 64%. At a concentration of 2.5 μg./ml., the figures were 19% for ampicillin, 8% for chloramphenicol and 45% for tetracycline. Proteus mirabilis was generally highly sensitive to ampicillin, 83% of the strains being inhibited by 5 μg./ml. and 74%

(6) J. Clin. Path. 17: 461-465, July, 1964

by 2 5 μg./ml. Chloramphenicol and tetracycline were considerably less active at these concentrations. All strains of P. morgani and P. vulgaris were relatively resistant to ampicillin. Ampicillin was highly active against strains of Streptococcus faecalis, 95% being inhibited by 2 5 μg./ml., whereas chloramphenicol and tetracycline were relatively ineffective. Ampicillin showed low activity against Aerobacter aerogenes. About half the strains of paracolon organisms studied were inhibited by 5 μg./ml. ampicillin. All three antibiotics showed low activity against Pseudomonas pyocyanea.

Against 20 E. coli strains chosen at random, colistin sulfate, kanamycin, polymyxin, streptomycin and tetracycline were more active than ampicillin, but colistin methane sulfonate was less active and cycloserine and nitrofurantoin were relatively ineffective. Ampicillin was much more active against P mirabilis than any of the other antibiotics tested It was outstandingly active against 20 strains of Str. faecalis, but showed little activity against 10 strains of A. aerogenes

► [Ampicillin does not seem to be the drug of first choice in most clinical situations but is nevertheless useful at times, e g against enterococci Proteus mirabilis, salmonella and some coliform infections – Ed]

Oral Treatment of Bacterial Endocarditis with Penicillins. I R Gray, A R Tai and J G Wallace (Coventry, England) and J H Calder[7] (Brentford, England) successfully treated 13 patients Streptococcus viridans was isolated in 8, Str faecalis in 2 and both Str viridans and Str pneumoniae in 1 Propicillin was used when the infecting organism was Str. viridans Two of the 10 patients given this drug received 250 mg every 4 hours, and the others received 500 mg 4-hourly; one dose was usually omitted during the night Five patients received 500 mg probenecid every 6 hours. Ampicillin was the drug of choice for Str faecalis infections Three patients were so treated; 250 mg 4 hourly did not control the fever in 1, whereas 500 mg 4-hourly was effective The other 2 patients received 500 mg initially and 1 of them also received erythromycin. The patient with recurrent infection received 1 Gm. ampicillin 4-hourly along with streptomycin. Treatment was given for 6 weeks except in 1 patient in whom it was stopped a little sooner because of suspected penicillin hypersensitivity.

Infection was controlled in all patients One patient had recurrence at 2 months, but a second course of therapy was

(7) Lancet 2:113-114, July 18, 1964.

effective. Two patients died within 3 months of cardiac failure, and a third died during attempted repair of a perforated aortic valve. To date, the 10 survivors have all done well. The penicillins were well tolerated by mouth. One patient taking propicillin had mild gastrointestinal symptoms which passed in a few days. Two had unexplained pyrexia, and 1 of them had a rash. Steroid therapy was given as a cover to 1 of these. The eight strains of Str. viridans were all sensitive to both drugs. The required concentration of propicillin was greatly increased in the presence of serum, whereas with ampicillin the presence of serum made no difference to the mean inhibitory concentration. The one strain of Str. faecalis tested was more sensitive to ampicillin than to propicillin. Two patients given propicillin alone had peak serum levels of 6.5 and 11.5 μg./ml. at 1½-2 hours after 500 mg. orally, and high levels persisted for 4 hours. When probenecid, 0.5 Gm. 6-hourly, was also given, the levels were about 50% higher.

Apparently, most patients with bacterial endocarditis can be treated successfully with penicillins by mouth. The advantages of oral over intramuscular therapy are unquestionable in long-term therapy, provided adequate bactericidal levels are obtained. Ampicillin seems preferable for the initial treatment before the results of blood culture and sensitivity testing are available. If the organisms are found to be highly sensitive, one of the phenoxypenicillins can be substituted later.

► [My first reaction to this title was of apprehension, because this disease is not one in which second-best methods of treatment are justified but, on careful study, it seemed the authors had not subjected their patients to unnecessary risk. Long courses of parenteral administration of antimicrobials are uncomfortable for the patients and, at times, are technically very difficult, especially in children. These workers, aided by good laboratory facilities, were able to insure that they were achieving satisfactory antibacterial concentrations in the blood of their patients throughout the course of therapy. – Ed.]

Clinical and Bacteriologic Studies of Effect of "Massive" Doses of Penicillin G on Infections Caused by Gram-Negative Bacilli were conducted by Louis Weinstein, Phillip I. Lerner and William H. Chew[8] (Tufts Univ.). When penicillin G was first used clinically, the limited amounts available dictated its application in situations involving highly "sensitive" organisms, such as pneumococci, Streptococcus pyogenes, etc. The fact that other species, e.g., the gram-nega-

(8) New England J. Med. 271:525-533, Sept. 10, 1964.

tive bacilli, were suppressed only by 50-100 times or more the accepted level of "sensitivity" led to their being considered "resistant," and such infections were not treated with penicillin. High concentrations of this agent have been shown to inhibit the growth of some of these species. Laboratory studies using the tube-dilution method indicated that the bulk of strains of gram-negative organisms such as Escherichia coli, Aerobacter aerogenes, Alcaligenes faecalis, salmonella, shigella and indole-negative Proteus mirabilis were inhibited by concentrations of penicillin G ranging from 2.5 to 625 units per ml. in most cases. Pseudomonas and indole-producing proteus were suppressed only by 5,000-10,000 units per ml.

Intravenous administration of 20,000,000-60,000,000 units daily to patients with severe infections due to gram-negative bacteria, many complicated by bacteremia, resulted in bacteriologic and clinical cure in most patients. Serious underlying disease led to relapse or death, unrelated to infection, in some. Peak penicillin G levels were as high as 737 units per ml. Generalized seizures in patients with renal failure or underlying central nervous system disease were the only untoward effects noted.

The results suggest redefinition of the "sensitivity" of bacteria to penicillin G, so that, based on tube-dilution determinations, organisms may be classed as "sensitive" when inhibited by 78 units per ml. or less, "moderately sensitive" when suppressed by 156-625 units per ml. and "resistant" when sensitive to more than 625 units per ml. Because of its almost complete lack of toxicity, the use of penicillin G as a substitute for other antimicrobial compounds with a greater potential for untoward effects merits serious consideration in managing infections caused by gram-negative bacilli if the bacteria are shown to be sensitive in vitro to clinically attainable serum concentrations

► [Weinstein and his colleagues have made a useful contribution here, in emphasizing the therapeutic effectiveness of massive doses of penicillin for gram-negative infections. Conventional laboratory sensitivity tests would not alert the clinician to their possible value.—Ed.]

Ampicillin in Treatment of Hemophilus Influenzae Infections of Respiratory Tract was evaluated by J. Robert May and Doreen M. Delves[9] (Inst. of Diseases of Chest, London). The role of H. influenzae as the most important pathogenic

(9) Thorax 19:298-303, July, 1964.

bacterium in chronic bronchitis and bronchiectasis is now widely accepted Infections caused by it show a strong tendency to relapse when chemotherapy is stopped As a rule, benefit from tetracycline therapy lasts for little longer than the duration of the therapy, even if given for many months Previous studies suggested that ampicillin might be able to kill H. influenzae in the bronchial tree rather than merely inhibit it as does tetracycline. Twenty men and 9 women, aged 30-75, with chronic bronchitis were observed in the present study.

All 36 strains of H. influenzae tested in vitro were inhibited by 0.6 μg. ampicillin per ml , two-thirds by 0.3 μg /ml. and one-fourth by 0.15 μg./ml. In 4 instances, minimal bactericidal concentrations were 4, 2, 2 and 8 times the corresponding minimal inhibitory concentrations The sputum concentration obtainable during administration of 250 mg ampicillin every 6 hours is likely to be about 0.1 μg /ml., whereas on a dosage of 500 mg. every 6 hours it is likely to be about 0.2 μg./ml. Less than one fourth of H influenzae infections can be expected to respond to 250 mg every 6 hours, and only about one half of the infections to double this dose. Elimination of H. influenzae from the sputum was as unpredictable as was the elimination of pus As a rule, isolation of the organism became increasingly difficult while ampicillin was being given The quantity of sputum expectorated daily was often reduced during ampicillin treatment

Ampicillin has not proved capable of overcoming the problem of relapse in doses similar to those used for other antibiotics. The results of a small preliminary study of a daily dose of 4 Gm. are encouraging. It seems probable that on economic as well as therapeutic grounds 1-week courses of ampicillin, 4 Gm. daily, would be acceptable, provided that the encouraging results obtained were confirmed in a more extensive trial.

► [This method of treatment will indeed require further careful testing. Treatment of chronic bronchitis is difficult to evaluate.—Ed.]

Successful Treatment of Proteus Septicemia with New Drug, Trimethoprim, is reported by R. G. Cooper (Royal Perth Hosp.) and M. Wald[1] (Univ. of Western Australia). Trimethoprim is a new chemotherapeutic agent that is said to be particularly active against proteus organisms

(1) M. J. Australia 2:93-96, July 18, 1964

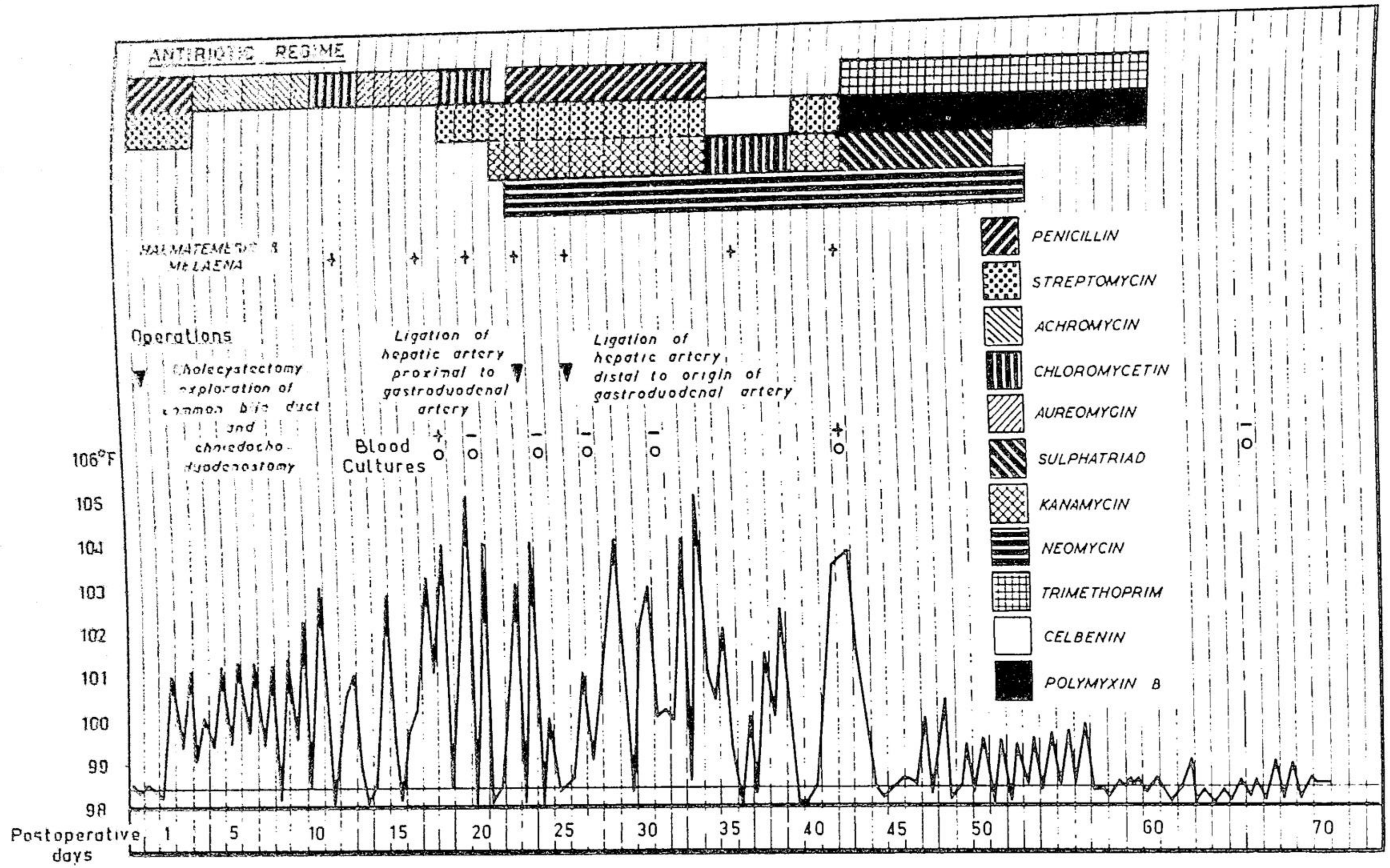

Fig. 1.—Chart shows temperature, antibiotics used, episodes of blood loss, operations performed and dates on which blood culture reports were received. (Courtesy of Cooper, B. G., and Wald, M., M. J. Australia 2: 93-96, July 18, 1964.)

Man, 50, was admitted for cholecystectomy and exploration of the common bile duct Cholecystectomy, exploration of the bile duct and choledochoduodenostomy were performed for calculous disease. Fever was noted immediately after operation, and rigors and periodic exsanguinating losses of blood from the gastrointestinal tract developed after 12 days (Fig. 1). The first "positive" blood culture was reported as showing a growth of proteus organisms sensitive to streptomycin and chloramphenicol and insensitive to penicillin, tetracycline, erythromycin, bacitracin and polymyxin B The second culture showed proteus species sensitive only to streptomycin and kanamycin, with a growth of coliform bacilli sensitive to streptomycin and polymyxin B The second course of chloramphenicol was terminated because the patient's condition was deteriorating rapidly Treatment with kanamycin had no effect From the 43d postoperative day, 200 mg trimethoprim was given every 4 hours orally for 18 days, along with 500,000 units of polymyxin B intramuscularly 6-hourly for 18 days and 1 Gm Sulfatriad orally 4-hourly for 9 days The temperature fell and the only toxic effect was nausea, which disappeared when Sulfatriad was stopped Two hepatic artery ligations were carried out and 57 bottles of blood were given Neomycin was given orally to depress gastrointestinal ammonia production Since discharge, the patient has remained well

Trimethoprim had a bacteriostatic effect on the P mirabilis in terms of therapeutically obtainable blood levels All the dual drug combinations showed presumptive evidence of synergism, especially polymyxin B with sulfadiazine. The Escherichia coli was extremely sensitive to polymyxin B and resistant to sulfadiazine and trimethoprim. The more important organism causing the systemic infection in this case was believed to be proteus Treatment directed almost exclusively against this organism produced a gratifying result.

► [Trimethoprim is a new pyrimidine compound which shows in vitro activity against proteus species The patient reported here was dreadfully ill, and other drugs as well as surgical procedures had to be used in treatment Still there is reason to agree that the trimethoprim aided his recovery, and one hopes that further encouraging reports of its use in proteus infections will be forthcoming —Ed]

Successful Treatment of Pneumocystis Carinii Pneumonitis in Patient with Congenital Hypogammaglobulinemia is reported by John B. Robbins, Robert H. Miller, Victor M. Arean and Howard A. Pearson[2] (Univ. of Florida).

Girl, 8, was admitted because of fever, dry cough and increasing respiratory difficulty She had had respiratory infections all her life, including severe bronchitis and pneumonia When seen about 5 months earlier, she was in the 3d percentile for height and weight, and had a vital capacity of 0.7 L (normal 2 L.). X-ray study showed minimal pulmonary scarring Immunoelectrophoresis and gel diffusion study showed absent γM- and γA-globulins; γ_{α}-globulin levels

(2) New England J Med 272 708-713, Apr 8, 1965

were 200-250 mg./100 ml. The Schick test was positive despite three previous injections of diphtheria toxoid. Bone marrow study showed no indentifiable plasma cells, decreased lymphocytes and a granulocytic hyperplasia. Treatment was started with pooled commercial Cohn fraction II, 0.6 ml./kg. body weight monthly, intramuscularly. A dry cough developed 4 weeks before admission and fever occurred 2 weeks later. Tetracycline therapy did not help. Diffuse bilateral infiltrates were found on admission. Decreased breath sounds and hyporesonant percussion were noted bilaterally. The white blood cell count was 21,000/cu. mm. The sputum contained a polymorphonuclear exudate and scanty bacterial flora.

High doses of penicillin, kanamycin and oxacillin were ineffective. Removal from a moist, oxygen-enriched environment provoked severe cyanosis. A lung biopsy specimen showed P. carinii pneumonitis. Hydroxystilbamidine, 4 mg./kg., was given daily, intravenously. This was replaced 3 days later by pentamidine isothionate, 4 mg./kg. intramuscularly, given for 14 days. Also, 2 Gm. γ_g-globulin was given. Clinical improvement began after 1 week of treatment, and x-rays showed improvement in 3 weeks. Bone marrow study showed gradual development of erythroid hyperplasia with marked megaloblastic changes. Little respiratory embarrassment was found 1 month after discharge and weight gain was maintained.

Ivady and co-workers treated 212 patients with antiprotozoans, including pentamidine isothionate and stilbamidine. Marshall and co-workers reported success in treating P. carinii infection with Pentamidine isothionate. The megaloblastic activity found in the present case was accompanied by an extremely low serum folate activity. The primary action of pentamidine may be that of a folic acid antagonist. The bone marrow was converted to an essentially normal appearance 3 weeks after the drug was discontinued.

► [This is worth further trial in those rare instances where the diagnosis of pneumocystis infection can be made ante mortem.—Ed.]

Prevention of Streptococcic Pharyngitis among Military Personnel and Their Civilian Dependents by Mass Prophylaxis. William F. Schneider, Stephen Chapman, Victor B. Schulz, Richard M. Krause and Rebecca C. Lancefield[3] studied the occurrence of streptococcic pharyngitis in a military population of 14,625, consisting of both Armed Forces personnel and their civilian dependents at Loring Air Force Base in Maine. There were 2,600 preschool subjects, 2,100 in elementary school, 400 in junior high school, 325 in high school, 3,300 wives, 3,300 married military subjects and 2,600 bachelor airmen.

The number of patients with streptococcic pharyngitis

(3) New England J. Med. 270:1236-1242, June 4, 1964.

increased markedly during January and February, 1963. Type 12 was the commonest, although types 1, 2, 3 and 18 were prevalent. Penicillin prophylaxis was administered to children in the 3d week of February; bachelor military personnel also received penicillin. All contacts who had a positive throat culture were given 1,200,000 units of benzathine penicillin G intramuscularly. Immediately after this measure there was a 10-fold decrease in the attack rates of streptococcic pharyngitis in military and dependent personnel. The attack rates remained at the low level throughout the rest of the respiratory infection season.

The spread of streptococcic disease in a population such as that at Loring Air Force Base is more typical of a civilian community than a military population such as a recruit training command. In the former case, the health of the military personnel is largely influenced by the health of the family members.

THERAPY OF MENINGITIS

Studies on Pathogenesis of Meningitis: V. Action of Penicillin in Experimental Pneumococcic Meningitis. Pneumococcic meningitis in man often culminates in death, despite adequate therapy with penicillin, to which the pneumococcus is exquisitely sensitive. None of the explanations given is wholly satisfactory. Death in meningitis appears to be a complex phenomenon, not related solely to failure of drug action or intensity of exudation. James J. Plorde, David Hovland, Manuel Garcia and Robert G. Petersdorf[4] (Seattle) studied the action of penicillin on pneumococci in broth, cell-free cerebrospinal fluid and cerebrospinal fluid containing leukocytes in vitro and in infected cerebrospinal fluid in intact animals.

METHOD.—Aseptic meningitis was produced in mongrel dogs by injecting 6 ml. of sterile saline containing 2 μg. Pyrexal, a purified endotoxin preparation of Salmonella abortus equi into the cisterna magna. The cerebrospinal fluid at 4 hours contained 4,000-8,000 white blood cells per cu. mm., 96-99% of which were polymorphonuclears. Bacterial meningitis was produced by injecting 1 ml. of a 10

(4) J. Lab. & Clin. Med. 65:71-80, January 1965.

dilution of an overnight culture of a smooth type III pneumococcus into the cisterna magna, the inoculum contained 10^7 organisms per ml. Some animals received 30,000 units of aqueous penicillin per kg intramuscularly every 2 hours beginning 4 or 12 hours after inoculation of bacteria.

When 10^4 type I pneumococci were suspended in tryptose phosphate broth, the number of bacteria rose rapidly to a concentration of over 10^8/ml. in the first 12 hours. When penicillin was added 4 hours after beginning incubation, there was prompt killing of bacteria, and at 12 hours, no viable organisms were detectable. When penicillin was withheld until 12 hours after onset of incubation, the decrease in organisms was no greater than in control studies. Similar results were found with 10^6 viable organisms in the inoculum. Penicillin added to 10^6 type III pneumococci per milliliter was strongly bactericidal in the logarithmic phase of growth but produced no appreciable killing when added during the static phase. These studies showed that penicillin exerts its optimal killing effect on a young, rapidly multiplying bacterial culture in the logarithmic phase of growth.

Organisms did not grow as luxuriantly in spinal fluid as in broth, presumably because of the lower concentration of bacterial nutrients in the former. Penicillin exerted a killing effect only when added 4 hours after beginning incubation. When the drug was added at 12 hours, the death rate of bacteria was the same as in control studies.

Of 48 dogs inoculated intracisternally with 10^7 pneumococci, 24 were untreated and 12 were treated with penicillin at 4 hours and 12 at 12 hours. Untreated animals showed gradual decrease in number of bacteria throughout the study, but viable organisms were cultured for its duration. Maximum exudation occurred at 8 hours, with relatively rapid bacterial killing thereafter. Treatment begun at 4 hours produced rapid killing of bacteria, the spinal fluid being sterile within 24 hours; however, penicillin did not affect the inflammatory response. Treatment begun at 12 hours produced a rapid decrease in viable organisms, not, however, appreciably different from that seen in untreated animals. Viable bacteria was cultured 24 hours after onset of treatment. Treatment early in the course of infection before maximum exudation resulted in significantly more rapid killing of bacteria than in untreated animals or animals treated later in the course of infection. Ad-

ministration of penicillin did not diminish the number of leukocytes.

The results confirm previous in vitro observations that penicillin affects sensitive microorganisms only during their logarithmic phase of growth when there is rapid synthesis of cell walls. Leukocytes or their products apparently played a role in bacterial death. The results tend to negate the postulate that the continued high mortality rate in pneumococcic meningitis is due to presence of a virulent exudative response in an enclosed space adjacent to structures responsible for maintaining vital functions. Penicillin does not affect this response, and its beneficial effect is not related to its ability to suppress the inflammatory reaction. It is suggested that perhaps most patients who survive after antibiotic therapy may be those who receive drugs "early," during the period of rapid bacterial growth, perhaps even before the exudative reaction reaches its maximum. The combination of a low leukocyte count and a high bacterial count may prove to be a valuable prognostic profile of early meningitis.

► [This may help to explain our disappointing results in treatment of pneumococcic meningitis. We have tended to meet the problem by using larger and larger doses of the drug, which never seemed very rational in view of the uniform sensitivity of pneumococcus to penicillin.—Ed.]

GRAM-NEGATIVE BACTEREMIA

Bacteremia Due to Gram-Negative Rods: Clinical, Bacteriologic, Serologic and Immunofluorescent Study of 100 unselected patients seen at Boston City Hospital is reported by J. I. Maiztegui, J. Z. Biegeleisen, W. B. Cherry and E. H. Kass.[5] Patients with apparently transient bacteremia were excluded. A total of 132 isolates from the blood of the 100 patients were studied (table). Specimens from 6 patients yielded more than one gram-negative bacillus. Bacteriologic study of the isolated organisms showed that 9 different genera and at least 11 different species of gram-negative bacilli were involved. Testing in vitro of 101 isolates for sensitivity to commercial antibiotic disks was carried out (Fig. 2).

(5) New England J. Med. 272:222-229, Feb. 4, 1965

GRAM-NEGATIVE BACILLI ISOLATED FROM BLOOD OF 100 PATIENTS

ORGANISM	NO OF CULTURES	NO OF GROUPS OR TYPES	NO. OF PATIENTS
Salmonella enteritidis	1	–	1
Providence Group B	2	–	2*
Citrobacter	1	–	1
Pseudomonas aeruginosa	10	–	10*
Pseudomonas maltiphilia	3	–	2
Proteus mirabilis	14	–	14*
Proteus rettgeri	1	–	1
Herellea vaginicola	11	4†	9*
Klebsiella pneumoniae	39	16	30*
Aerobacter cloacae	3	–	2*
Escherichia coli	47	–††	35*
Totals	132		107*

*Patients from whom more than 1 kind of organism isolated, including 5 from whom 2 organisms and 1 from whom 3 isolated, thus giving total of 100 patients.

†Capsular types determined by immunofluorescence methods

††14 O-antigen groups and possibly as many as 16 K-antigen groups

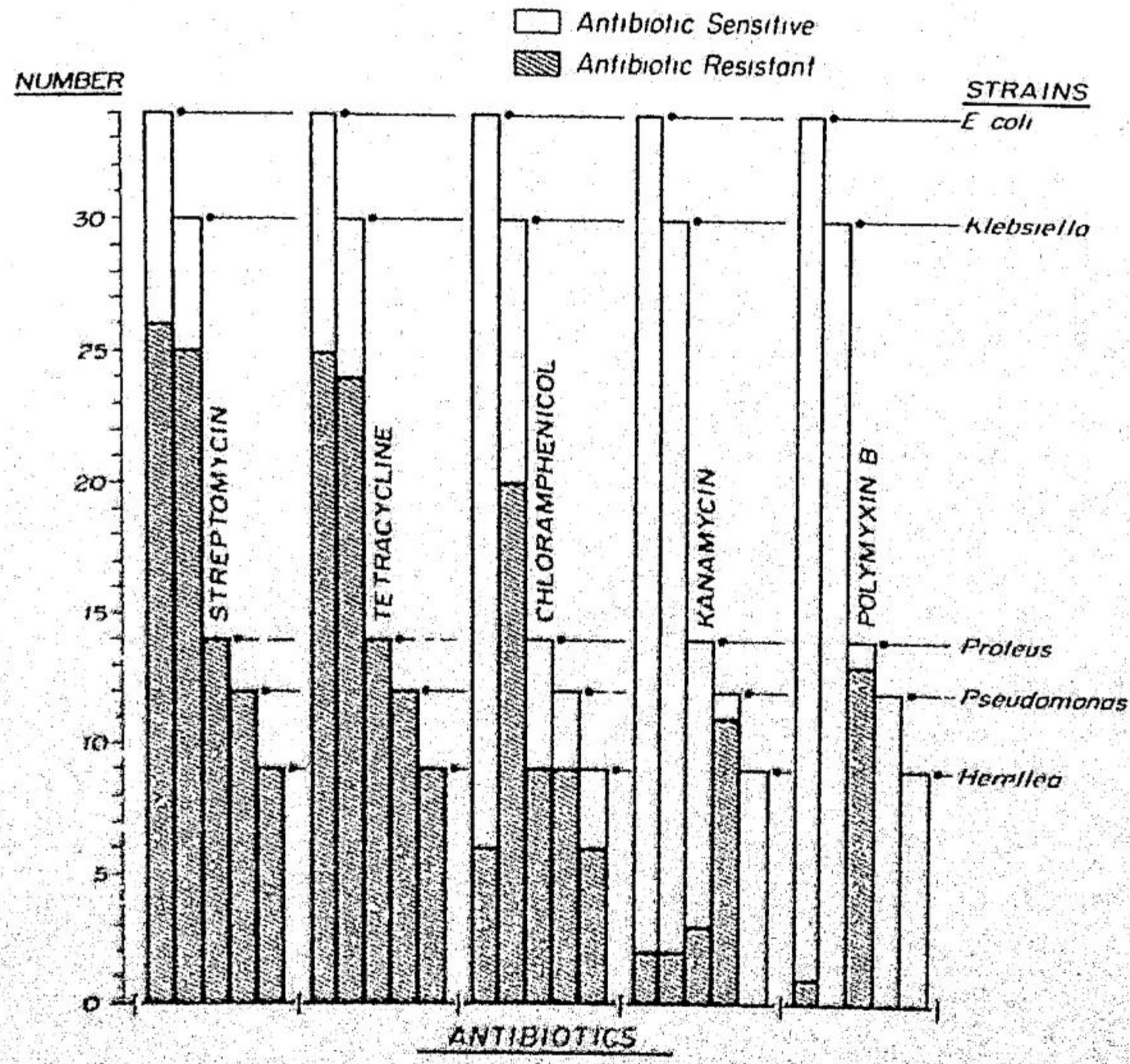

Fig. 2 – Results of testing gram-negative isolates against antibiotics by the disk method. (Courtesy of Maiztegui, J. I., *et al.* New England J. Med. 272 222-229, Feb. 4, 1965.)

The over-all mortality was 55%. Many patients suffered simultaneously from more than one disease or had more than one complication. In general, the presence of hepatic cirrhosis or the development of vasomotor collapse carried a severe prognosis in association with gram-negative bacteremia. The source of bacteremia could be established clinically or bacteriologically in all but 7 patients A urinary tract origin was found in 65 patients. The skin was the portal of entry in 14 patients, including all 9 with herellea and 3 with pseudomonas infections. Of the 45 patients with vasomotor collapse, 35 (78%) died. Thirteen of 16 diabetic patients had urinary tract infection, and in 7, proteus organisms were the responsible agents. Eight patients had underlying cirrhosis.

Most patients received chloramphenicol initially, and most also received other antibiotics. Treatment was usually adjusted according to the results of sensitivity tests, although the patient often died before the proper antibiotic could be given in sufficient amount. Some patients improved despite the fact that the isolated organisms were resistant in vitro to the drug given, but in some of these, other therapeutic measures may have accounted for the improvement. The portal of entry of herellea was usually along polyethylene catheters, and removal of the catheter or drainage often cleared both the local infection and bacteremia in patients who were not responding to antibiotic therapy.

Autopsy data were obtained in 29 of the 55 fatal cases. The same bacteriologic species were found in antemortem and postmortem cultures in 20 of the 29 cases. Specimens were studied for metastatic foci of infection or acute splenitis secondary to the bacteremia. Evidence of such dissemination was found in 83% of the patients coming to autopsy.

The great serologic diversity of the gram-negative bacteria involved in this study suggests that hospital-transmitted infection was not a significant feature of these cases. It is assumed that the patients generally were infected by organisms from their own flora. The frequent association with underlying diseases and the higher incidence in older persons strongly indicate a relation to disturbances in host resistance.

► [This kind of infection, in large measure a consequence of defective host resistance, is becoming proportionately more common as we are better able to

control pneumococcic, streptococcic and staphylococcic infections Nowadays, debilitated patients receive better supportive care in hospitals and survive long enough to become subject to gram negative bacteremia —Ed]

Use of Noradrenaline in Hypotensive States Complicating Bacterial Infection. G. Walters (New Cross Hosp., Wolverhampton, England) and G K McGowan[6] (United Bristol Hosp.) studied 32 patients in whom hypotension was thought to be due primarily to infection and persisted despite transfusion and in whom there was no primary cardiac insufficiency. The blood pressure rose to former levels in 12 of the 16 patients treated without noradrenaline. The others included 3 of 7 patients with peritonitis in whom operation was not performed, and 1 of 6 with urinary tract infection in whom adequate antibiotic therapy was delayed. Those who recovered all showed the syndrome of "warm hypotension," with a good pulse volume, warm limbs and satisfactory renal function despite the hypotension. Of the 16 patients given noradrenaline intravenously, 5 maintained the blood pressure easily at normal levels with doses of 4-12 μg per minute, all had had "warm hypotension " In 2 of these, the blood pressure fell when noradrenaline was stopped, but it recovered spontaneously after 3 and 5 days, respectively. Of the other 11 patients, 4 did not respond to noradrenaline, and 7 needed progressively larger doses to maintain the blood pressure at a given level The dose was 16-60 μg. per minute in 10 patients In all but 2, resistance to noradrenaline was associated with progressive deterioration and "cold hypotension," with a small pulse volume and cold limbs

It is believed that noradrenaline had little if any beneficial effect, the outcome depending rather on the underlying condition and efficacy of antibiotics and other treatment The patients showing a good respouse were those who, after adequate fluid therapy, exhibited warm hypotension, and this type of patient did well when treated without noradrenaline. Patients who continued to show cold hypotension after adequate transfusion usually died whether or not noradrenaline was given. Hydrocortisone given intravenously in doses of 100 mg. did not improve the response to noradrenaline once resistance developed.

There is no indication for the use of noradrenaline unless the circulation continues to fail despite adequate fluid re-

(6) Lancet 2:225-227, Aug 1, 1964.

placement and antibiotic therapy. In hypotensive states associated with bacterial infection, the circulatory state must be assessed by the pulse volume and skin temperature rather than on the basis of blood pressure.

► [I agree that one seldom gets the impression that pressor compounds are lifesaving in shocklike states associated with infection Norepinephrine is considered to have a further disadvantage tendency to cause hepatic damage characterized by centrolobular necrosis We prefer metaraminol because of this —Ed.]

Endotoxin-Like Activity of Serum from Patients with Severe Localized Infections. Philip J. Porter, Alan R Spievack and Edward H. Kass (Harvard Med. School) sought evidence of endotoxemia in diverse clinical disorders using the method of Thomas, which consists of injecting endotoxin or endotoxin-containing materials intravenously into rabbits, with intradermal epinephrine given at the same time. Hemorrhagic necrosis develops in the skin within 8-10 hours

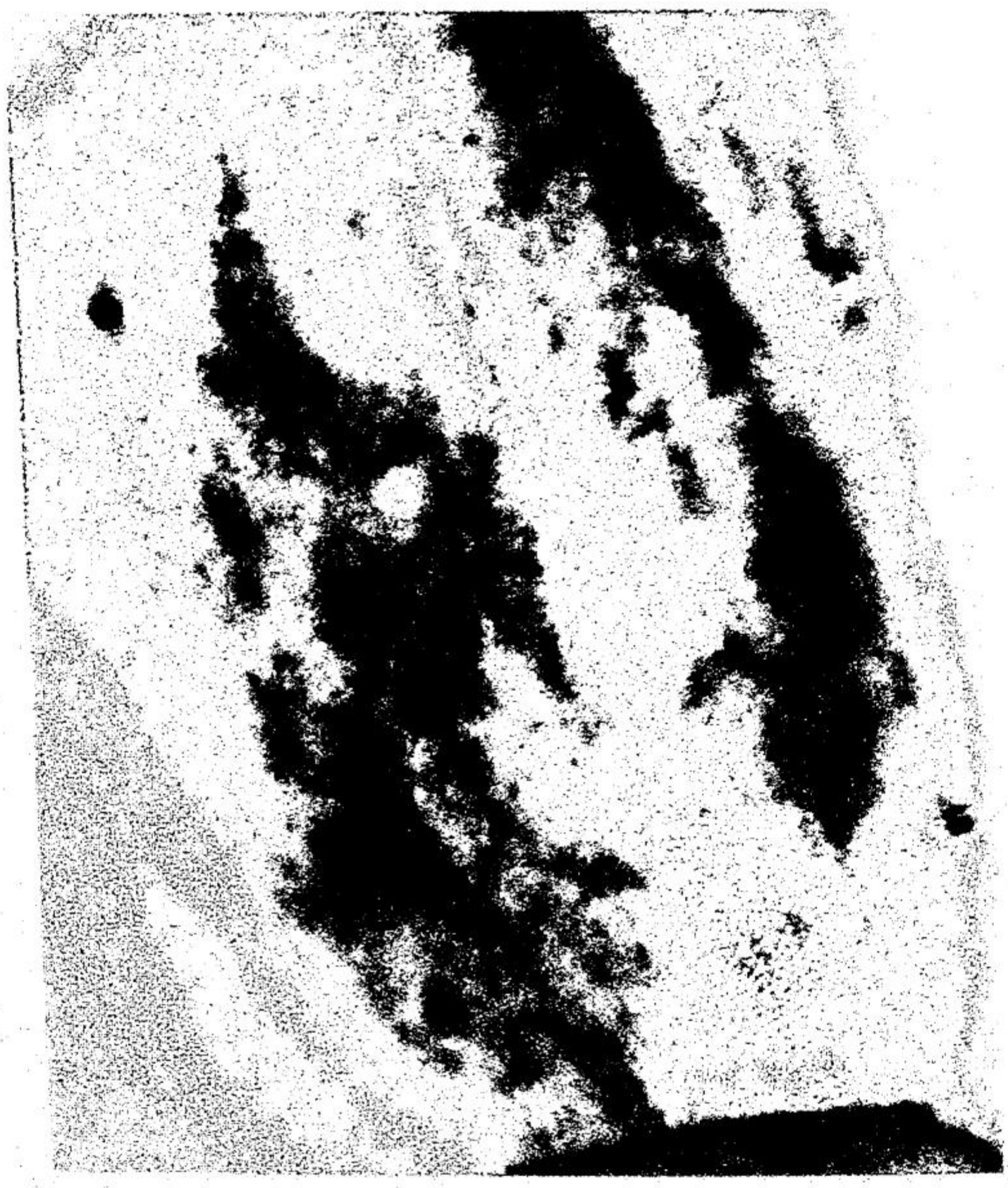

Fig. 3.—Positive test in rabbit given serum from patient with klebsiella aerobacter infection (Courtesy of Porter, P. J., *et al.* New England J. Med. 271:445-447, Aug. 27, 1964.)

(7) New England J. Med. 271:445-447, Aug. 27, 1964

(Fig. 3). Female rabbits were given 100 μg. epinephrine in the abdominal skin and then 2 ml. of a patient's serum intravenously. Endotoxin derived from Escherichia coli 0111 was used as a standard.

Of 38 patients, 29 gave negative skin tests. These were patients with a wide variety of diagnoses; many had bacteremia or vasomotor collapse and some, both. All 9 patients giving positive tests had foci of gram-negative rod infections, but none had positive blood cultures. All but 1 were in vasomotor collapse, the exception having hypothermia associated with peritonitis. All but 1 had marked irregularities of thermoregulation. All died within 24 hours of the time that the test was found to be positive. Blood from 8 healthy subjects gave negative tests. Specimens from 2 patients with positive tests were administered to rabbits in doses of 1 ml. serum daily for 5 days, with no apparent untoward effects. Both animals survived challenge with 4 LD_{50} of purified endotoxin on the 6th day. Animals given serums from 5 patients that did not produce positive skin tests died with typical manifestations of a fatal endotoxic reaction after challenge.

The observations are not conclusive evidence of the presence of endotoxin in the serums of the patients, but they are suggestive.

► [Although it is customary to speak of gram negative bacteremic shock we usually are unable to demonstrate bacteremia in patients considered to have the syndrome as recounted here. A sensitive test for the presence of bacterial endotoxin in the blood would be very useful.—Ed.]

URINARY TRACT INFECTION

Presentation, Diagnosis and Treatment of Urinary Tract Infections in General Practice. N. C. Mond, A. Percival, J. D. Williams and W. Brumfitt[3] (Edgware, England) report a prospective study of all patients with definite symptoms of urinary tract infection seen in a general practice in 18 months. Fifty-three women without such symptoms served as controls. Alternate patients received 2 Gm. sulfadimidine, followed by 1 Gm. 4 times daily for 8 days. The others received sulfdimethoxypyrimidine with sulfadimidine, 2 Gm.,

(3) Lancet 1:514-516, Mar. 6, 1965.

followed by 1 Gm. daily for 7 days. Of 83 patients with symptoms, only 38 (45%) were infected (100,000 or more bacteria per ml. urine). The distribution of symptoms and the history of previous symptoms were almost identical in the infected and noninfected groups. Five infected patients had second episodes of infection by a different organism during study. Infection was about 4 times as common in married as in single women.

All infected patients had an excess of white cells in the urine, and 85% had proteinuria. An excess of white cells was found in 47% of noninfected patients, and 8% had proteinuria. No control subjects had proteinuria, and only 6% had excess white cells in the urine. Of the infecting organisms, 81% were strains of Escherichia coli, 12% Proteus mirabilis and 7% Staphylococcus albus. Agglutination titers at levels indicative of renal-tissue infection were found in 8 of the 9 patients with clinically evident pyelonephritis and 8 of the 31 with symptoms confined to the lower urinary tract. Only 1 strain of E. coli was resistant to sulfadimidine. The rate of success was 90% with sulfadimidine and 75% with the mixture, but the difference was not significant.

Findings suggest that many women presenting with symptoms of urinary tract infection in general practice have urethritis without infection of the urine. If treatment is based on the presence of white cells in the urine, many patients without urinary infection will be treated, but this may prevent subsequent development of cystitis and even pyelonephritis in women with urethritis. Sulfonamides are still the first choice for treatment. After treatment, cure should be confirmed bacteriologically.

► [Studies of this kind give extremely valuable clinical and epidemiologic information that cannot be obtained by clinical investigators working in hospitals. The frequency of negative cultures in women with symptoms of "cystitis" may, as the authors suggest, mean that infections are often secondary, being superimposed on some kind of noninfectious urethritis. Considering cost and ease of administration, the authors are also doubtless correct in recommending sulfonamides as the first choice in cases cropping up in office practice.—Ed.]

Retention Catheterization and Bladder Defense Mechanism. Although controversy over the role of urinary instrumentation in the etiology of urinary tract infections still exists, now there can be little doubt that benefits of diagnostic and therapeutic specialized instrumentation far outweigh risk of postinstrumental urinary tract infections. Clair

E. Cox and Frank Hinman, Jr.[9] believe that inordinate fear of the retention catheter has led to inappropriate deprivation of its use and in some cases to total prohibition of the Foley catheter. A more rational approach consists of consideration of determinants of infection and of appropriate measures to prevent infections.

Determinants include the initial catheterization, care of the catheter and its drainage system and the initial condition of the bladder. In a prospective study, retention catheters were placed in 80 healthy subjects with normal bladders for 18-72 hours, without special care. The incidence of infection was 6 6% at 24 hours and less than 50% after 72 hours of continuous "open" drainage. Cultures showed spontaneous clearing of infection in all those with infection. The overdistended, traumatized, congested or otherwise abnormal bladder provides an excellent opportunity for bacterial invasion. clmical experience indicates that infection after catheterization commonly occurs in patients with such bladders. The systemic health of patients also influences onset of infection with use of inlying catheters.

In vitro multiplication of bacteria in urine is similar to that in nutrient broth; urine is not antibacterial. An experiment using a simulated bladder and Escherichia coli showed that periodic emptying did not completely remove bacteria, but did restrict the rapid accumulation of bacteria that occurs in standing urine. Voiding therefore is a limited defense mechanism. Some urine undoubtedly is present after normal voiding.

In another experiment, a culture of 2,000,000 E coli organisms was placed into the bladders of 4 healthy young males and into containers of previously voided urine. Periodic bacterial counts showed that bacterial growth in a normal bladder is inhibited compared with bacterial growth in vitro in urine from the same bladders. After inoculation of 10,000,000 organisms into the bladder, initial colony counts in voided urine were above the currently accepted level of bacteriuria, but succeeding colony counts made at 3-hour intervals showed rapid decrease in all cases, no subject had E. coli in the urine after 72 hours. It must be concluded that the initial rapid reduction of bacterial count and the total removal of bacteria in 72 hours was due to at least two fac-

(9) J.A.M.A. 191:171-174, Jan. 12, 1965.

tors, voiding and vesical inhibition of bacterial growth. ► [I don't think it's surprising to find that healthy persons subjected to bladder infection via an indwelling catheter can rid themselves of the infection after the catheter has been removed. The trouble is that healthy persons aren't the people likely to be treated with indwelling catheters. The danger is real, and the indwelling catheter should not be used without good reason. Of course, there *are* good indications for its use, and I agree with the authors that inordinate fear of infection should never deprive a patient of catheterization when the procedure is called for. My guess about the "inhibitory effect" of the bladder mucosa on bacterial growth is that it mainly involves removal of bacteria via lymph channels of the bladder wall.—Ed.]

Recurrent Urinary Infections in Girls: The Case for Conservative Management is discussed by Duncan Macaulay[1] (Manchester, England). Up to 75% of girls with persistent or recurrent urinary infection have renal tracts which appear structurally normal. A proportion of patients with urinary infections either fail to respond to treatment or have a relapse after treatment is stopped. It is generally believed that recurrent or persistent infections in males can usually be accounted for by structural anomalies, especially of a kind that obstruct urine flow. In many females, however, no such lesion can be found. In the author's experience, the frequency of recurrence of infection in girls with apparently normal renal tracts was about 10%. For every known case of urinary infection, there could be 10 undiagnosed ones. A vast public health problem, of which physicians are largely unaware, could exist. Some investigators believe that recurrent infections indicate urinary stasis, and others think that they are manifestations of a continuing disease process, chronic pyelonephritis. When looked for, ureteral reflux is found in about 40% of children with urinary infections, but it is not known how often, if ever, reflux can be demonstrated in uninfected persons or whether it is the cause or the result of urinary infection.

It is impossible to speak with any assurance of the role of pyelonephritis as a cause of death at any period of life. Evidence indicates that it may account for 2% of deaths in both children and adults. There are some impressive reasons for believing that acute pyelonephritis may not be the forerunner of what is called chronic pyelonephritis. One such reason is the far greater incidence of acute pyelonephritis in females. The assumption that, in otherwise structurally sound renal tracts, acute infections terminate in chronic pyelonephritis is not supported by pathologic studies.

(1) Lancet 2:1319-1321, Dec. 19, 1964

The author hypothesizes that, in girls with structurally normal renal tracts, recurrent infections tend to subside without serious sequelae. This does not mean that these infections should not be treated, but it implies that treatment should be carried out with the eventual outcome clearly in mind. Major operations on the urinary tract to "improve drainage," such as plastic reconstruction of the bladder neck or of the ureterovesical junction, should be considered only on the clearest indications. That medical treatment is repeatedly followed by reinfection is not a sufficient indication.

► [It is time for someone to speak up for conservative management of recurrent urinary infections, as most of us have been swept away by enthusiasm for searching out a surgically approachable defect and dealing with it.—Ed.]

Increased Susceptibility of Mice Infected with Mouse Adenovirus to Escherichia Coli-Induced Pyelonephritis is reported by David R. Ginder[2] (Univ. of Missouri). In man, it is evident that urinary tract lesions decrease the resistance of kidneys to E. coli infection. Since most persons in whom E. coli pyelonephritis develops do not have clinically evident pre-existing urinary tract abnormalities, the possibility of inapparent renal injury, such as injury by virus infection, arises. Hartley and Rowe found that mouse adenovirus induces prolonged viruria in adult mice and produces disseminated lesions in many organs, including the kidney, in infant mice. In the present study, mouse adenovirus was injected intraperitoneally into mice and the kidneys were harvested. Kidney extracts were used as seed virus for making stock mouse tissue culture virus. At intervals after intraperitoneal injection of adenovirus, E. coli were injected intravenously into mice. A group of male mice received intraurethral injections of E. coli at intervals after intraperitoneal injection of adenovirus.

Virus was found in the kidney in significant amounts after administration of adenovirus. Focal mononuclear cell infiltrates were found in the cortex and medulla at 4 days. At 10-25 days, the infiltrates had become extensive and areas of tubular epithelial cell necrosis were found, as were extensive mononuclear perivascular infiltrates and dilated proximal tubules. Occasional groups of very large dilated tubules were found at 40 days, and isolated wedges of collapsed tubular tissue were noted at 70 days. Infection with adenovirus was shown to predispose the mouse kidney to pyelonephritis when

(2) J. Exper. Med. 120:1117-1136, December, 1964.

PYELONEPHRITIS INDUCED BY INTRAVENOUS INJECTION OF E COLI IN MICE INFECTED WITH MOUSE ADENOVIRUS

INTRAPERITONEAL INJECTION	INTRAVENOUS CHALLENGE	GROSS PYELONEPHRITIC LESIONS
Adenovirus	E coli	39/113*
Virus diluent	E coli	4/100
Adenovirus	Brain heart infusion	0/110
Virus diluent	Brain heart infusion	0/36

* Numerator, number of mice bearing gross pyelonephritic lesions denominator, number of mice harvested

the host was challenged either intravenously or by the retrograde route with E. coli. The results of intravenous injection are shown in the table.

The extensive and persistent nature of the renal lesions raises the possibility that mouse adenovirus may cause chronic renal disease. Early in the course of adenovirus infection, increased susceptibility to E. coli challenge may result from increased renal tissue pressure produced by the extensive cellular infiltrate. Also, intracellular multiplication and the "toxic" action of adenovirus may decrease resistance to infection by interfering with tubular cell metabolism. Herpes simplex and vaccinia produced only minimal infiltrates in the renal cortex, but low titers seemed to decrease resistance to E. coli challenge significantly. The greater incidence (50%) of bacterial pyelonephritis seen in mice challenged with E. coli 12-64 days after adenovirus infection, as compared to that (33%) in mice challenged 3-9 days after, appears to reflect tubular obstruction and consequent increased renal tissue pressure.

► [A nicely conducted piece of investigation. People have wondered whether virus infection may sometimes play a part in human pyelonephritis. This work in animals shows a possible mechanism.—Ed.]

Prevention of Pyelonephritis by Water Diuresis: Evidence for Role of Medullary Hypertonicity in Promoting Renal Infection. The renal medulla is much more susceptible to infection than is the cortex. This has been ascribed in the past to its anatomic location and chemical composition.

Vincent T. Andriole and Franklin H. Epstein[3] studied experimental pyelonephritis in rats. Chronic water diuresis was induced in white female Sprague-Dawley rats by adding 5%

(3) J Clin Invest 44:73-79, January, 1965

glucose to drinking water. Animals were challenged with 0.5 or 1 ml. of Candida albicans or Staphylococcus aureus intravenously; most were killed after 8 days. The animals drank large amounts of the glucose water, and the glucose was apparently metabolized. Water intake and urinary output increased several fold, and urinary osmolality dropped below 200, often below 100 mOsm./kg. The average pH of urine was 7.88, compared with 7.14 for control animals. Weight of the rats did not change significantly.

After challenge with candida, pyelonephritis was observed in 16 of 17 control animals and in only 3 of 17 animals undergoing water diuresis. Gross abscesses were common in the kidneys of control animals but were not present in those of infected rats undergoing water diuresis.

Staphylococcic pyelonephritis was found in 20 of 21 control animals, in 3 of 12 animals with onset of diuresis 1 day before inoculation with staphylococci and in 4 of 12 with onset 1 day after inoculation. When diuresis was begun as late as 3 days after inoculation, infection was present in 6 of 13 rats 5 days later. The number of organisms in the kidneys of control and test animals 2 and 6 hours after inoculation with staphylococci was almost identical. At 1 day there was more than a log difference, which remained until the 8th day, when viable organisms were no longer found in kidneys undergoing diuresis. Staphylococci never appeared in the urine of test rats and did not appear in the urine of control rats until 1 day after inoculation, when renal parenchymal infection was grossly obvious. Colony counts of viable staphylococci in liver and spleen were similar in control and test animals. Extracts of renal medulla from animals undergoing diuresis did not inhibit bacterial growth.

Water diuresis was associated with a fall in concentration of sodium in inner medullary tissue from 215 ±21 to 123±23 mEq./kg. of tissue water; urea concentration also decreased. The content of sodium and urea per 100 Gm. of dry solids in medullary tissue also decreased. Tissue levels of potassium and ammonium were unchanged by water diuresis. Total calculated osmolality of medullary tissue was reduced by diuresis from 1,101 to 476 mOsm./kg. Total solute concentration of the cortex was unaltered by water diuresis. Sodium and potassium levels in the water of cortical tissue fell slightly, while ammonium and urea levels rose.

single booster dose intradermally. This was attempted in primary vaccination of 155 young, healthy women without histories of previous inoculation or specific enteric infection. Fourteen other subjects were inoculated subcutaneously. For subcutaneous injection, doses of 0.25, 0.5 and 0.75 ml were given at intervals of 5-7 days. Intradermally, injections of 0 1, 0.15 and 0.2 ml. were given at the same intervals.

Intradermal injections were felt as a sting lasting less than a minute, sometimes followed by local erythema and itching, which lasted a few days. Slight general reactions were, as a rule, more common after subcutaneous injections. The local reactions consisted of erythema, swelling and muscle stiffness, but marked adenitis was rare. The antibody response to intradermal vaccination was, on the whole, slightly less pronounced but as persistent as that after subcutaneous administration of the same vaccine in slightly higher doses. The O agglutinin contents of serums 1-1½ years after intradermal vaccination were higher than those after subcutaneous injections of the vaccine.

► [Most people would prefer the intradermal to the subcutaneous route of inoculation if as good an immune response could be expected – Ed.]

Treatment of Chronic Typhoid Carriers by Cholecystectomy. Julia L. Freitag[6] (New York State Dept. of Health, Albany) followed 54 chronic typhoid carriers who underwent cholecystectomy during 1945-63. These patients had not had typhoid fever within 1 year but had typhoid bacilli in the feces, urine or other discharges. Release from restrictions was granted after 8 successive specimens each of feces and urine and 3 of duodenal contents, after gallbladder removal, were free from Salmonella typhosa. Average age of the 49 women and 5 men was 57 years.

The minimum cure rate, excluding 2 deaths, was 88.2%. Of the 34 carriers whose postoperative status was determined, 26 had cholecystectomy primarily to cure the carrier state and 24 (92.3%) were cured. In the same period, 14 carriers were released without previous cholecystectomy; at least 9 were considered to represent "spontaneous cures."

Release of typhoid carriers in New York State no longer requires submission of duodenal specimens, primarily because gallbladder carriers consistently excrete typhoid bacilli in their stools. If cured by cholecystectomy, carriers convert

(6) Pub Health Rep 79 567-570, July, 1964

to consistently negative stools; and no carrier would have been released prematurely if examination of duodenal specimens had been omitted.

Role of Endotoxin during Typhoid Fever and Tularemia in Man: II. Altered Cardiovascular Responses to Catecholamines were investigated by Sheldon E. Greisman, Richard B. Hornick, Frank A. Carozza, Jr., and Theodore E. Woodward[7] (Univ. of Maryland). Studies of tularemia and typhoid fever during vaccine trials have led to reproducible clinical forms of the disease in man. Such clinical models have permitted observations of a variety of physiologic parameters in the same subject before, during and after infection. The findings suggest release of physiologically active amounts of circulating endotoxin during human typhoid fever and tularemia.

Control responses of systemic arterial blood pressure to intravenous infusions of l- norepinephrine were obtained in 9 volunteer subjects, who then, several days later, received viable Salmonella typhosa orally. The reactivity of the systemic arterial pressure to norepinephrine was reassayed during overt typhoid illness and subsequent convalescence. Increased responsiveness of both diastolic and systolic pressures was noted consistently during illness and the early phase of convalescence. The hyperreactivity was highly significant in all subjects. The reactivity of the nail-fold capillary bed to norepinephrine paralleled that of the arterial pressure. In all subjects, the rate of infusion capable of obliterating visible capillary blood flow during illness was half or less that required during the control state. Intradermal injection of 0.1 ml of 100 μg. epinephrine and norepinephrine during the control period induced an intense central blanching surrounded by an irregular zone of erythema, both of which subsided after several hours. During typhoid fever, local hemorrhagic reactions appeared in 7 of 9 subjects tested. These became grossly visible within 30 minutes of injection and were maximum for the next 3-4 hours. A typical lesion is shown in Figure 4. Hyperreactivity to the catecholamines was not found in volunteers during the course of tularemia or sandfly fever.

The similarities between the clinical and pathologic manifestations of typhoid fever and the reactions induced by bacterial endotoxin suggest that the latter may be important

(7) J. Clin. Invest. 43:888-898, May, 1964

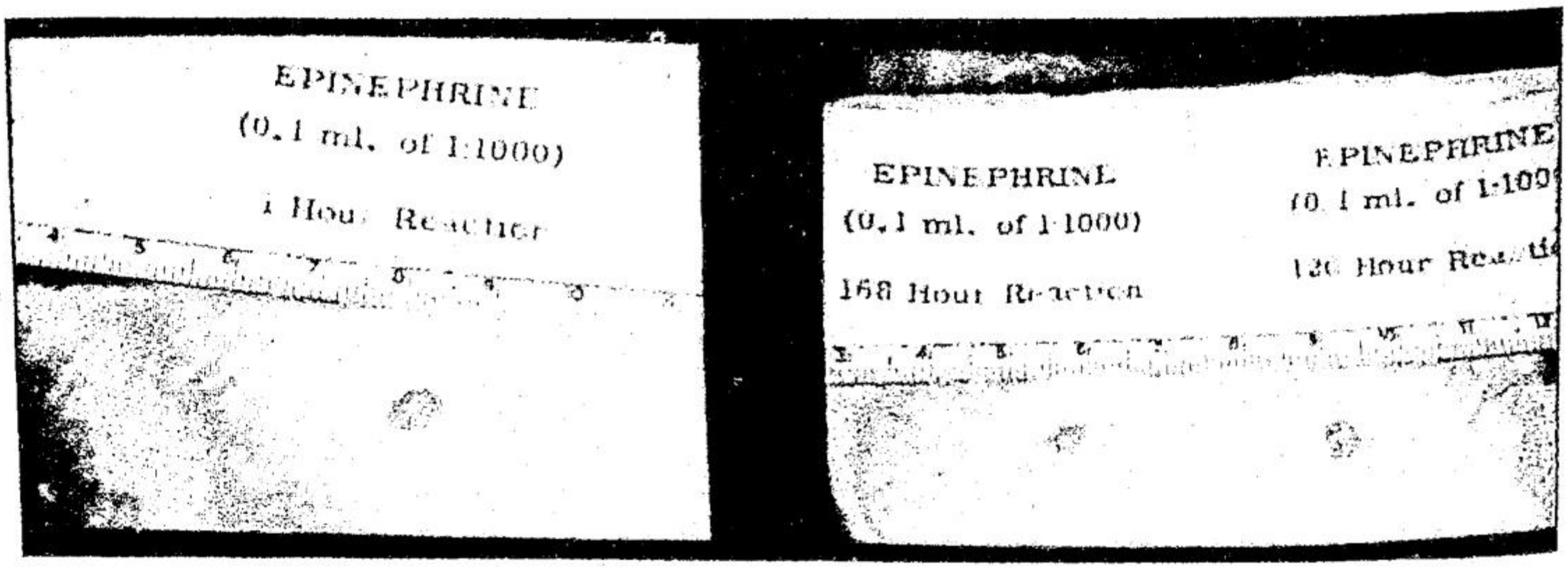

Fig. 4.—Vascular reactivity in typhoid fever. Typical gross appearance of hemorrhagic reactions after intradermal injection of 0.1 ml. of 100 μg. epinephrine during typhoid illness. (Courtesy of Greisman, S. E., *et al.*: J. Clin. Invest. 43: 986-999, May, 1964.)

in pathogenesis of this infectious illness. In support of this hypothesis, a previous study showed that significant tolerance is acquired to the pyrogenic activity of homologous and heterologous bacterial endotoxins after typhoid fever.

Although the present findings suggested that endotoxin might be responsible for the augmented cardiovascular reactivity to catecholamines during typhoid illness, subsequent observations required reconciliation with this interpretation. Administration to normal subjects of single intravenous doses of endotoxin sufficient to evoke febrile and toxic reactions as severe as those seen during the early phase of typhoid failed to induce vascular hyperreactivity to catecholamines. Intradermal injection of mixtures of endotoxin with epinephrine in normal subjects did not elicit local hemorrhagic lesions. The cardiovascular hyperreactivity persisted 1 or more weeks into the afebrile convalescent phase of typhoid fever. Hyperreactivity failed to appear during tularemia, a disease clinically similar to typhoid, induced by gram-negative bacteria containing endotoxin and resulting in endotoxin tolerance. The findings remain compatible with the hypothesis that endotoxin initiates the vascular hyperreactivity to catecholamines observed during typhoid fever in man, but this relationship is unproved, and other mechanisms may be operative.

Pneumococcic Bacteremia with Especial Reference to Bacteremic Pneumococcic Pneumonia. Robert Austrian and Jerome Gold[5] reviewed about 2,000 cases of pneumococcic pneumonia and 529 of pneumococcic bacteremia recognized since 1952, when technics for isolation and identification of pneumococci were introduced as routine procedures in their laboratory. All patients were over age 12 years. The first eight capsular types accounted for two thirds of the cases of bacteremia; types XII, XIV, XVIII, XIX and XX were also recovered with relative frequency from the blood. Only 3% of positive blood cultures were accounted for by numerical types higher than XXXIII. Mortality was least when bacteremia was associated only with pneumonia and was 2 or 3 times as great when an extrapulmonary focus of pneumococcic infection was present. The mortality rate for type I pneumococcic bacteremia was 8%, compared with 55% for type III infection. Mortality from infection with other capsular types ranged from 15 to 25%. Prognosis for type III infections has been improved significantly less than that for infections caused by other capsular types.

Mortality rates by age and sex are shown in the table. The mortality after involvement of two lobes was twice that when only a single lobe was affected. A third of the patients had pneumonia involving more than one lobe. A total leukocyte count of 10,000-25,000/cu. mm. appeared most favorable. The presence or absence of alcoholism seemed to be of little prognostic import. Significant systemic disease was present in 56% of patients with pneumococcic pneumonia and bacteremia. Mortality was 4 times greater in those with complicating illness than in those without. Of the fatal illnesses, 43% resulted from infection with one of the pneumococcic types I, III, IV, VII, VIII or XII in persons aged 50 or over with complicating illness. Penicillin and tetracyclines appeared to be equally effective in treatment. The mortality rate for all patients, irrespective of therapy, was 19.5%. Of all deaths, 43% occurred within 24 hours of admission. The data suggest that antimicrobial therapy has little or no effect

(5) Ann. Int. Med. 60:759-776, May, 1964

MORTALITY ACCORDING TO AGE AND SEX IN PNEUMOCOCCIC BACTEREMIA (ALL CASES)

Age	All Cases	Fatal Cases	
yr	*no.*	*no.*	*%*
12–19	11	0	0
20–29	40	4	10
30–39	95	5	5
40–49	110	19	17
50–59	99	18	18
60–69	80	34	43
70–79	58	28	48
80–89	30	18	60
90+	6	5	83
Total	529	131	24.8
Males	384	90	23.4
Females	145	41	28.3

on the outcome among those destined at onset of illness to die within 5 days.

It is questionable that a more effective antipneumococcic drug than penicillin can be developed. Death from pneumococcic infection appears to result from failure of the host's defensive mechanisms before start of antimicrobial treatment. That the preponderance of serious infections is engendered by a limited number of pneumococcus types makes immunization potentially feasible. Production of a vaccine containing capsular polysaccharides of types I, III, IV, VII, VIII and XII is advocated. If given to persons with systemic illness, those aged 50 years or over, or both, it should significantly reduce the mortality from pneumococcic diseases among those most likely to die of such infection. It is essential to the success of such a program that continuous surveillance of the prevalence of pneumococcus types be carried out over a wide geographic area.

► [This excellent clinical study is an eye-opener and a source of useful, reliable information. Pneumococcic pneumonia is still with us, still an important cause of death. Because pneumococcus typing is no longer done in most hospitals, this kind of information on results of chemotherapy is scarce. Note the remarkable difference in fatality rate of types I and III infection. Austrian's suggestion of vaccinating elderly or debilitated patients against the commonly occurring pneumococcic types deserves careful consideration. —Ed.]

Clinical Entity of Cryptogenic Mycotic Aneurysm: Report of Six Cases. Lester Blum and Edward B C. Keefer[9] (New York) observe that the cryptogenic type of mycotic aneurysm occurs in older persons in the absence of endocarditis and is becoming more common. The chief organisms involved are staphylococcus and salmonella, which are notoriously resistant to antibiotics. The organisms may arrive as minute septic emboli at a site of degenerative arteriosclerotic change in the vasa vasorum or, more likely, by surface implantation. The consequent suppurative arteritis results in extensive necrosis of the vessel wall, and arterial pressure causes rupture, with formation of a false aneurysm. Secondary infection and necrosis about the ruptured artery follow. Gangrene of a limb results or rupture into a free space with death by exsangui-

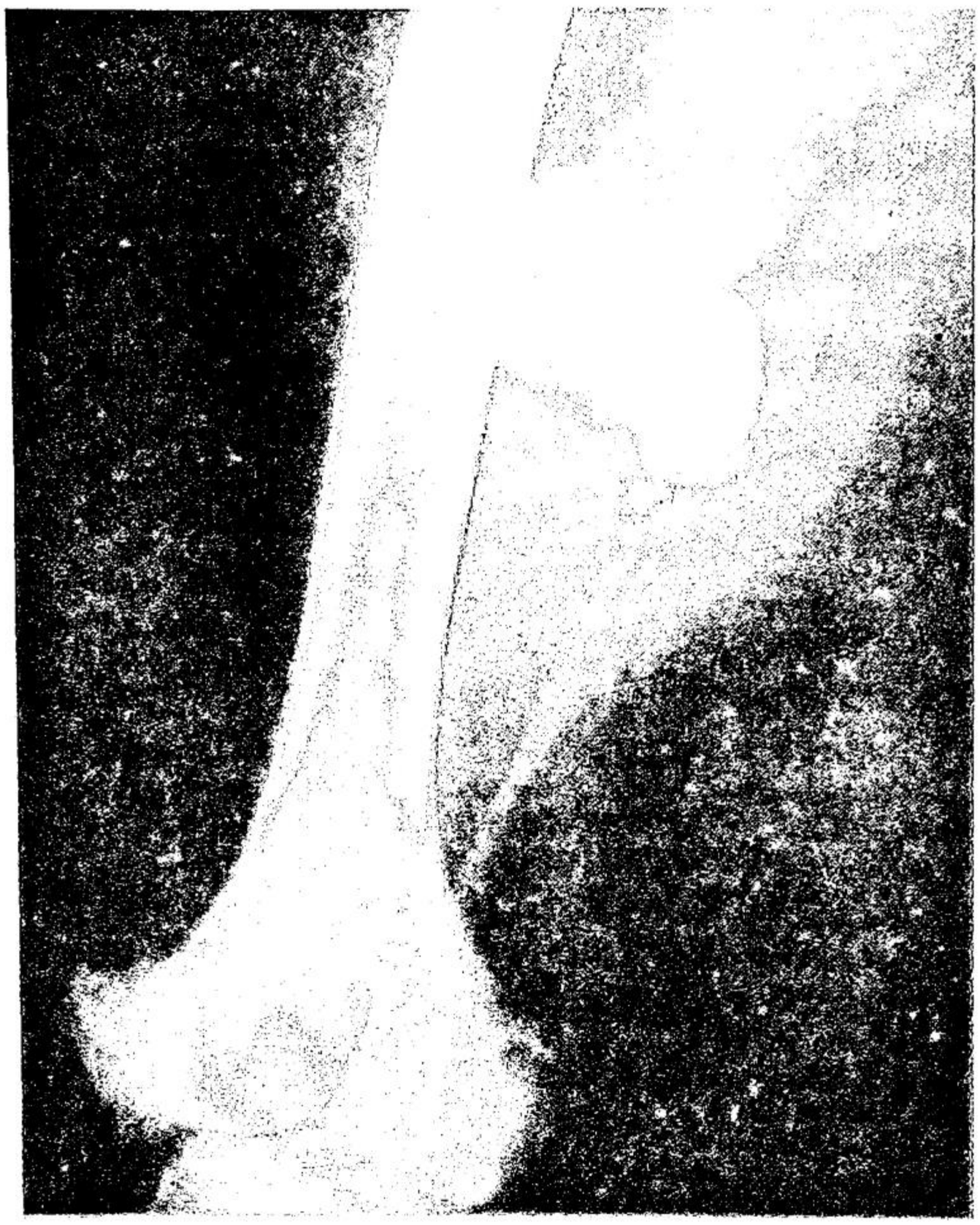

Fig. 5. – Preoperative arteriogram. Note ruptured artery with loculated false aneurysm. (Courtesy of Blum, L., and Keefer E. B. C., J.A.M.A. 195:505-509, May 11, 1964.)

(9) J.A.M.A. 195:505-509, May 11, 1964.

nation No specific physical signs occur before rupture The preceding soft-tissue swelling is invariably diagnosed as thrombophlebitis When the extremity first begins to show some edema, arteriography is of great help.

Treatment invariably follows arterial rupture. Infection remains a threat during the entire convalescence. The arterial trunk is isolated proximal to the operative field and the contaminated perivascular tissues are cleared of blood clot and debris An autogenous vein graft probably offers more security than an arterial homograft or plastic prosthesis. Although 217 cases of mycotic aneurysm were reported by 1923, Barker could present data on only 11 successfully treated patients by 1954. Of 22 successes reported by Sullivan and Mangiardi, only 2 involved grafts in continuity.

Man, 64, reported fever and difficulty in walking because of a painful right knee Examination showed a tender, warm, reddened swelling above the right knee Only the femoral pulse was felt in the extremity One week after admission an expansile pulsation became recognizable in the right thigh with a loud bruit over it An arteriogram confirmed the diagnosis (Fig 5) A saphenous vein graft was inserted after excision of the involved portion of femoral artery Culture yielded staphylococcus and Proteus vulgaris Persisting infection and deterioration of the foot made thigh amputation necessary after operation Convalescence was uneventful

►[Considering the tendency of bacterial colonization to develop on roughened endocardium, the remarkable thing is that more infections such as those described here don't develop on atheromatous disease of the aorta —Ed.]

Gonococcic Perihepatitis: Report of Three Cases with Comments on Diagnosis and Treatment is presented by F. Norman Vickers and Philip J. Maloney[1] (Louisville, Ky.). Although the syndrome of gonococcic perihepatitis has been known for three decades, most physicians are unacquainted with this entity. In the authors' cases, the diagnosis was originally obscure.

Woman, 21, was admitted to the hospital with dull aching pain in the right upper quadrant of the abdomen and vomiting of 1 week's duration. Acute pelvic inflammatory disease had been diagnosed 3 weeks earlier, and treatment with penicillin and streptomycin had been given for 4 days Examination showed only tenderness over the liver area on percussion and some guarding and minimal rebound tenderness in the right upper quadrant and epigastrium Routine cultures of vaginal secretions, and also fluorescent antibody methods, showed Neisseria gonorrheae Uneventful recovery followed penicillin therapy

The clinical picture of gonococcic peritonitis of the upper

(1) Arch Int Med 114 120 123, July, 1964

part of the abdomen was first described in 1919 by Stajano of Montevideo, Uruguay. Curtis in 1930 reported the violin string adhesions between the liver and anterior abdominal wall and the association with pelvic inflammatory disease due to N. gonorrheae. Fitz-Hugh reported 3 cases in 1934 and subsequently popularized the term "gonococcic perihepatitis." The most common eponym is the Fitz-Hugh-Curtis syndrome Gonococcic perihepatitis occurs in women, most often at ages 20-35 years. There is usually a history of previous pelvic pain, vaginal discharge or gonorrheal infection. On oral cholecystography, the gallbladder may not be visualized during the acute stage, but a normal cholecystogram may be obtained after the inflammatory process subsides. A friction rub over the liver area is of great diagnostic value, but this has been found in only a few cases. Direct spread over the peritoneum from the pelvic organs seems the most likely possibility.

The United States Public Health Service recommends a minimum of 1,800,000 units of penicillin for females with uncomplicated gonorrhea For those known to be allergic to penicillin, any of a number of broad-spectrum antibiotics may be used For complications of gonorrhea, intensive penicillin therapy for several days after subsidence of symptoms is indicated

► The pathogenesis of this infection is worth speculation These patients don t show evidence of general peritonitis or of parenchymal liver disease One wonders, then, whether the surface of the liver provides some specially favorable growth medium on which a few gonococci lodge and proliferate So far as I know they have never been demonstrated by culture on the surface of the liver; therefore, the possibility must be considered that this is a manifestation of infection by some other parasite which happens to accompany gonococcic salpingitis.--Ed.]

Abscess of Myocardium Complicating Infarction: Report of Two Cases in which purulent pericarditis was also present is made by Allan Katz[2] (St. Michael's Hosp., Toronto)

CASE 1.--Man, 63, was admitted with crushing retrosternal pain and a history of precordial pain on effort for 2 months. An E.C.G. showed recent anterior myocardial infarction. On bed rest and anticoagulant therapy, the temperature was 100-101 F in the 1st week and rose to 105 F. 3 weeks after admission A blood culture showed no growth. A low-grade fever with temperature up to 101 F. continued, and the patient suddenly became hypotensive and died during his 7th hospital week.

At autopsy, the pericardial cavity contained 20 ml greenish yellow fluid, and a loculated collection of pus measuring about 40 ml

(2) Canad. M. A. J. 91:1225, 1227, Dec. 5, 1964.

was found in the region of the apex Recent and old infarcts were noted in the anterior wall of the left ventricle and adjacent septum at the apex The myocardium in this region was the site of an abscess, adjacent to the loculated pus collection Thrombi were seen in the left anterior descending and right coronary arteries and left circumflex artery Microscopically, the abscess showed massive necrosis and acute inflammatory cell infiltration Bilateral pleural effusions, pulmonary congestion and edema and congestion of liver and spleen were present. Smears showed a moderate number of gram-negative bacilli in the abscess, which proved to be Escherichia coli No source of infection was found

CASE 2 —Man, 66, was hypertensive 3 months before admission and was treated; 1 month later he had retrosternal chest pain and dyspnea and still later he noted ankle swelling A tooth was extracted 1 week before admission On admission, he was cyanotic and blood pressure was not obtainable. The white blood cell count was 26,700/cu mm An ECG showed S-T elevation and negative T waves in leads V_1 to V_5 with right bundle-branch block A blood culture showed no growth Digitalis, intravenous antibiotics, steroids and vasopressors were given, but he died the day after admission

At autopsy, the pericardium was thickened and covered with a fibrinopurulent exudate, about 100 ml purulent material was found in the pericardial space A smear showed gram-positive cocci, and a culture grew coagulase-positive Staphylococcus aureus. A recent hemorrhagic infarct was found in the apex and posteroseptal regions of the left ventricle, with myocardial necrosis and abscess formation The right coronary artery revealed a recent thrombus Microscopy showed recent and old infarcts at the apex and posteroseptal regions of the left ventricle Other findings were bilateral pleural effusions, edema and congestion of the lungs, pulmonary emboli in medium-sized arteries in the right lung and severe chronic passive congestion of the liver Apart from carious teeth, no focus of infection was found

In all 4 previously reported cases of myocardial infarction with superimposed abscess formation, infection was believed to have resulted from a septicemia, the organisms entering the infarcted area via collateral vessels. A recognizable source of infection was present in each case, and similar organisms were recovered from distant septic foci and the myocardium. In view of the marked tissue necrosis that occurs in myocardial infarcts, it is surprising that abscesses are not a more frequent complication.

► [Surprising it is, one would guess that an area of myocardial infarction would be a very favorable site for metastatic infection —Ed]

Clinical and Laboratory Observations on Type E Botulism in Man. M Glenn Koenig, Anderson Spickard, Matteo A. Cardella and David E. Rogers[3] performed studies during an

(3) Medicine 43 517-545, September, 1964

outbreak of type E botulism in which 8 cases occurred among 18 persons ingesting fish from one contaminated shipment of commercially prepared smoked whitefish. Seven of the 8 cases were initially misdiagnosed.

Symptoms in the 8 cases were early onset of severe nausea and vomiting followed by generalized weakness, blurred vision, dizziness, dysphonia, dysphagia, respiratory difficulty and urinary retention. Signs observed included dilated, non-reactive pupils; severe dryness of mouth and tongue; respiratory muscle paresis; varying degrees of abdominal distention; weakness of specific muscle groups in the face, neck and extremities; pharyngeal edema and erythema; and hypotension. Fever was not present in uncomplicated cases, and patients were mentally alert even when severely ill.

Type E botulinus toxin could be demonstrated by simple mouse inoculation studies in serums from 5 of 6 patients with clinical disease at 1 5-10.5 days after ingestion of the fish and in 1 of 7 persons without clinical illness at 7 days. When crude toxin was added to normal serum, brief exposure to trypsin at acid pH increased mouse toxicity 10- to 1,000-fold, whereas type E toxin-containing serums from patients with disease showed loss of toxicity

Failure to develop disease was not related to protective antitoxic immunity Neither overt clinical botulism nor ingestion of foods containing botulinus toxin evoked detectable antibody response Only individuals given preformed horse botulinus antitoxin therapeutically or prophylactically showed circulating antibodies to toxin on testing during a 67-day follow up Such antitoxin remained detectable in serum up to 41 days after administration Early use of tracheostomy and mechanical assistance to respiration were important in management of patients with severe disease. Since Clostridium botulinum organisms were not present in stool specimens, antimicrobials were reserved for treatment of secondary infections. Cleansing of the colon to remove residual toxin may be a useful adjunct to other treatment

There is impressive evidence that type E antitoxin is beneficial in treatment of disease caused by type E strains. None of the patients given type E antitoxin died, and rapid improvement was noted after its administration to 2 severely ill patients. It seems advisable to administer types A, B and E antitoxin immediately to all patients with clinical botulism

and to all persons known to have eaten contaminated food during an outbreak. It is recommended that a polyvalent antiserum including type E antitoxin be made available for treatment and prevention of botulism in the United States.

Acute Constrictive Pericarditis. Ross Robertson and Craig R. Arnold[4] (Vancouver, B.C.) encountered 5 cases of constrictive pericarditis in 1961 and 7 others in the next 2 years. A tuberculous etiology could not be proved in any of these cases, and the tuberculin test was negative in 10. During this period, there was an epidemic of acute nonspecific pericarditis, with 125 cases, in 5 of which positive cultures of Coxsackie B5 were obtained from the feces, but constriction did not occur. Twenty-one other patients with aseptic meningitis and pleurisy also had positive stool cultures for Coxsackie B5.

The history of onset of pericarditis in the present cases was much the same as in tuberculous constrictive pericarditis, but the patients did not respond to antituberculous therapy. There were remissions with frequent recurrences, and constriction progressed with greater rapidity. The pericardium excised at operation consisted of proliferating, vascular connective tissue with no caseation or calcification; it averaged less than half the usual thickness of constricting tuberculous pericardium. Four patients had bloody effusion at operation, but cultures were negative for tuberculosis. Constriction developed in less than 2 years in all the cases and in less than 1 year in 8. A significant rise in Coxsackie B5 titer was found in 4 of 8 cases in which neutralization tests were performed. These patients had had no illnesses suggesting a virus infection since operation.

Man, 48, reported dyspnea on walking a short distance on the level and tightness in the head and neck and pain across the shoulders and upper part of the chest on exertion. About 2 years previously, he had had an attack of fever with malaise, with a gurgling sound in the left part of the chest; his son had a similar illness diagnosed as acute nonspecific pericarditis. About 3 months later, fever with dyspnea and fatigue recurred, and a pericardial friction rub was noted. A large left pleural effusion was found 2 months later. Tuberculin skin tests were negative up to 1:100.

The liver was palpable 4 fingerbreadths below the costal margin. The eyelids were puffy, and the neck veins were distended up to the mandibular angle with the patient erect. The jugular pulse was marked. The percussion note was dull, and breath sounds were distant throughout the left part of the chest. X-rays showed retrac-

(4) J. Thoracic & Cardiovas. Surg. 49:91-102, January, 1965

tion of the heart and mediastinum to the left with pleural thickening over the apex and obliteration of the left cardio- and costophrenic angles On fluoroscopy and kymography, cardiac pulsations appeared markedly decreased The ECG showed nonspecific T-wave changes.

At operation, the left lung was found to be encased in fused pleura 5 mm. thick It was decorticated readily. The pericardial layers were fused and about 4 mm thick. Both ventricles were freed completely, including the A V grooves The pericardium was adherent to the left ventricle in areas Cardiac movements were greatly improved after pericardiectomy A year later, the patient reported that he had begun to feel well about 4 months after discharge He was working hard as a farmer, without dyspnea Serum neutralization tests for Coxsackie B5 gave a titer of 1 177 about 19 months after operation.

Operation for acute constrictive pericarditis is advisable as soon as the diagnosis is reasonably certain; many months of invalidism will be avoided. In 2 cases, the visceral pericardium appeared normal and could not be excised safely, but there has been no evidence of subsequent constriction. There were no postoperative deaths, but 1 late death occurred in a woman aged 56 years who was much improved after operation but died suddenly from a myocardial infarct. The other 11 patients are well and working.

► [We tend to ascribe constrictive pericarditis to tuberculosis, whether that etiology is proved or not The epidemiologic circumstances here suggest strongly that viral infection can produce the clinical entity of acute constrictive pericarditis - Ed]

Case of Rabies in England is reported by S. Ghosh[5] (Gen'l Hosp., Dewsbury, England)

Man, 22, a Pakistani, had generalized aches and pains about 2 months after coming to England On admission, he complained of pain all over the body, especially in the right leg and lumbosacral region. Some blood had been passed in the urine 4 days previously The patient was restless, sweating profusely and extremely apprehensive. The temperature was 96 F There was no evidence of meningeal irritation A healed linear scar was noted on the right ankle Renal colic was diagnosed provisionally and an analgesic given, but he continued to be restless and took drinks several times during the night. He passed 285 ml turbid urine and had several rigors Pyrexia to 100 F. developed the next morning The urine contained a trace of albumin. The white blood cell count was 12,000/cu mm. He became violent and manic. The cerebrospinal fluid was clear and under normal pressure. Tachycardia and hypotension developed and opisthotonos was noted. The father reported that his son had been bitten by a dog on the right leg 3 months previously. The patient died of cardiorespiratory failure the day after admission.

Autopsy showed a congested brain and meninges; petechial spots

(5) Brit M J 2:167-168, July 18, 1964.

were present on the meninges The cerebral vessels were dilated Intracerebral inoculation in mice produced paralysis, and impression smears of the cut brain surface 8 days after inoculation showed Negri bodies

England has been kept free from rabies by strict quarantine of domestic animals brought into the country. The diagnosis in the present case was difficult owing to lack of history of dog bite as well as the unusual presentation suggesting ureteral colic. The incubation period was 3 months; in man, it is usually at least 2 months after a bite on the leg.

Anthrax: Continuous Problem in Southwest Iran. Elfriede Kohout, Abolghassem Sehat and Mansur Ashraf[6] (Pahlavi Univ.) state that despite a vaccination program promoted by the government, the incidence of anthrax is still high in both man and animals in Iran. Among domestic animals, cattle, sheep, goats, horses and swine are the most frequent source of human infections. Human infections occur more often among those handling infected material, including shepherds, wool merchants and their workers, tanners and butchers. The most frequent type, cutaneous, is acquired by direct contact of the skin with infected material, usually after injury to the skin surface. A red macule surrounded by edema for 1 or 2 days is followed by a central blister, which necroses and lasts up to 3 weeks; healing, usually with a scar, then ensues. Edema may spread over large areas of the body. More than one primary pustule is often seen. Pulmonary infection produces severe pulmonary edema and hemorrhagic pneumonia, usually terminating in death. Malaise, myalgia and cough are followed by high fever, respiratory acceleration and stridor, diaphoresis, pulmonary edema and septicemia; often there is pleural effusion and sometimes specific meningitis. In gastrointestinal anthrax there is a bowel pustule with necrosis and surrounding hemorrhage and massive edema sometimes occluding the bowel lumen; the terminal ileum is most frequently affected.

Analysis of 25 cases of anthrax seen in 18 months showed that anyone in close contact with infected material may acquire the disease at any age. Treatment was with penicillin and, in some, Meticorten, to reduce edema and support the patient's reactivity. Immediate intravenous therapy with penicillin is recommended in patients with septicemia or rapidly spreading, life-endangering edema. Otherwise, a dose

(6) Am J M Sc 247 565 575, May, 1964

of 400,000 units intramuscularly twice daily seems sufficient. The mortality of 16% was due to 2 cases of malignant edema and 2 of generalized anthrax, 1 pulmonary and 1 gastrointestinal. It is believed that mortality in areas not yet reached by health services must be unchanged since Pasteur's time As long as anthrax-infested areas exist, sporadic infections must be expected elsewhere in the world.

Fatal Myocarditis in Adolescent Caused by Coxsackie Virus, Group B, Type Four. Fatal myocarditis caused by Coxsackie viruses has not been reported in children beyond age 2 years or in adults. Shyamal K Sanyal, Mehdy Mahdavy, Mary O Gabrielson, Romeo A. Vidone and Marie J. Browne[7] (New Haven, Conn.) report a case in which isolation of Coxsackie B virus from the pericardial fluid strongly suggested the etiologic role of this pathogen

Girl, 13, was hospitalized with a diagnosis of pneumonia She had had a mild cough lasting 2 days Two weeks later, she was quiet and anorectic and had abdominal pain One week later, there were severe cough with occasional hemoptysis, stabbing chest pain worsened by deep inspiration, nausea, vomiting and, later, severe diarrhea The temperature was not elevated at this time, but fever and signs of congestive heart failure subsequently developed

The patient was unresponsive and in marked respiratory difficulty The pulse rate was 120 per minute and the blood pressure 90/70 mm Hg Poor quality heart sounds and a protodiastolic gallop rhythm were noted There were decreased breath sounds with diffuse rales over both lung bases posteriorly, hepatomegaly and pitting edema of both feet and pretibial areas

She was placed in oxygen and digitalized with digoxin, with improvement in the first 24 hours The heart sounds then became poorer in quality with occasional ectopic ventricular beats The protodiastolic gallop reappeared, and the peripheral pulses became weak The temperature rose to 103 F Antibiotics, a diuretic and prednisone were given, but sudden cardiac arrest occurred 64 hours after admission and did not respond to vigorous attempts at resuscitation. Pericardial paracentesis produced about 30 ml of straw-colored fluid

The white blood cell count was 15,000 with 76% polymorphonuclears An ECG on admission showed inversion of T waves, peaked P wave and nonspecific ST-segment changes. Chest x rays revealed gross cardiomegaly and evidence of increased pulmonary congestion and pleural effusion.

At autopsy, mural thrombi were seen in the ventricular apexes, extending into the thebesian veins. The myocardium showed necrobiosis, intercellular edema and infiltrates of lymphocytes and mononuclear cells predominantly in the subendocardial region of the apex beneath the mural thrombi. The pancreas showed recent necrosis and

(7) Pediatrics 35 35-41, January, 1965.

focal interstitial infiltration of lymphocytes, mononuclear cells and occasional polymorphonuclears The other organs showed marked congestion In none of the tissues examined were organisms or inclusion bodies seen

No cytopathogenic effects were seen when pericardial fluid and several autopsy specimens were inoculated into Rhesus monkey kidney and Hep_2 cell cultures On inoculation of monkey kidney cells, using the agar overlay plaque technic in bottle cultures, 6 hazy plaques appeared after 6 days A neutralization test identified the agent as Coxsackie B virus, type 4

In this case, pneumonia and myocarditis appear to represent different stages of generalized infection by Coxsackie virus. An elevated white blood cell count with predominant polymorphonuclears is now known to be a frequent concomitant of viral infections. The possible role of mural thrombi in production of diffuse endocardial fibroelastosis has been postulated. Perhaps a healed, previously undiagnosed myocarditis of viral origin should be considered as an etiologic factor in cases of so-called idiopathic endocardial fibroelastosis in children and young adults, especially when no associated heart disease exists. In some of these cases, the fibrosis may be organized mural thrombi resulting from a previous viral inflammatory process in the heart.

Etiology of Primary Atypical Pneumonia in a Military Population was investigated by Ben R. Forsyth, Henry H. Bloom, Karl M Johnson and Robert M. Chanock.[8] Adenoviruses have been implicated as an important cause of primary atypical pneumonia in military populations. Recently, Mycoplasma pneumoniae (Eaton agent) was shown to be associated with a major portion of primary atypical pneumonia at a Marine Corps recruit training camp. The role of these agents was studied in the course of an intensive investigation of pneumonia patients seen at the Infantry Training Regiment, Camp Lejeune, N. C , during 3 months of 1962. Also, a 30-month survey was made of results of studies of military patients with primary atypical pneumonia admitted to the United States Naval Hospital at Camp Lejeune during 1959-63

The study population consisted of male marines aged 17-21 years who were undergoing advanced recruit training. Data were compared with those of patients without respiratory disease seen at sick call and patients with afebrile and fe-

(8) J A M.A. 191 364-368, Feb 1, 1965

brile respiratory disease but no x-ray or physical evidence of pneumonia

Adenovirus was recovered significantly more often from patients with pneumonia and febrile respiratory illness than from control subjects; all isolations were type 4. Only 1 individual with adenovirus did not have a fourfold or greater complement-fixing antibody rise. No association between adenovirus and respiratory illness was found using antibody rise as evidence for infection. Over half the patients without respiratory disease had a fourfold or greater antibody rise. M. pneumoniae was recovered from 3 pneumonia patients only, these and 4 other pneumonia patients developed a fourfold or greater complement-fixing antibody rise to M. pneumoniae, whereas none of the other subjects developed such antibody. Influenza and parainfluenza viruses were not associated with any of the respiratory illnesses. While 84% of the M. pneumoniae-negative pneumonias were associated with adenovirus infection, M. pneumoniae was etiologically associated with 33% of the adenovirus-negative pneumonias; 70% of the pneumonia patients seen had evidence of either M. pneumoniae or adenovirus infections.

In the 30 month study, both organisms were independently associated with pneumonia; 44% of patients with primary atypical pneumonia had evidence of infection with one of the organisms, but none had evidence of double infection. Adenovirus infection occurred primarily during the winter months, while M. pneumoniae did not exhibit seasonal predilection.

Existing knowledge and technology make it possible to prevent pneumonia due to these agents by effective immunization. However, other as yet unrecognized agents still account for much of primary atypical pneumonia. Also, more than one agent may be an important cause of pneumonia during the same period.

Nature of Herpes Zoster: Long-Term Study and New Hypothesis. R. Edgar Hope-Simpson[9] (Cirencester, England) reviewed all cases of zoster occurring in a general practice within 16 years. Two major characteristics dominating the present knowledge of zoster are its association with the sensory ganglions and its relation to varicella. Weller and

(9) Proc. Roy. Soc. Med. 58:9-20, January, 1965.

lished as a latent infection. It is in an incomplete provirus state at this point, insulated from neutralizing antibody in the circulation. Because neurons do not replicate, neither does the latent virus. Occasionally, one latent virus component reverts and is immediately neutralized. If, however, antibody has fallen below a critical level needed to blanket the explosion, virus will be able to muliply at the next reactivation, perhaps at the expense of the nuclei of the satellite cells in the ganglion. The infectious virus then is transported antidromically down the sensory nerve, causing a fierce neuritis and neuralgia, and is released into the skin. The most important precipitants of zoster, i.e., leukemia and x-rays, both depress antibody production.

► [This excellent epidemiologic study is an example of the opportunity for worthwhile research which can be found in general practice.—Ed.]

MONILIAL INFECTION

Candida Endocarditis. J. Soler-Bechara, John L. Soscia, Richard J. Kennedy and William J. Grace[1] (St. Vincent's Hosp., New York) report on a patient in whom C. albicans endocarditis developed unassociated with cardiac surgery.

Woman, 63, was treated for pyelonephritis with chloramphenicol, and later with tetracycline and novobiocin for 2 weeks. Thrush, diarrhea and perineal irritation developed, but disappeared over the next 2 weeks. Fever recurred with moderate dyspnea on exertion. The temperature was 102.6 F., and petechiae were noted on the hard palate and buccal mucosa. A grade 2/6 holosystolic murmur was heard at the apex. The hemoglobin content was 9.6 Gm./100 ml. and the white blood cell count 15,400/cu. mm. Alpha hemolytic streptococci were grown from five blood cultures. Streptomycin intramuscularly and penicillin intravenously were begun on the 8th hospital day. Hydrocortisone, 400-600 mg. daily, was given intravenously for the first 6 days, followed by 30 mg. daily. The penicillin dose was raised to 40,000,000 units daily and continued until 5 days before discharge. The fever disappeared the day after start of therapy. Superficial thrombophlebitis developed in the arm overlying an indwelling catheter 1 week after insertion; the catheter was removed and placed in the other arm. On removal 11 days later, purulent material exuded from the site, and cultures yielded pure colonies of yeast.

Fever, nausea and fatigue developed about 5 weeks after

(1) Am. J. Cardiol. 13:820-824, June, 1964.

Coons (1954) showed that the virus was the same whether it came from a case of varicella or zoster. The 192 cases seen during 1947-62 gave an average annual rate of 3.4/1,000 persons. There was no apparent seasonal effect. If zoster were caught from other persons with zoster, it would be bound to come in epidemics. Over the 16 years, zoster flowed fairly steadily, averaging 12 cases annually, with a minimum of 8 cases in a year and a maximum of 18. No case of zoster was reported among 318 domiciliary contacts. If zoster were caught from contact with persons having varicella, it should be abundant at times when varicella is epidemic, and this was not so. Three of 4 years with over 100 reported cases of varicella provided the lowest prevalence of zoster. Virus latency is probably the most widely accepted explanation at present.

In the present series, each of 6 patients under age 10 had had an attack of varicella. Children aged 2 or over usually gave a history of varicella, whereas younger infants often had a prenatal history of maternal contact with varicella virus. Children under age 10 were attacked lightly, whereas octogenarians had a rate over 14 times higher. The average annual rate among males was 3.6/1,000 and among females 3.2/1,000. Laterality had no influence. Real differences in incidence between anatomic areas were found. The 5th cranial nerve and the trunk from the 3d dorsal to the 2d lumbar segments were more heavily attacked than segments supplying the limbs. Reminiscent is the distribution pattern of varicella rash. Steroid therapy may be added to the classic precipitants of zoster. Subsequent attacks of zoster are not rare; 8 of the 192 patients had second attacks and 1 had a third attack.

The author suggests that varicella follows the lines discovered for mousepox by Fenner in 1948. If so, the infecting virus dose gains lodgment, probably in the nasopharynx, where it produces an insignificant lesion and multiplies for perhaps a week. It then produces primary viremia. The virus multiplies in the reticuloendothelial cells. A second, larger viremia occurs a week after the first, causing fever and malaise and distributing virus to all parts of the body, especially the skin and mucous membranes. The virus also enters the contiguous endings of the sensory nerves, whence it is transported to the sensory ganglions where it becomes estab-

lished as a latent infection. It is in an incomplete provirus state at this point, insulated from neutralizing antibody in the circulation Because neurons do not replicate, neither does the latent virus. Occasionally, one latent virus component reverts and is immediately neutralized. If, however, antibody has fallen below a critical level needed to blanket the explosion, virus will be able to muliply at the next reactivation, perhaps at the expense of the nuclei of the satellite cells in the ganglion The infectious virus then is transported antidromically down the sensory nerve, causing a fierce neuritis and neuralgia, and is released into the skin The most important precipitants of zoster, i.e , leukemia and x rays, both depress antibody production

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(1) Am. J. Cardiol. 13:822-824, June, 1964.

discharge, and the patient was admitted with right hemiplegia and aphasia No petechiae appeared and her speech improved One blood culture yielded yeast forms Methylprednisolone, 48 mg , was given on the 17th hospital day, and the next day, shortly after intravenous penicillin was begun, an anaphylactic reaction occurred, penicillin was stopped thereafter On the 28th day, the temperature rose to 102 6 F , and yeast organisms identified as C albicans were cultured from the blood Amphotericm B, 25 mg , was begun intravenously on the 32d day The dose was increased by 5 mg daily until a daily dose of 55 mg was reached, this was continued for 17 days Blood cultures were sterile 3 days after cessation of therapy The spleen became palpable Severe abdominal pain, nausea and frequent bowel movements occurred on the 73d hospital day Laparotomy showed a large pulsating retroperitoneal hematoma dissection of which revealed a ruptured aneurysm of the right common iliac artery measuring 10×6×7 cm This was resected and a Teflon graft inserted Examination showed a ruptured mycotic aneurysm Left sided clonic seizures and shock followed and the patient died 18 hours after operation

At autopsy, the abdominal cavity contained 1,000 cc blood mixed with clots Vegetations were found attached to the atrial surface of the anterior mitral valve leaflet The chordae tendineae of the mitral leaflets were shortened and thickened, the free borders of the mitral leaflets were also thickened The aortic valve was normal The spleen contained an infarct, and a hemorrhagic infarct was seen in the midparietal region of the left cerebral hemisphere Candida organisms were found in the mitral valve vegetation Areas near the annulus showed infiltration of lymphocytes, mononuclear cells and fibroblasts Small foci of perivascular fibrosis were noted in parts of the myocardium, with focal collections of chronic inflammatory cells

Among 37 reported cases of candida endocarditis, it was related to antibiotic therapy in 28, rheumatic heart disease in 23, intracardiac surgery in 13, bacterial endocarditis in 9, narcotics addiction in 6, adrenal steroid therapy in 4 and indwelling venous catheters in 3 The combination of predisposing factors suggests that the disorder may be in great part iatrogenic, or at least may be considered one of the "diseases of medical progress."

► [All 3 articles in this section could have been placed in the first chapter, Some Hazards of Contemporary Therapy Note the development of these mycotic infections following therapy with antimicrobial drugs, steroids, antimetabolites, etc —Ed]

Painful Dysphagia Due to Monilial Esophagitis. On occasion, esophageal involvement may be the dominant feature of a monilial infection. Richard M. Buckle and W. D. Nichol[2] (St. Bartholomew's Hosp , London) describe 2 patients who

(2) Brit M J 1 821-822, Mar 28, 1964

presented with retrosternal dysphagia due to monilial esophagitis but in whom there was little evidence of thrush elsewhere.

CASE 1 —Man, 54, had acute leukemia with pallor and hepatomegaly. He was transfused and given 15 mg. prednisolone and 150 mg. mercaptopurine daily. One week later retrosternal pain developed on swallowing. Tetracycline was given for basal pneumonia. The dysphagia became so severe that only fluids could be swallowed. A barium study showed a shaggy, irregular outline of the entire thoracic esophagus, with multiple small filling defects along its length (Fig. 6) Hypopharyngeal and esophageal secretions showed many yeast spores and pseudomycelia with desquamated epithelium invaded by pseudomycelia, cultures yielded Candida albicans. Tetracycline was stopped, the prednisolone dose was reduced to 10 mg. daily, and 500,000 units of nystatin was given every 6 hours. Rapid

Fig 6 Barium swallow before treatment with nystatin (Courtesy of Buckle, R M , and Nichol, W D Brit M J 1 821 822, Mar 28, 1964)

improvement followed, the dysphagia disappearing completely by the 4th day The nystatin dose was reduced to 250,000 units every 6 hours and stopped after 10 days The yeasts disappeared from the pharyngeal secretions and stools, and a repeat barium swallow 9 days after starting therapy showed a normal esophagus

CASE 2 —Woman, 30, was treated for acute ulcerative colitis with 1 Gm. sulfasalazine and 5 mg prednisolone every 6 hours, with initial improvement One week later she reported retrosternal pain on swallowing, and 3 days later a few patches of thrush appeared in the oropharynx A barium swallow showed an irregular outline of the thoracic esophagus The oral lesions contained monilial spores and pseudomycelia, and the stools contained yeasts Cultures yielded C albicans The sulfasalazine was stopped and 500,000 units of nystatin was given as a mucilage every 6 hours By the 4th day swallowing was normal The dose was reduced to 250,000 units every 6 hours and stopped on the 9th day. Subsequent swabs from the mouth and stool specimens no longer contained yeasts A repeat barium study showed a normal esophagus

When thrush involves the esophagus, painful retrosternal discomfort develops. The x-ray changes are often confined to the thoracic esophagus, of which the distal third may be the first and only area affected. Nystatin is the treatment of choice and should be given, preferably as a mucilage, in a dose of 250,000-500,000 units every 4-6 hours.

► [This form of moniliasis can be very painful, it is not difficult to diagnose if one knows the manifestations and the setting —Ed.]

Esophageal Moniliasis in Malignant Neoplastic Disease. K. Björn Jensen, A. Stenderup, J. Brown Thomsen and J. Bichel[3] (Univ. of Århus) found, among 694 patients admitted to the Cancer Hospital for Jutland during 1956-61, 98 (14%) with moniliasis in the oral cavity or elsewhere and 35 (5%) with moniliasis of the esophagus. The latter included 26 men and 9 women of all ages. The diagnosis of esophageal moniliasis was made by esophagoscopy in 33 patients and x-ray examination at the same time in 32. Candida albicans alone was isolated in most patients; other yeasts were found also in 3, and Torulopsis glabrata was the only organism in 1.

The patients received various combinations of antibacterial and antineoplastic drugs and corticosteroids; some also received radiation. Amphotericin B was given in 29 courses to 23 patients, whereas 3 received nystatin or Pentamidine and 9 had no antimycotic therapy. Amphotericin B was given intravenously by infusion over at least 6 hours in a

(3) Acta med scandinav 175 455-459, April, 1964

daily dose of 12 50 mg. in 5% glucose solution The dose was raised from about 0.25 mg./kg to, usually, 0.50-0.75 mg./kg , and therapy was usually given for 1-2 weeks Definite improvement was noted in 16 patients, a satisfactory result in 3 and no effect in 4. The other 6 courses were of short duration (4 days or less) and were considered insufficient for evaluation Rigors, fever or local reactions, or both, were observed in 9 patients There were no serious side effects.

The finding of moniliasis in the oral cavity combined with a pathologic x-ray result is nearly conclusive as to diagnosis Cure was often obtained with smaller doses and a shorter duration of treatment than is used in treating other mycoses.

► I wouldn't think amphotericin justified as treatment of first choice, because of its toxicity As described in the preceding article, the infection can usually be brought under control with nystatin – Ed]

VIRUSES IN NEOPLASTIC DISEASE

Human Wart Virus: In Vitro Cultivation was carried out by Stephen Oroszlan and Marvin A Rich[4] (Albert Einstein Med Center, Philadelphia) Human warts were removed surgically and then frozen and homogenized A suspension was treated with high-frequency sound Antiserums were prepared in rabbits against wart virus partially purified by differential centrifugation The complex resulting from a mixture of immune globulin and crude wart virus extract suggested the presence of wart virus-specific antibody. Primary and secondary cultures were prepared of skin removed from a 4-month human fetus Within 24 hours, severe cytotoxicity was found in cultures inoculated with the virus preparations; less severe changes were noted in cultures inoculated with heated virus preparations Intense nuclear fluorescence appeared within 8 days after staining of cells with fluorescein-conjugated immune globulin Both marked nuclear and cytoplasmic fluorescence were found in 12-day cultures. The cytotoxicity seen shortly after inoculation persisted for 6-8 days. The appearance of wart virus antigen in the nucleus of inoculated cultures was accompanied by

(4) Science 146:531-533, Oct 23, 1964.

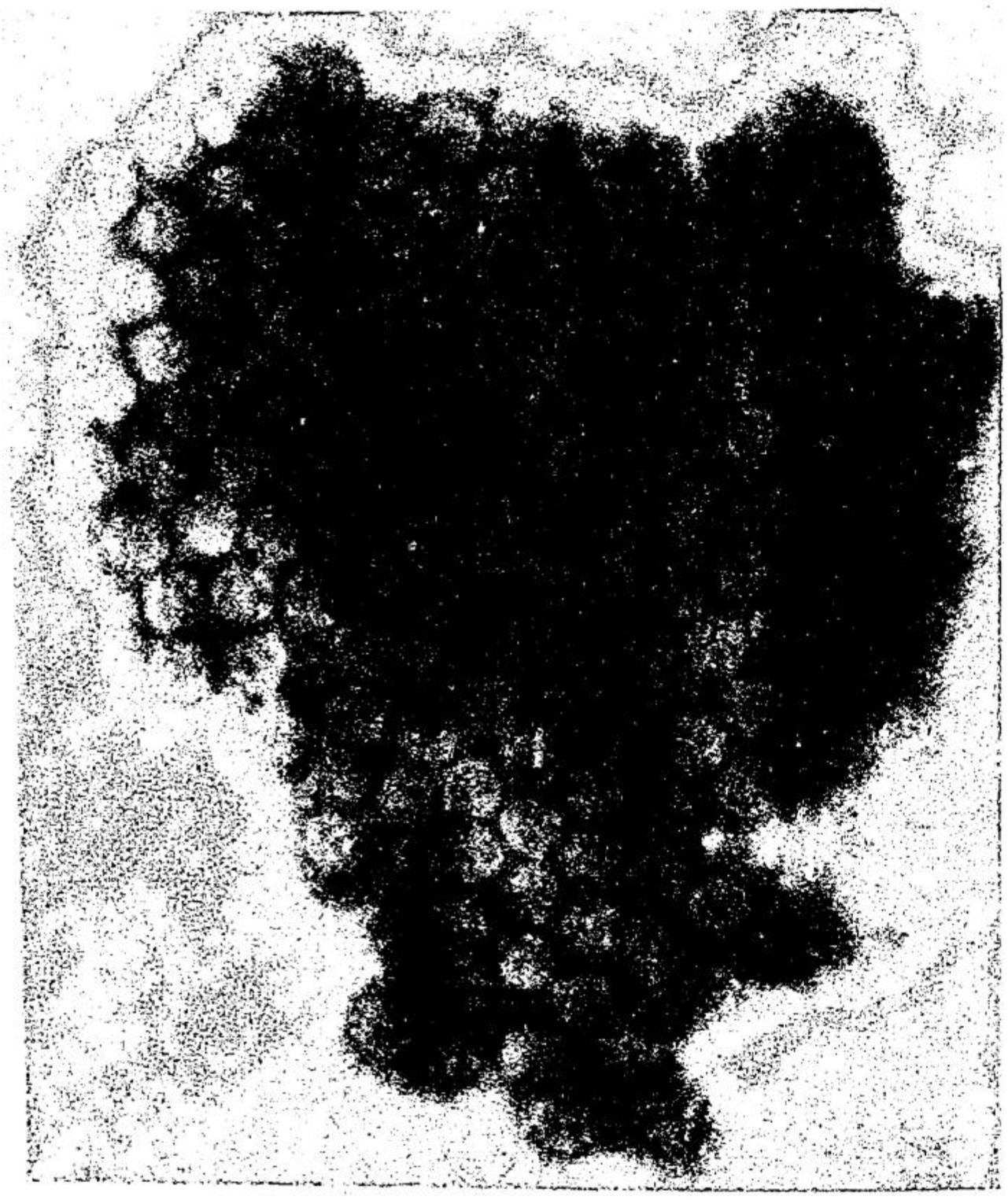

Fig 7 – Human wart virus isolated from 13 day cultures of cells of mouse embryo skin Phosphotungstic acid (Courtesy of Oroszlan, S , and Rich M A Science 146 531 533 Oct 23, 1964)

accumulation of large numbers of virus particles in the culture medium

Concurrent studies were done with secondary skin cell cultures prepared from 15-day mouse embryos Characteristic nuclear fluorescence appeared 2 days after inoculation, at which time only a few cells contained detectable viral antigen. Intensity of nuclear staining was decreased in later cultures showing cytoplasmic fluorescence. The initial cytotoxicity was less severe than that found in cultures of human skin. Large numbers of characteristic virus particles accumulated in the culture medium (Fig. 7).

► [The authors are cautious in their interpretation of these findings, but the evidence on viral etiology of warts seems pretty conclusive – Ed.]

Virus-Like Particles in Myeloma Cells of Man. In 1961, George D. Sorenson[5] (Washington Univ.) reported observation of numerous intracytoplasmic particles with the ultrastructural characteristics of viruses in neoplastic plasma

(5) Proc Soc Exper Biol & Med 118 250-252, January, 1965

cells from a patient with multiple myeloma. Recently, apparently identical particles were observed in myeloma cells from 2 similar patients with typical clinical features.

One patient was a man aged 66 with symptoms for 2 months and osteolytic lesions in the skull, ribs and vertebrae. The bone marrow contained numerous plasma cells, many with round cytoplasmic inclusions varying in size up to 7 μ in diameter and appearing pink to colorless on Wright's staining He died 2 months after admission after temporary symptomatic remission. Inclusions were noted in myeloma cells in bone marrow sections obtained at autopsy that were identical to those previously found in the bone marrow smear. The other patient was a woman aged 57. The bone marrow contained a greatly increased number of plasma cells, a few of which contained cytoplasmic inclusions identical to those in the first patient Abnormal β_2A-globulin was found on immunoelectrophoresis The same type of inclusion was present 6 months later

On election microscopy, most of the inclusions in the first case appeared as large vacuoles surrounded by two closely spaced membranes. Small round particles, uniformly 50-70 mμ in diameter, occurred about the edge of these vacuoles and less commonly were seen filling smaller vacuoles Most of the particles were doughnut forms with concentric double membranes and a central area with little electron density A few had a dense central core about 15-20 mμ in diameter with an appearance consistent with that of a nucleoid Identical vacuoles and particles were found in the other patient. The vacuoles in both cases appeared identical to those seen in the previously reported case.

These particles possess general ultrastructural characteristics essentially the same as those of known viruses Similar inclusions were not observed in neoplastic plasma cells from 15 other patients with multiple myeloma. The possibility that the particles represent a passenger virus has not been excluded. The specificity in their relation to neoplastic plasma cells, however, suggests that, if the particles are viruses, they may have an etiologic relationship to multiple myeloma.

► [Quite a few reports of this type are appearing now. The question is whether the particles seen are artifacts or passenger viruses or are truly related to the disease process. There is much disagreement among the experts.—Ed.]

Studies on Immunity to Measles were carried out by Saul Krugman, Joan P. Giles, Harriet Friedman and Shirley Stone (New York) in institutionalized and home-dwelling children and infants. Live attenuated measles virus vaccine (Edmonston B type), live further attenuated vaccine and formalin-inactivated vaccine were studied

Study of the Edmonston vaccine showed that neutralizing and hemagglutination inhibition antibody were both detectable by the 12th day after vaccination; complement-fixing antibody appeared on the 15th day. Peak antibody titers were noted by 21-28 days. Neutralizing and hemagglutination inhibition antibodies persisted longer than complement-fixing antibodies. The hemagglutination inhibition antibody test was the most sensitive and practical serologic procedure for studying immunity to measles.

A longitudinal study of measles immunity in 107 infants during the 1st year of life showed passively acquired hemagglutination inhibition antibody in 94% at 1 month, 47% at 4 months, 26% at 6 months and none at 7 months. Of 8 exposed infants, 6 had modified disease or subclinical infection with evidence of passive-active immunity.

A longitudinal study 1-4 years after natural infection and vaccination showed a similar pattern of hemagglutination inhibition antibody response after natural infection and after vaccination with Edmonston B type vaccine and further attentuated type, with and without γ-globulin. Addition of γ-globulin and further attenuation of live vaccine was followed by a lower geometric mean antibody titer and an increased percentage of children with low or nondetectable hemagglutination inhibition antibody levels. After a combined inactivated-live vaccine regimen, the hemagglutination inhibition antibody level was higher and persisted longer when the interval between the last killed vaccine inoculation and the live vaccine was increased from 1 to 8-10 months.

When children with minimal or nondetectable hemagglutination inhibition antibody were challenged 1-4 years after a successful vaccination with live vaccine, by exposure to

measles or revaccination with live vaccine, no clinical reactions were observed A significant booster type of response occurred in 70% of the children. Peak hemagglutination inhibition antibody titers were reached by the 12th day. No booster response was noted in children with high antibody levels Study with a more sensitive hemagglutination inhibition antibody test showed a titer of 1:16 in most convalescent serums having no detectable antibody with the conventional test Passively acquired maternal antibody was found as late as age 11 months, but not at age 12 months or later.

Infants whose mothers have had measles are born immune to the disease. Those with a high titer of transplacentally acquired antibody should be solidly protected if exposed to measles If exposure occurs when passive antibody has declined, some multiplication of virus may occur despite presence of antibody This may lead to passive-active immunity which may follow a subclinical infection or a mild illness with or without rash This type of immunity appears to be solidly protective and permanent, a similar type may be seen in older infants and children given γ-globulin just before or after exposure to measles

After classic unmodified measles, most individuals have antibody at a level that completely neutralizes virus acquired by intimate exposure to contagion In a few persons, the antibody titer may decline to minimal or nondetectable levels, and virus multiplication leads to a booster type of response and mapparent infection The pattern and persistence of antibody response after a single inoculation of live attenuated measles virus vaccine is remarkably similar to the response to natural infection. These studies provide strong support for the prediction that one such inoculation will be followed by lifelong immunity.

► [A solid contribution by reliable workers.—Ed.]

Epidemiologic Study of Inactivated Measles Vaccine. Harold S. Medoff, Albert R. Hunt, Felix E. Karpinski, Jr., Sherwood Salitsky and James E. Wheeler (Drexel Hill, Pa.) evaluated a concentrated, alum-absorbed, formalin-inactivated measles virus vaccine. This is a tissue culture product prepared by injection of the Edmonston strain of attenuated measles virus into monolayer chick embryo cell culture. Persons from middle and upper economic groups were stud-

(T.: J.A.M.A. 156:723-728, Sept. 7, 1954)

ied at the height of a moderate measles epidemic in suburban Philadelphia The 964 children aged six months to 6 years who were vaccinated were compared with nonimmunized controls Three 1-ml. doses of vaccine were given intramuscularly at 2-week intervals A group in a challenge study included 225 vaccinated patients and 230 controls.

Clinical measles occurred in 23 vaccinated patients and 139 controls in the 91 days after the first immunization, and in 19 and 48, respectively, in the first 14 days. All 4 vaccinated patients in whom measles developed in the next 11 weeks had received two injections of vaccine By 15 months, measles was observed in 46 more controls and no vaccinated patients, but modified measles was diagnosed in 5 of the vaccinated group. At 24 months, there were 51 new cases of measles in the control group and 2 new cases of possible modified measles among the vaccinated group. The incidence of measles for the 2-year period, excluding the first 14 days, was 19.2% in the controls and 1.2% in the vaccinated children. There were no local or systemic reactions to 2,854 injections.

The results demonstrate conclusively the clinical effectiveness of this vaccine. Thus far, antibody levels are being maintained, and direct known challenge with "wild" virus may boost the titers to fully immune levels Challenged vaccinated patients may show a clinical and serologic response similar to that of exposed controls given modifying doses of human γ-globulin. In effect, the data suggest that immunization with inactivated measles virus vaccine is equivalent to providing long-term coverage with the patient's own γ-globulin. Its safety and absence of reactions make it a most desirable immunizing agent for the office practitioner

Inhibition of Measles Rash by Chickenpox is reported by Vernon Knight, William F. Fleet and David J. Lang[8] (Nat'l Inst. of Health).

Boy, 7, acquired brightly flushed cheeks and slight malaise, followed 3 days later by the vesicular rash characteristic of chickenpox The rash spread maximally within 2 days and gradually faded with recovery from illness Febrile illness recurred 6 days after onset of the rash, with considerable prostration, irritation of the eyes and a dry, hacking cough Next day there was a rash typical of measles, and the day after, the crusted healing lesions of chickenpox were surrounded by zones of apparently normal skin completely free from measles rash These zones persisted until they were no longer visible

(8) J A M A. 188:690-691, May 18, 1964

because of fading of the measles rash with recovery Illness lasted only 3 days and was mild

The virus of chickenpox and probably that of measles are present in the skin. The interference of chickenpox lesions with measles rash could be due to interferon, local inflammation, direct virus interference or a nonspecific effect of a previous local lesion. The interference was noted in areas of skin apparently free from inflammatory reaction. Interferon has been stimulated by practically all viruses studied, has been seen in the skin of guinea pigs infected with vaccinia virus and is characteristically localized around the site of virus infection Virtually all viruses studied are inhibited by sufficient quantities of interferon

Protection against Lethal Effect of Lymphocytic Choriomeningitis Virus in Mice by Neonatal Thymectomy was demonstrated by John Hotchin and Edward Sikora[9] (New York State Dept of Health) Evidence was recently summarized for a hypothesis stating that the lethal effect of lymphocytic choriomeningitis virus infection in mice depends on a severe immunologic conflict between the rapidly multiplying viral parasite and the immune response of the host The lymphocytic response is seen as a part of the immune response acting to eliminate the infected tissue by a mechanism comparable with the homograft response This hypothesis integrates the protective effect of x-radiation, amethopterin treatment, the ability of newborn and congenitally infected animals to tolerate the virus by immunologic tolerance or paralysis, and also the extreme hypersensitivity to endotoxin developed during the incubation period of acute infection by this virus. Based on recent work concerning the role of the thymus and the effects of thymectomy, it might be

RESPONSE OF THYMECTOMIZED MICE TO LYMPHOCYTIC CHORIOMENINGITIS (LCM) VIRUS INFECTION

NO. MICE	NEONATAL OPERATION	INOCULATION OF 100 LD_{50} LCM VIRUS INTRACEREBRALLY ON DAY 15	MORTALITY	VIREMIA 25–27 DAYS POSTVIRUS
12	Thymectomy	+	0/12	6/6
2	Sham	+	2/2	NA*
6	Thymectomy	–	0/6	0/3
5	None	+	5/5	NA*

*NA, not applicable

(9) Nature, London 202:214-216, Apr. 11, 1964.

postulated that thymectomized mice would not react to the lethal effect of the virus; thymectomy should not prevent growth of the virus

A total of 18 albino mice, Albany strain, were thymectomized when less than 24 hours old Two had sham operations and 5 had no operations. Twelve operated mice and the 2 sham-operated ones, as well as the 5 controls, received 100 $LD_{50}M/B_7$ lymphocytic choriomeningitis virus intracerebrally on day 15 after birth The results are shown in the table

The findings fulfill the prediction that lymphocytic choriomeningitis virus infection should not be fatal to thymectomized mice, and thus add further weight to the immunologic conflict theory of lymphocytic choriomeningitis virus pathogenesis in mice.

► [This is one more piece of evidence which fits nicely with the recently proposed hypothesis that the clinical manifestations of lymphocytic choriomeningitis are essentially those of a violent allergic reaction to the parasite How many other acute infectious diseases belong in this category? - Ed.]

Circulating Autoantibodies and Human Disease: With Note on Primary Atypical Pneumonia. Lewis Thomas[1] (New York Univ.) points out that the past decade has seen the growth of a unitary theory to explain the cause of human disease, which now bids fair to encompass virtually all ailments. It concerns the role of autoimmunity in pathologic states and proposes that because of mutational changes in the immunologic attitude of lymphoid cells, or the appearance of antigenically foreign characters in the cells of target tissues, whole organs can undergo inflammatory and destructive lesions as though they had been placed in the biologic circumstances of homografts. It has been shown that autoallergic destruction of a particular organ can be extended by immunization with extracts of various organs in company with Freund's adjuvants to involve a wide array of organs. Evidence in the form of circulating antibodies reacting specifically in vitro with extracts of appropriate human organs has accumulated on a broad scale. Many autoantibodies have been demonstrated in the blood of patients with disseminated lupus erythematosus, and this disease has come to be regarded as a general incapacity of antibody-forming cells to discriminate between the antigenic determinants of "self" and "not self." Similar types of antitissue

(1) New England J. Med. 270 1157 1159 May 28, 1964

antibodies have been demonstrated in a wide variety of disease

Such a large concept of pathogenesis requires a more substantial body of supporting data than now exists before it can be accepted The possibility that autoantibodies are the result of tissue damage rather than the cause can be supported by several examples in laboratory animals and human disease It is remarkably easy, by appropriate immunization with Freund's adjuvants, to cause the appearance of circulating antibodies that react with extracts of homologous and heterologous organs, without necessarily causing disease of these organs It may be that certain types of tissue damage are associated with minor but significant degrees of denaturation of cell constituents that render them antigenic for the host Conceivably, the formation of antibody against such elements is of value in recovery from damage, facilitating removal of debris by immunologic mechanisms perhaps involving complement and leukocytes In the human, mere detection of an antiorgan antibody cannot be taken as evidence for autoimmune disease, even in the presence of extensive disease of the organ in question

Primary atypical pneumonia provides a unique example of a spontaneous human disease of known etiology in which an autoantibody directed against the tissue involved appears early in convalescence If it had not been conclusively established that this disease is due to infection by a mycoplasma, there would be justification for including it among the diseases now classed as autoimmune The immunologic reactions in primary atypical pneumonia suggest caution in interpreting the role of autoantibodies as causative agents in disease. They also suggest caution in interpreting the presence of autoantibodies as evidence for a primary, genetically determined disorder of the antibody-forming system of cells The possibility that infection with pleuropneumonia like organisms is implicated in other conditions characterized by autoimmune serologic reactions warrants further study

► [A readable and instructive discussion of a currently debated subject by one of our leading thinkers in the field of immunity and disease. – Ed.]

Immune Aspects of Glomerulonephritis Associated with Pulmonary Hemorrhage. The simultaneous appearance of pulmonary hemorrhage and an acute glomerulonephritis has been observed often enough to warrant the conclusion that

the association represents a distinct clinical entity; this condition has been called Goodpasture's syndrome Robert L Scheer and Murray A. Grossman[2] (Syracuse, N Y.) report results of immunologic studies in 2 women who died with this syndrome.

Woman, 21, had a history of nonproductive cough for 1 month and weakness, pallor, palpitations, dyspnea and orthopnea in the week before admission She had a grade II blowing systolic murmur over the base of the heart, a hemoglobin level of 5 Gm. 100 ml and hypochromia The reticulocyte count was 2 4%, the serum iron 7 μg 100 ml and the iron-binding capacity 274 μg /100 ml The urine contained 3+ albumin and 10-15 white cells and 25-30 red cells and 1 or 2 granular casts per high-power field Blood urea nitrogen was 25 mg /100 ml and creatinine, 3 6 mg /100 ml A chest x ray showed diffuse patchy densities along the periphery of both lung fields Repeated chest x-rays showed considerable clearing in the next week An antistreptolysin O titer was normal Renal biopsy showed subacute glomerulonephritis Despite prednisone therapy, severe oliguria and a rising blood urea nitrogen developed Peritoneal dialysis was performed 4 times, but marked dyspnea and tachypnea developed, and the patient died suddenly on the 27th hospital day

The lungs appeared hemorrhagic and firm at autopsy and showed "red hepatization" bilaterally Microscopically, there was fresh intra-alveolar hemorrhage with siderophagocytosis The interalveolar septa were thickened and showed hemosiderin deposit and infiltration with mononuclear cells The kidneys showed late subacute capsular glomerulonephritis, with much fibrinoid degeneration of the glomeruli

The other patient, a woman, 43, was ill for 12 years with spontaneous remissions lasting 8 and 4 years. The first attack consisted of pulmonary hemorrhage only, whereas the last two were complicated by acute glomerulonephritis. Glomerular capillary involvement was found at autopsy.

Specimens of kidneys and lungs from these patients were stained with fluorescein-labeled antibodies to human serum proteins and products of group A streptococci. The glomerular capillary walls in both instances strongly bound fluorescein-labeled antibody to human γ-globulin (Fig. 8), there was no evidence of the presence of more human albumin than normal. Staining of renal tissues with antibody to human complement was essentially absent Antistreptococcic serums were not bound to glomeruli or to lung tissue excessively.

In this syndrome, relatively minor episodes of pulmonary hemorrhage may escape detection. The lung lesion is unique,

(2) Ann Int Med 60 1009 1021, June, 1964

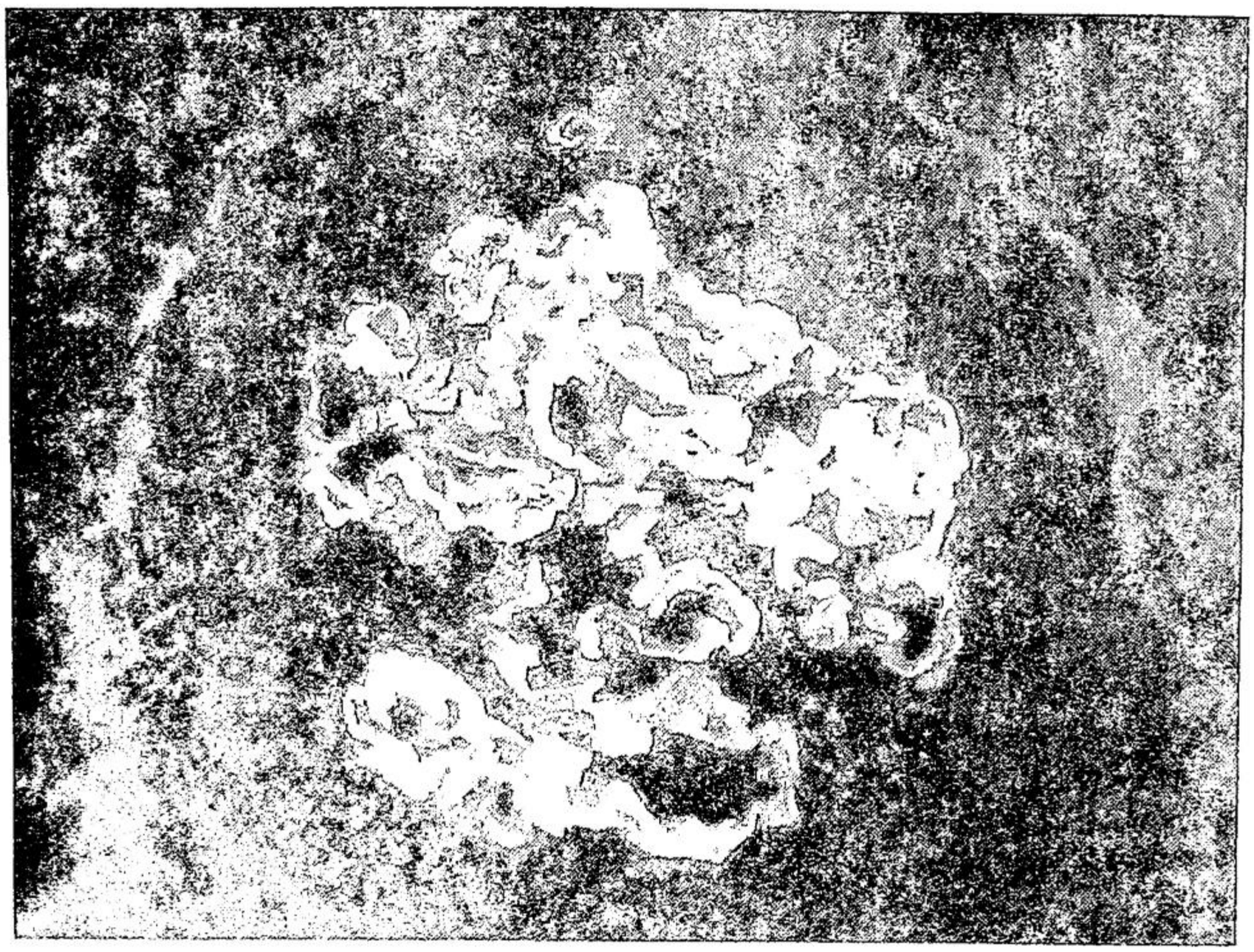

Fig. 3.—Section of kidney stained with fluorescein labeled antiserum to human 7S γ-globulin. Note binding of fluorescent antibody in capillary walls of glomerular tufts, indicating presence of large amounts of γ-globulin in these areas. Space between tufts and pale ring of Bowman's capsule is filled with collar of nonfluorescent proliferating cells. (Courtesy of Scheer, R. L., and Grossman, M. A.: Ann Int Med 60:1009-1021, June 1964.)

but the renal lesion is not specific. It is unlikely that nephritis in these patients was related to streptococcic disease. The pathogenesis of the pulmonary hemorrhage remains obscure. The possession of common antigens by lung and kidney could be a factor in the association of the pulmonary and renal lesions in Goodpasture's syndrome.

► [Goodpasture's syndrome is getting a lot of attention these days. It seems close to the disorder called idiopathic pulmonary hemosiderosis, and the two may be variants of a similar disease process. Very possibly an allergic mechanism of tissue damage, either in lung or kidney, plays a role.—Ed.]

Recurrent Aphthous Ulceration and Autoimmunity. Recurrent aphthous ulceration of the mouth fulfills several of Burnet's criteria for an immunologic disorder. Thomas Lehner[3] (Guy's Hosp., London) applied the sensitized tanned red cell hemagglutination technic of Boyden to serum specimens from patients with aphthous ulcers and other diseases, as well as from controls, using saline extracts of fetal oral mucosa as the sensitizing agent. Study was made of 20 normal controls, 15 patients with systemic disease, 13 with oral

(3) Lancet 2:1154-1158, Nov. 28, 1964.

gens Extremely good adjuvant activity was found for young, adult and aged persons alike and for various influenza virus antigens prepared by the Sharples centrifugation or protamine eluate method Persons responded serologically within 7 14 days of vaccination Two doses of adjuvant 65 vaccine, whether given 1 or 3 months apart, produced a slightly better response than a single dose of vaccine, but the shorter period was superior to the 3-month interval. Serologic responses were excellent in persons who were without detectable antibody before vaccination as well as in those with pre-existing antibody Local and systemic reactions were nonexistent or clinically inconsequential

Short-term studies in animals have shown that adjuvant 65 vaccine is largely removed from the injection site within 60 days, in contrast with persistent and striking inflammatory response in animals given mineral oil adjuvant vaccine

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LUPUS ERYTHEMATOSUS

Systemic Lupus Erythematosus: Statistical Evaluation of Mortality Based on Consecutive Series of 299 Patients. Though a grave prognosis was attributed to systemic lupus erythematosus before the early 1950's, the disease actually has a wide range of severity, from the acute fulminating variety to the chronic "smoldering" forms that are compatible with a long life expectancy. Robert E. Kellum and John R Haserick* (Cleveland Clinic) reviewed data on 299 patients treated during 1949-59. They had positive L E tests, skin biopsy results compatible with the diagnosis and clinical, laboratory and/or autopsy findings consonant with systemic lupus erythematosus.

Women were affected 6 times as often as men Peak age distribution was in the 3d and 4th decades, the median age being 32 years. The annual mortality was reduced after the first 2 years, in which 52 patients died. The estimated survivorship of all patients was 53.7%, compared with a life table

(*) Arch Int Med 113:200-207, February, 1964

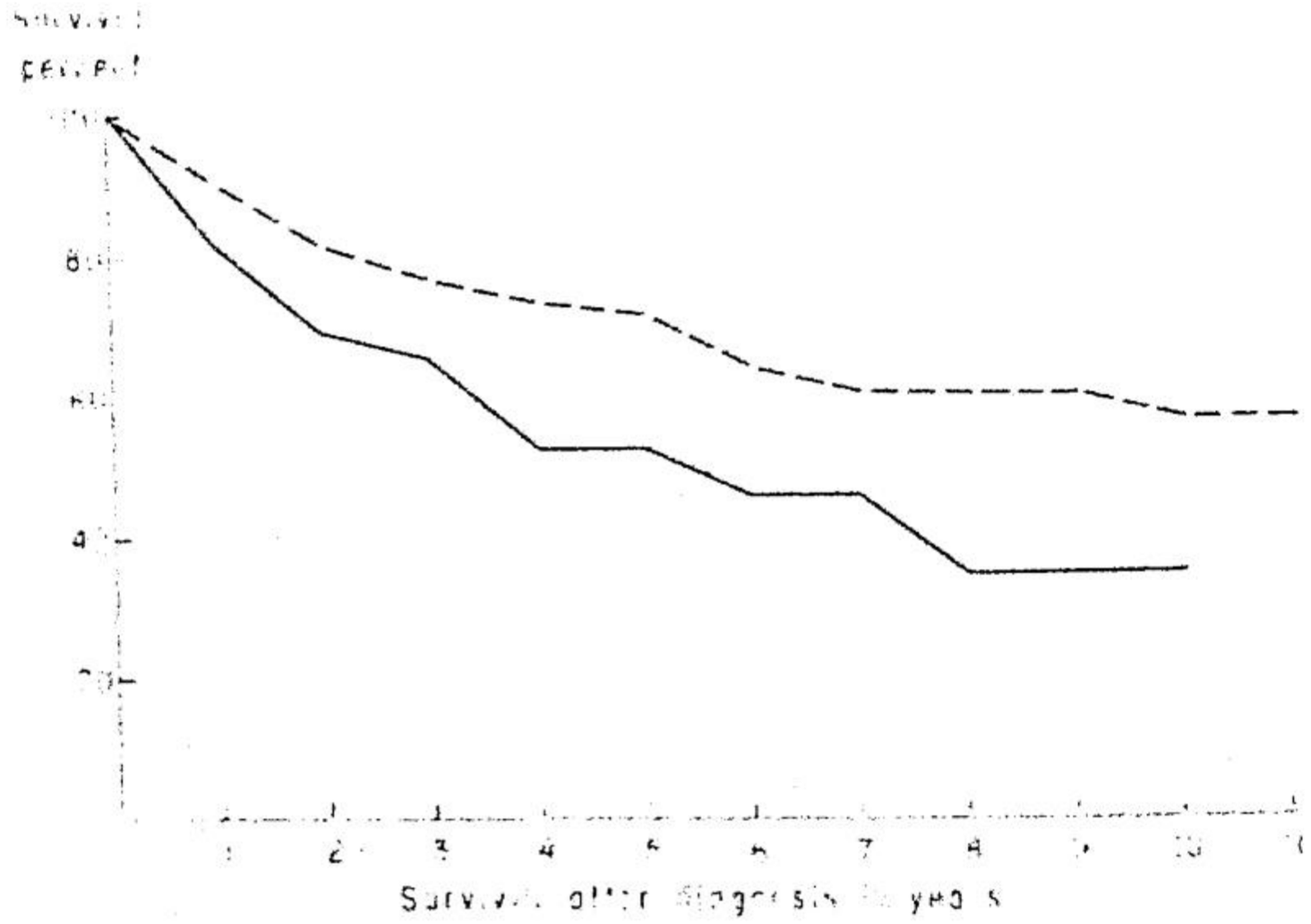

Fig. 9. Survival of patients with systemic lupus erythematosus by sex. Broken line represents females; solid line indicates males. (Courtesy of Kellum, R. E., and Hasenick, J. R.: Arch. Int. Med. 113:200-207, February, 1964.)

life expectancy of a comparable group of 96.7%. The prognosis was significantly poorer in males than in females (Fig. 9). Negroes appeared to have a lower mortality during the early years of the disease. A significant decrease in mortality was found in patients given steroids, particularly in the 1st year after diagnosis. It is postulated that once a patient has survived 2 years after diagnosis, the need for steroids may be less important, except in the control of subsequent obvious acute exacerbations. In many instances it was difficult to designate a specific cause of death. It is believed that 14 patients died in the acute stage of the disease, whereas 52 died of the complications, including infection, renal disease and pericarditis. Two patients committed suicide, both deaths being directly attributable to the disease.

► [I thought this was a worthwhile case review. It seems to show beyond reasonable doubt that steroids are sometimes lifesaving in lupus erythematosus, in contrast with the uncertain long term advantage of steroid therapy in such entities as rheumatoid arthritis and rheumatic fever.—Ed.]

Natural History of Renal Manifestations of Systemic Lupus Erythematosus. Victor E. Pollak, Conrad L. Pirani and Franklin D. Schwartz[6] (Univ. of Illinois) studied 87 patients with systemic lupus erythematosus who had renal biopsies and were followed from 7 months to 8 years. Ten had no

(6) J. Lab. & Clin. Med. 63:537-550, April, 1964.

histologic evidence of renal involvement, whereas 23 had lupus glomerulitis. Active lupus glomerulonephritis, characterized by a more severe proliferative and membranous process often associated with necrotizing features and including tubular and interstitial changes, was found in 47 patients. Membranous lupus glomerulonephritis was shown in the initial biopsy of 7. Diffuse thickening of glomerular basement membranes and abnormalities of the tubules and interstitial tissue were the only lesions found in these patients. At the time of initial biopsy, no clinical differences were found between the four histologic groups with respect to extrarenal manifestations of systemic lupus erythematosus

Of the 10 patients with initially normal renal biopsies, 8 were alive at the time of the final assessment, compared with 17 of the 23 with lupus glomerulitis; all 7 with membranous glomerulonephritis were living an average of 44 months after initial study. and 15 of the 47 with active lupus glomerulonephritis were alive an average of 34 months after initial study Of the latter, 26 died of renal failure, and 23 of these had the nephrotic syndrome.

The previous observation that treatment with large doses of prednisone for a prolonged period results in a significant increase in the life span of patients with lupus glomerulonephritis, by delaying onset of renal failure, was confirmed in the present study Treatment was for an average of 6 months with 40-60 mg prednisone daily A second renal biopsy was done in most patients 6 months after treatment with prednisone was begun, and the dose was then reduced gradually to maintenance levels of 15-20 mg. daily, provided there was minimal or no evidence of disease activity

Lupus glomerulitis does not necessarily represent an early stage of active lupus glomerulonephritis Changes in the clinical course of active lupus glomerulonephritis by use of large doses of prednisone is accompanied by a suppression of active lesions in the kidney It is probably mediated through effective suppression of the immune response by the prednisone.

► [Further evidence in support of the importance of steroid therapy. Many of us have been discouraged at times about the effect of steroids when renal manifestations were prominent. This kind of analysis may indicate which forms are likely to respond.—Ed.]

MISCELLANEOUS INFLAMMATORY DISORDERS OF UNCERTAIN ETIOLOGY

Fever of Sarcoidosis. James P Nolan and Gerald Klatskin[7] (Yale Univ.) studied 75 patients who met the following criteria: granulomas histologically consistent with the diagnosis of sarcoidosis; absence of tubercle bacilli; x-ray evidence of hilar adenopathy or pulmonary infiltration consistent with sarcoidosis; a negative or only weakly positive reaction to second strength PPD; failure to demonstrate tubercle bacilli on sputum culture or gastric washings, or both, negative reactions to histoplasmin, blastomycin and coccidioidin skin tests; and a negative brucella agglutination reaction. Fever was considered significant if the rectal temperature was at least 101 F. for a minimum of 3 days. The 45 whites and 30 Negroes included 38 males and 37 females; two-thirds were under age 40.

Significant fever was found in 31 patients (41%); the incidence was greater in Negroes than in whites. The fever reached peak levels of 101-103 F. in 77% of the febrile group and exceeded 103 F. in the rest. In over half, it was intermittent, with a daily rise and fall in temperature. Three patients had a typically hectic fever with a daily chill followed by an abrupt temperature rise to 104 or 105 F., profuse sweating and rapid defervescence. Fever was the major complaint of 58% of the febrile patients; it lasted longer than 2 weeks in half the group and subsided spontaneously in 10 of the 16 untreated patients, of 15 treated, 12 became afebrile after taking corticosteroids, ACTH, aspirin or aminopyrine.

All febrile patients, but only 64% of those without fever, had symptoms referable to sarcoidosis. Erythema nodosum was more common in the febrile group. There was no other significant group difference in distribution of clinical by demonstrable lesions or the number of granulomas found on liver biopsy. Leukocytosis was seen in almost one fourth of the febrile patients but was rare in those without fever.

Sarcoidosis may be accompanied by fever of significant magnitude and duration This feature is not limited to pa-

(7) Ann Int Med 61 455-161, September 1964

tients with erythema nodosum, uveoparotitis or intercurrent infection.

► [Twenty years ago it was frequently said that systemic manifestations were inconspicuous in sarcoidosis, but our concepts of the disease have been changing This paper shows clearly that fever may in fact be prominent.—Ed]

Treatment of Weber-Christian Disease is discussed by R. Benson and P D. Fowler[6] (Leicester, England), with report of a case. Weber-Christian disease is characterized by periodic attacks of crops of painful and tender subcutaneous fatty nodules associated with fever. Duration of attacks and periods of remission are irregular. The cause of the disease is unknown Although the subcutaneous fat is generally affected, any area of fat deposit may be. The disease occurs in females more often than in males Patients may be any age. The thighs are most often involved; the legs, arms and trunk sometimes. and the buttocks, breasts, hands and face rarely. Many agents have been recommended for treatment of this disease, but few have been satisfactory. The natural remissions make assessment and treatment very difficult, especially in view of its rare occurrence.

Woman 46, had a 7 year history of recurrent painful swelling in the arms and legs associated with tiredness and weakness Biopsy showed nodular nonsuppurative panniculitis Improvement occurred with 10 mg prednisolone 3 times daily, but the drug had to be withdrawn when a chest infection and skin sepsis developed Prednisolone was resumed on recurrence of the nodules but was not helpful. Tandearil (oxyphenbutazone), 200 mg 3 times daily, was given, and the nodules disappeared within 7 days However, within 4 days of cessation of therapy, the nodules reappeared Tandearil was again given, 200 mg 3 times daily for 3 days and then 100 mg 3 times daily The nodules disappeared completely Three subsequent exacerbations were successfully treated A maintenance dose of 100 mg Tandearil daily was given for 6 months On two occasions, there had been slight localized swelling and tenderness in the thigh, which quickly disappeared when the dose was increased to 300 mg daily for 3-4 days. Routine urine analyses and blood counts during treatment showed no abnormality.

Undoubtedly, in this case, the response to Tandearil was rapid and reproducible and better than that to steroid therapy. The drug was extremely well tolerated by this patient. Serious side effects have however been reported after Tandearil therapy The present case suggests a new line of therapy in intractable cases of Weber-Christian disease

► [Well, it would be worth trying. Steroids aren't harmless either —Ed]

[6] Brit M. J. 2:615-616, Sept 5, 1964.

tus. All patients had onset of Takayasu's arteritis at age 18-25.

Relapsing Polychondritis: Clinical and Pathologic Features in 14 Cases are described by Ronald L. Kaye and Donald A. Sones[1] (Mayo Clinic and Found.).

Man, 62, had had progressive hoarseness and difficulty breathing for 9 months. Frequent colds began about 3 years before admission, followed by weight loss and rhinorrhea. Nasal surgery resulted in nasal cartilage collapse. Postoperatively, there was infection of the upper respiratory tract, and the right elbow became painful and swollen. Bilateral swelling, redness, severe pain and tenderness of the external ears lasted several weeks, followed by mild hearing loss and tinnitus. Examination showed a typical saddle deformity of the nose (Fig. 10). The ears had a deep violaceous hue and appeared atrophic, with loss of normal contours of the helix and anthelix; they felt soft and boggy. The voice was moderately hoarse. There was extensive loss of the firm elements of the nasal septum, the false vocal cords were enlarged, and there was pectus excavatum and a 20-degree loss of extension of the right elbow. The sedimentation rate was 90 mm. per hour, and there was moderate rouleau formation on the blood smear. X rays showed calcification in the cartilage of both ears and destruction of the articular cartilage of the right elbow (Fig. 11). The true vocal cords showed myxomatous polypoid thickening. Biopsy of ear cartilage showed chondrolysis, infiltration by mononuclear cells, replacement of degenerating cartilage by dense inflammatory fibrous tissue and loss of the normal basophilia of cartilage.

The patient did quite well on prednisone therapy, 5 mg. every 6 hours for 2 weeks, followed by a reduction of 1-2 mg. daily every 4 or 5 days. Maintenance was with 5 mg. After 4 months the right ear

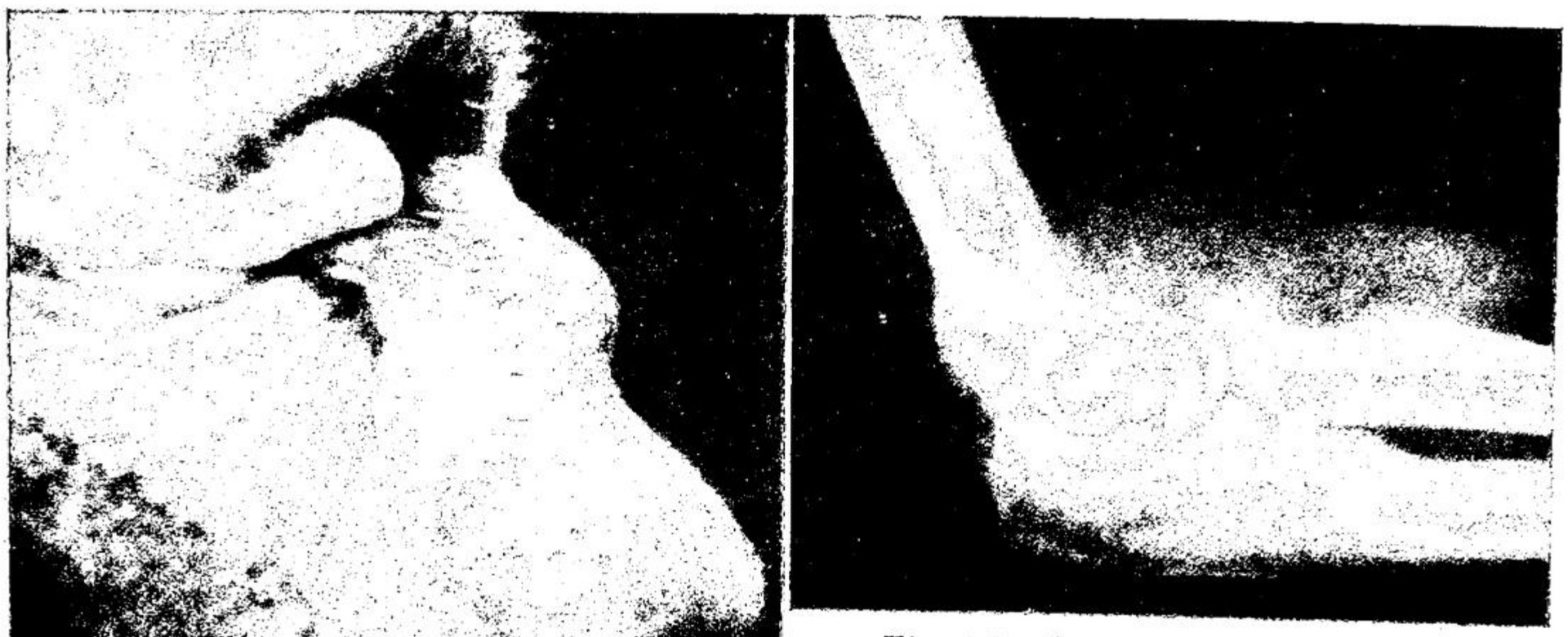

Fig. 10 (left).—Saddle deformity of nose.

Fig. 11 (above).—Right elbow, showing advanced destruction of cartilage with minimal change in adjacent bone. (Courtesy of Kaye, R. L., and Sones, D. A.: Ann. Int. Med. 60:653-664, April, 1964.)

(1) Ann. Int. Med. 60:653-664, April, 1964.

Summary of Clinical Data in 14 Cases of Relapsing Polychondritis

	Sex	Age at Onset	Duration of Disease when Last Examined	Involvement of		Saddle nose Deformity*	Involvement of				Ocular Involvement‡	Biopsy Sites	Treatment	Other Conditions Present
				External Ear*	Inner Ear†		Joints*	Trachea*	Larynx*	Other Sites				
1	F	37 41	37 1	+		+					I, EX, EOM	Ear	Steroids, salicylates, hydroxychloroquine	
2	M	61	2	+	II	+	+	+	+			Ear	Steroids, salicylates	Pectus excavatum
3	F	28	15		II	+	+	+	+	Bronchi		Bronchi, Ear	Steroids	Diabetes insipidus, tuberculosis
4	F	53	1	+	II	+	+		+	Costal cartilage	E, C, KS	Ear	Steroids, salicylates, hydroxychloroquine	Systemic lupus erythematosus, Sjögren's syndrome, Raynaud's phenomenon, arthritis
5	M	17	1	+		+		+	+					Pectus excavatum Diabetes mellitus
6	M	38	1	+	II	+								
7	M	2	19			+		+	+	Epiglottis				
8	F	2	24		II	+	+	+	+		EX	Trachea		Bronchopulmonary sclerosis, pectus excavatum
9	M	20	1	+		+	+				I, CR	Nose	steroids	
10	M	35	3	+	II, V		+				E, O, C, I, K	Ear	steroids	
11	M	38	3	+			+							
12	F	47	1	+		+	+	+	+	Epiglottis, Thyroid		Trachea, Larynx		Pericholangitis, hepatitis
13	F	31	4	+		+	+		+	Costal cartilage		Costal cartilage		Rheumatoid arthritis
14	F	45	1	+		+	+	+	+	Epiglottis, Thyroid	C, I			Hashimoto's thyroiditis, myasthenia, rheumatoid arthritis, subependymitis

*+ inflammation of cartilage present
†II loss of hearing, V vertigo
‡E episcleritis, C conjunctivitis, I iritis, CR chorioretinitis, O optic neuritis; EX exophthalmos, EOM extraocular muscle palsy, K keratitis, KS keratoconjunctivitis sicca.
§American Rheumatism Association criteria for definite rheumatoid arthritis

became painful, red and swollen The flocculation test for rheumatoid factor became weakly reactive, and an L.E. clot preparation showed nucleolysis The carbazole-creatinine ratio of urinary acid mucopolysaccharides was 3.65 The left ear became painful and swollen, and prednisone was increased to 10 mg daily, with prompt remission The patient was able to perform active farm work.

Onset of cartilaginous involvement occurred at an average age of 32 years In 11 of the 14 patients, three or more cartilaginous sites were involved. The clinical features are summarized in the table. Relapses were common and tended to occur in the same sites. Anemia and increased erythrocyte sedimentation rates were common Rheumatoid factor was present in 2 of the 3 females and in the 1 male tested The carbazole creatinine ratio increased temporarily with exacerbations of polychondritis There was definite rheumatoid arthritis in 3 patients and systemic lupus erythematosus and Hashimoto's thyroiditis in 1 each Treatment included administration of corticosteroids and salicylates. The initial daily dose of prednisone was 30 mg and maintenance doses were 5-20 mg.

► [Results of steroid therapy seem encouraging in this comparatively large series of cases The diagnosis is not difficult to make if one knows of its existence.—Ed.]

Caplan's Syndrome: Clinicopathologic Study was conducted by Jose Ramirez-R., Vincent Lopez-Majano and Gunter Schultze[1] (VA Hosp., Baltimore) A relationship between rheumatoid disease and pneumoconiosis was proposed by Caplan in 1953, who found a threefold increase in the incidence of conglomerate shadows among 51 miners with rheumatoid arthritis In 13, the densities were rounded and discrete, 0.5-5cm in size and often multiple and bilateral The nodules were frequently peripheral, developed rapidly and often appeared when only the first x-ray signs of simple pneumoconiosis were evident Since 1953, over 550 cases of this syndrome have been reported in Europe, but only 3 cases were reported in America. Two are described by the authors. One of these patients with an 18-year history of the disease had cavitation and pyogenic infection of the rheumatoid lesions. The second patient, whose lesions resembled those seen in category III pneumoconiosis, responded to prednisolone and later to chloroquine therapy

Miall and co-workers found rheumatoid arthritis in nearly half the miners studied with the x-ray picture described by

[1] Am. J. Med. 37:643-652, October, 1964.

Caplan, whereas the prevalence among miners with massive fibrosis was only 3%. Petry found category II or III pneumoconiosis in 40% of 190 arthritic miners after 20 years' exposure to coal dust; however, only 11% of those without rheumatoid arthritis had pulmonary lesions of comparable severity after 30 years' exposure.

Rheumatoid pulmonary nodules are rare in patients with severe rheumatoid arthritis, but it appears that in arthritic patients exposed to mineral dusts, even though the silica content of the lungs is normal, rheumatoid pulmonary nodules are more likely to develop Exposure to fibrogenic inhalants in the presence of the "rheumatoid state," even in the absence of arthritis, is likely to result in diffuse and permanent pulmonary changes. Silica may play a role in enhancing the manifestations of the "rheumatoid state." Silica, unlike other organic dusts, adsorbs protein antigens and thus may serve as a target for further antigen-antibody reactions.

Ectodermosis Erosiva Pluriorificialis, Stevens-Johnson Syndrome and Other Febrile Mucocutaneous Reactions and Behçet's Syndrome in Cold-Agglutination-Positive Infections. In 1964, Ludlam and his associates reported an interesting observation concerning a possible relation between infection with Mycoplasma pneumoniae and febrile mucocutaneous syndrome. Justus Ström[3] (Hosp. for Infectious Dis., Stockholm) reports his observations concerning the relation between febrile mucocutaneous reactions and cold-agglutination-positive infections on the basis of study for nearly 20 years.

Eighteen cases were reviewed. All patients had upper respiratory and pulmonary symptoms and protracted fever; some had headaches. Radiography showed pulmonary and/or hilar lesions in 14 patients. The white blood cell count was relatively low in most patients. Cold agglutination tests were positive during the course of the illness; maximum titers ranged from 16 to 1,024.

The febrile mucocutaneous syndrome has been described under many names. The author prefers a designation covering the chief criteria (fever, exanthema and mucous lesions affecting at least two of the orifices). His series of about 200 cases so far includes 16 variants. The cause of these reactions is uncertain. They have generally been as-

(3) Lancet 1 457 458, Feb 27, 1965.

sumed to derive from some specific infection, particularly viral, or from an allergic reaction. Although drugs may manifestly be the cause of the syndrome, the same applies to some infections. Earlier reports have suggested a relation between primary atypical cold-agglutination-positive pneumonia and the mucocutaneous syndrome.

▻ [For convenience, we, in the United States, tend to use the term Stevens-Johnson syndrome to designate what seems to be a form of erythema multiforme with predominance of mucosal lesions. The 18 cold agglutinin positive cases reported by the author were part of a series of 200 cases in the general category.—Ed.]

Familial Paroxysmal Polyserositis: Analysis of 50 Cases was carried out by Sheppard Siegal[1] (Mount Sinai Hosp., New York). In this condition, elevated temperatures, although often brief, may reach 105 F. Of the four chief syndromes of familial paroxysmal polyserositis, paroxysmal peritonitis is the most frequent, either alone or combined with paroxysmal pleuritis, the second most common syndrome. Intermittent arthralgias, monoarthritis and paroxysmal pyrexia are less frequent. Occasionally, cutaneous eruptions are observed. Onset in the 36 males and 14 females was chiefly in childhood or youth. Attacks, usually lasting 2 or 3 days, often recurred every few weeks. Paroxysmal peritonitis closely simulates an acute surgical emergency, with direct and rebound tenderness, fever, gastrointestinal upset, constipation and usually leukocytosis. Paroxysms of pleuritis may recur independently but more often precede or follow peritonitis. A transient, small pleural effusion may be observed on x-ray study.

The surgical pathology of paroxysmal peritonitis may be localized or diffuse, with congestion or edema, with or without small amounts of serous fluid, or strands and clumps of fibrin. There is an acute polymorphonuclear exudate with congestion of the peritoneum and omentum. Moderate splenomegaly was observed in 5 cases. An accelerated erythrocyte sedimentation rate is frequent. Moderate anemia is occasional. Hepatic disturbance may accompany paroxysms. Evanescent small bowel changes are frequent during attacks of peritonitis. Cerebral dysrhythmia was noted in the EEGs in 2 childhood cases and was reported in a single adult case. Nephropathy was absent in 48 of the 50 patients. Two patients died in uremia; 1 had chronic glomerulonephritis and

(4) Am. J. Med. 36:895-918, June, 1964.

1 had renal amyloidosis. In a third patient, death was due to rheumatic mitral stenosis.

This disease is familial and genetic, affecting especially patients of Mediterranean origin, most often Jews, Armenians and Arabs and less often Italians, Maltese and Greeks. The incidence of atopy is about twice that in control subjects. Endocrine factors involving especially the formation of abnormal pyrogenic steroid metabolites probably derived from adrenal or gonadal hormones may play a significant role in familial paroxysmal polyserositis. Pregnancy is often associated with complete inhibition of attacks, and paroxysms may be strikingly associated with menstrual periods. In some cases emotional factors appear to initiate episodes of the disease. Prognosis as to life is generally favorable; 47 of the 50 patients are alive despite many years of illness. Most patients are remarkably well between acute episodes. The disease usually pursues a lifetime course. Administration of corticosteroids was distinctly helpful in aborting attacks in 3 of 15 patients. Rarely, exclusion of a specific food, especially milk and milk products, may produce a prolonged remission. A diet restricted in fat (20 Gm. daily) is of occasional benefit.

► [This case analysis has value chiefly because of its large size. There is great confusion about the whole field of periodic diseases; the terminology is a little different in each article, and each description tends to convey the impression that the author alone understands the situation. Very possibly, the trouble lies in trying to force several different pathogenetic entities into one clinical category, based mainly on periodic recurrences.—Ed.]

Epidemic Thyroiditis. G. Hintze, P. Fortelius and J. Railo[3] report 44 cases of thyroiditis occurring epidemically in a single factory in Helsinki during 1959-60, representing 2.4% of all the employees. Infection of the upper respiratory tract of the common cold type preceded thyroiditis by 1-3 weeks in all patients. The age distribution of the 28 females and 16 males corresponded well with the age distribution of the workers. In the acute phase, nodules were present uni- or bilaterally, and in every case new nodules were noted during the course of the disease. Pain radiating along the neck to the ears and chin was reported in 36 patients, and the same number had a rise in temperature up to 104 F. The sedimentation rate was elevated in 37. In no case did the white cell count exceed 8,000/cu. mm. The protein-bound iodine exceeded 8 μg./100 ml. in 4 patients and fell below 4 μg. in 5

(3) Acta endocrinol. 45:381-401, March 1964

In 24 patients, 24-hour urinary radioiodine excretion was increased. Circulating autoantibodies were not found in any patient Albumin was depressed in 20 cases, α_1-globulin was elevated in 20 and α_2-globulin was elevated in 21. The β-globulin was elevated in 21 cases and the γ-globulin in 10 Biopsy showed almost the same picture as in endemic goiter, but in some specimens nonspecific inflammatory changes were found Prednisolone relieved symptoms but did not affect the course of the disease

Renal Histopathology in Case of Nephropathia Epidemica Myhrman: Study of Successive Biopsies was conducted by Borje Kuhlback, Per Fortelius and Leif G. Tallgren[6] (Univ of Helsinki) Nephropathia epidemica, first described by Myhrman and Zetterholm, is an acute renal disease occurring in northern Scandinavia, believed to be due to a virus. The condition has many features in common with Far Eastern hemorrhagic fever and hemorrhagic nephrosonephritis, which occur in northern Asia and Russia

Man, 36, a timber worker, suddenly had a temperature up to 104 F and diffuse back pain, followed by scanty, dark red urine, chills and muscle pains. Headache, slight stiffness of the neck and moderate disorientation were present 2 days after onset, when he was hospitalized Urine output was about 100 ml per 24 hours He had proteinuria, and the blood nonprotein nitrogen was 90 mg /100 ml On the 6th day, temperature was normal and the sensorium was clear Blood pressure was 120/80 mm. Hg The sedimentation rate was 47 mm per hour The plasma creatinine was 12.1 and the blood urea was 257 mg./100 ml Urine output then rapidly increased to 2 3 L per 24 hours, and protein in the urine disappeared The sediment contained a few red cells per visual field Moderate acidosis was present. The electrolyte disturbances soon became normal The plasma creatinine dropped in 4 days to 1 33 mg /100 ml A pharyngeal swab yielded a hemolytic streptococcus and Neisseria catarrhalis. The patient quickly recovered and was well on follow-up examination 5 months after discharge, at which time renal function tests and renal angiography were normal.

Four percutaneous renal biopsies were performed during the illness. The first three showed nodular thickenings on the walls of many arterioles, affecting the whole vascular wall. The staining reaction was acidophilic and periodic acid-Schiff positive. The changes were most marked in the first specimen and occurred in both the medulla and the cortex, in particular close to the glomeruli and in part affecting the glomerular tuft. The fourth specimen, obtained 5 months after onset of the disease, was histologically normal. These

(6) Acta path. et microbiol. scandinav. 40:323-333, 1954

findings were closely similar to those in cases of Asiatic hemorrhagic nephrosonephritis, but the illness in this patient followed a much more benign course The histologic changes appeared to be reversible

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INFLAMMATION AND FEVER

Pathogenesis of Inflammation: I. Production of Inflammatory Substance from Rabbit Granulocytes In Vitro and Its Relationship to Leukocyte Pyrogen. Despite the fact that certain "mediators of inflammation" have been demonstrated in injured tissue, their precise function in pathogenesis of the lesion from which they have been isolated has not been determined. John M Moses, Robert H Ebert, Richard C. Graham and Katherine L. Brine[7] (Western Reserve Univ.) carried out experiments intended to demonstrate the capacity of viable polymorphonuclear leukocytes to liberate in vitro a substance (or substances) which induces both a slowly developing inflammatory reaction and fever in rabbits. Leukocyte sticking and emigration were observed in plastic ear chambers containing newly formed tissue 5-10 weeks after insertion of the chamber

The results suggest that rabbit granulocytes liberate a substance capable of initiating a delayed response to injury and offer one explanation for maintenance of naturally occurring inflammation characterized by leukocyte emigration. Granulocytic substance can be distinguished from other agents on the basis of its heat lability and the conditions necessary for its production. Use of the ear chamber as a means of observing leukocyte sticking and emigration has the great advantage over fixed tissue preparations of permitting a dynamic view of even the smallest reaction from its earliest stages. The dose of granulocytic substance given systemically was calculated invariably to produce fever based on the experience of others with leukocytic pyrogen. Although the dose of pyrogen prevented correlation of fever index with inflammatory index, the study confirmed the identity of

(7) J Exper Med 120:57-82, July, 1964

In 24 patients, 24-hour urinary radioiodine excretion was increased. Circulating autoantibodies were not found in any patient. Albumin was depressed in 20 cases, α_1-globulin was elevated in 20 and α_2-globulin was elevated in 21. The β globulin was elevated in 21 cases and the γ-globulin in 10. Biopsy showed almost the same picture as in endemic goiter, but in some specimens nonspecific inflammatory changes were found. Prednisolone relieved symptoms but did not affect the course of the disease

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(6) Acta path. et microbiol. scandinav. 60:323-333, 1964.

granulocytic substance with leukocytic pyrogen and distinguished it from other pyrogenic agents

The results indicate that the active principle of granulocytic substance has both inflammatory and pyrogenic activity. The possibility that two different but similar substances are responsible for these phenomena cannot be excluded until further chemical characterization and purification of granulocytic substance are accomplished

► This looks like an important piece of investigation, tending to show that polymorphonuclear leukocytes liberate a substance which causes many of the vascular phenomena of inflammation, furthermore, the findings are compatible with the thesis in that the same product is responsible for fever.—Ed.]

Cellular Reactions to Soluble Foreign Materials in Rabbit Knee Joint. J. William Hollingsworth[8] (Yale Univ.) studied the acute polymorphonuclear exudation that characterizes reaction to injection of foreign soluble materials in the rabbit suprapatellar bursa. To minimize inflammation due to the chemical nature of the materials, only whole heterologous serums or materials derived from biologic sources were used.

Fresh human serums caused greater exudation than did serums heated to 56 C. for 30 minutes. Materials of known antigenicity in the rabbit (human serum albumin and globulin, ovalbumin, bovine serum albumin) caused distinct inflammatory reactions. Materials of minimal antigenicity (human hemoglobin, dextran, gelatin) produced little reaction. Immune animals responded with greater synovial reaction than did normal animals, but the sequence of exudation was similar.

The observations suggest that the polymorphonuclear reaction to soluble proteins and polysaccharides is related to the immunologic reaction to these materials, rather than that the two phenomena represent different host reactions to foreignness. Boyden postulated that foreign recognition and inflammation occur only when some type of specific humoral substance is present, presumably factors in the group of naturally occurring antibodies and opsonins.

► [The findings here tend to indicate that a major factor determining the intensity of an early polymorphonuclear exudation to introduction of a foreign substance may be the presence of antibodies capable of reacting with that substance.—Ed.]

Studies on Pathogenesis of Fever.—*XII. Electrolytic factors influencing release of endogenous pyrogen from poly-*

(8) Yale J. Biol. & Med. 37:300-312, February, 1935.

morphonuclear leukocytes —Richard D Berlin and W. Barry Wood, Jr [9] (Johns Hopkins Univ.) state that evidence continues to accumulate that a pyrogen derived from host cells is the common mediator of fevers produced experimentally in rabbits by acute bacterial infections, endotoxemia, hypersensitivity to tuberculin, viremia and bacteremia This endogenous factor is indistinguishable from the pyrogen obtained from polymorphonuclear leukocytes Recent studies showed that incubation of granulocytes in 0 15M sodium chloride leads to the release of large quantities of pyrogen, whereas little or no release occurs on incubation of the cells in fresh serum or plasma

The metabolic reactions responsible for release of endogenous pyrogen from rabbit granulocytes incubated in 0 15M sodium chloride were found to be specifically inhibited by the presence of potassium ion in the medium This action of potassium apparently involves penetration of the cell membrane and is directly antagonized by ouabain Further study has shown that pyrogen release is preceded by accumulation of pyrogen within the cell, that it depends on the catalytic action of one or more sulfhydryl-containing enzymes, that it does not require energy and that its inhibition by potassium and by arsenite is qualitatively similar to the depression caused by these reagents on the release of other leukocytic proteins, i.e , lysozyme and aldolase

XIII Effect of phagocytosis on release of endogenous pyrogen polymorphonuclear leukocytes.—Since one of the principal functions of polymorphonuclear leukocytes in bacterial infections is phagocytosis of invading bacteria, both in the tissues and in the blood stream, Berlin and Wood, Jr.,[1] examined the effect of phagocytosis on the release of leukocytic pyrogen. Phagocytosis was found to promote the release of endogenous pyrogen from polymorphonuclear leukocytes Release of pyrogen was not synchronous with phagocytosis Release was not inhibited by sodium fluoride, but it was inhibited by arsenite, suggesting that it does not require continued energy production by the cell but does involve participation of one or more sulfhydryl-dependent enzymes Particle for particle, ingestion of heat-killed rough pneumococci causes the release of approximately 100 times as much

(9) J Exper Med 119 697-714 May 1964
(1) Ibid, pp 715 726

pyrogen as ingestion of polystyrene beads of the same size

The pyrogen release mechanism of polymorphonuclear leukocytes separated directly from blood, unlike that of granulocytes in acute inflammatory exudates, is not readily activated by incubation of the cells in potassium-free saline Despite this difference, both blood and exudate leukocytes after phagocytosis release large amounts of pyrogen, even in the presence of potassium ion. That the postphagocytic reaction is unmhibited by the concentrations of potassium present in plasma and extracellular fluids suggests that this mechanism of pyrogen release mav well operate in vivo

► [This elegant work, which has a bearing on the findings of Moses *et al* (see p. 94), is the kind of contribution that will eventually enable us to describe the mechanisms of fever and inflammation in molecular terms. Ed.]

FEVER OF UNKNOWN ORIGIN

Laparotomy for Unexplained Fever. James W. Keller and Roger D. Williams[2] (Ohio State Univ.) reviewed data on 46 patients in whom laparotomy was performed for unexplained fever. The temperature exceeded 100.5 F orally, lasted longer than 3 weeks and was unexplained after careful clinical study. The 27 females and 19 males were aged 6-74 (median 49); 2 children were under 16. Exploratory laparotomy established the cause of fever in 38 patients (82%). Nine had lymphoma, 10 had carcinoma, 14 had inflammatory diseases and 5 had more unusual causes of fever, including Whipple's lipodystrophy, sarcoidosis, active hepatic cirrhosis and periarteritis nodosa. In only 3 of the 10 carcinoma patients was the lesion localized to its primary site; all others had peritoneal seeding or hepatic metastases. Abdominal lymphoma involved primarily the mesenteric and retroperitoneal nodes in 6 patients and the liver and spleen in 3. Five had disseminated abdominal tuberculosis and 1 had coccidioidomycosis. Four patients had cholecystitis, complicated by a pericholecystic abscess in 1 patient and a cholecystocolic fistula in another.

A history of fever for over 2 months before operation was

(2) Arch. Surg. 90:494-496, April 1965

present in 80% of the patients in whom the diagnosis was established and only 20% of the others. Positive findings of splenomegaly and abdominal mass or ascites were invariably associated with diagnostic findings at laparotomy, and all but 2 of 14 patients with hepatomegaly had positive findings at operation. All 3 with pleural effusion had diffuse peritoneal tuberculosis. The alkaline phosphatase level was elevated in 8 patients, 7 of whom had positive operative findings. A positive genitourinary or gastrointestinal x-ray finding was invariably associated with positive findings at laparotomy. After laparotomy, all but 3 patients were ambulatory and on oral intake within 48 hours, only 2 were not ready for discharge within 10 days. In all, 35 patients (76%) benefited through surgery since the findings permitted therapy. Four patients with gallbladder disease were cured by operation. Antibiotic therapy resolved an inflammatory disease in 10. Radiotherapy and systemic antineoplastic agents gave symptomatic relief to 17 others. Cortisone therapy benefited 4 patients with various diseases.

The morbidity accompanying exploratory laparotomy should be considered with respect to the advantages of an earlier diagnosis. The 2 deaths occurring in this series, although related to surgery, were in elderly patients with disseminated incurable diseases. The institution of specific therapy based on a definitive diagnosis, which was achieved in over three fourths of the patients, is certainly preferable to blind therapeutic trials and tends to justify a complication rate of 15% from laparotomy.

► [I agree with the authors. Diagnostic laparotomy is justified and advisable in certain cases of prolonged unexplained fever. It often provides essential information required for cure or palliation of a grave illness.—Ed.]

THE CHEST

CARL MUSCHENHEIM, M.D.