INFECTIONOUS DISEASES

ANNUAL REVIEW OF SIGNIFICANT PUBLICATIONS

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Knowledge of infectious diseases advanced as usual during 1965. Evaluation of many newly introduced antimicrobial drugs continued. Their great number, however, confuses physicians as to which ones to use, and some of them are no better than the older ones. Much antimicrobial therapy still is misapplied. An anthelmintic agent successfully controlled a number of diseases. Antiviral drugs were sought. Attention was given to rubella, its effect on the fetus and its persistence in the body. Hemorrhagic fevers in Asia and South America received intensive investigation. The causal relation of viruses, mycoplasmas and toxoplasmas to cancer and leukemia in man remained obscure. Electron microscopy disclosed new information in microbiology and disease. The importance of urinary tract infections at all stages of life was re-emphasized. Recognition of infections caused by “atypical” tubercle bacilli that resist antimicrobial therapy served to extricate them from classic tuberculosis. Disturbed faunal and avian ecology incident to population shifts in some regions favoured an increase in the incidence of encephalitis, hemorrhagic fever and Rocky Mountain spotted fever. Inapparent attacks of several epidemic diseases were observed and their significance was recognised. A vibrio different from V. comma caused epidemics in the Far East.

Antimicrobial Agents

New Antimicrobial Agents. Nafcillin¹ and cloxacillin² were introduced as methicillin, oxacillin, and cephalosporin in the treatment of staphylococcal infections. Nafcillin was used successfully in many cases of staphylococcal pneumonia, sepsis, arthritis and pyelonephritis in oral dosage of 4 to 8 grams daily.³ The overall death-rate of patients treated with nafcillin was 38 per cent. All strains of staphylococci were sensitive. Cloxacillin was not active against enterococci. Ampicillin was not as effective as chloramphenicol for treating typhoid.⁴ The drug was as good as tetracycline for the prolonged treatment of chronic bronchitis⁵ and was said to be the agent of choice for meningitis caused by pneumococci, H. influenzae and meningococci⁶. The proper use of the new penicillins was outlined⁷. Cephalothin (Keflin) was active against nonindole-producing Proteus, less so against Klebsiella, Esch. coli and paracolon bacilli. Pseudomonas was resistant. Seventy-six per cent of patients infected by pneumococci, streptococci, nonpenicillinase-producing staphylococci, and the sensitive gram-negative just named were successfully treated. A rash occurred in three of 103 patients⁸. The drug has no particular advantage over other agents⁹. Motile strains of Klebsiella-Aerobacter were resistant to cephalothin and cephaloridine, but sensitive to many other antimicrobics. The opposite applied to non-motile strains. The bacilli rapidly acquired resistance. Colistin sulfate failed to rid salmonellas from 40 per cent of carriers. Bacilli were suppressed during therapy¹⁰. Colistin is potentially nephrotoxic. Lincomycin was effective against staphylococci, pneumococci and hemolytic streptococci and is useful against bacteria resistant to penicillin or erythromycin, and for patients allergic to those agents. Enterococci, meningococci, gonococci and gram negative bacilli were unaffected by lincomycin¹¹. Lincomycin was said to be as effective as penicillin for the treatment of streptococcal pharyngitis¹². Nalidixic acid (Negram) is effective for the treatment of urinary tract infections caused by Esch. coli, Proteus and other gram negative bacilli. Resistance to it develops¹³.

Thiabendazole, a broad spectrum anthelmintic, was effective for the treatment of infections caused by Strongyloides, Enterobius, Ascaris, and Necator, without serious toxic effects¹⁴. Successful treatment of cutaneous larva migrans was described in four papers in the May 1965 issue of Archives of Dermatology. It was ineffective for Taenia solium or saginata and weakly effective in trichiuriasis¹⁵. Borrelidin and vivomycin derived from streptomycin were said to be antiviral agents¹⁶. Cycloguanil pamoate (Camolar) was said to have been successful in the treatment of 26 of 30 patients with dermal leishmaniasis¹⁷.
Antimicrobial Therapy and Prophylaxis. A physician recommended the intravenous injection of 10 million units of penicillin every two hours to prevent surgical wound infections. Should this be done, from 20 to 40 million units (12 to 24 grams) would be administered in a short period, mostly unnecessarily. Year-around administration of single injections of benzathine penicillin to new recruits satisfactorily controlled hemolytic streptococcal infections and prevented ensuing rheumatic fever. Should this plan be applied routinely to all civilians, question arises if the harm therefrom, as yet inapparent, would overbalance the prevention of the few instances of rheumatic fever that occur and if such general prophylaxis is justifiable. For example, after an epidemic of streptococcosis in 1953, only one case of acute rheumatic fever was detected, and none of the victims had evidence of chronic nephritis.

Antimicrobial agents are of no value for prophylaxis against bacterial invasion during acute viral respiratory tract infections nor in unconscious patients. As examples of unnecessary prophylaxis and therapy, "vigorous" antimicrobial therapy was applied in a patient with esophageal stricture caused by an escharotic and in a patient with massive epistaxis. Prophylactically administered agents rarely prevent bacterial superinfection, and which does occur may be even more difficult to treat.

In guinea pigs injected with 50,000 units of penicillin, the cecal flora was greatly reduced within 12 hours but later, a 10-million-fold increase in coliform bacteria occurred accompanied by severe cecitis, ileitis and lymphadenitis and bacteremia. This is an example of superinfection resulting from disturbed normal flora.

A protracted outbreak of multiple drug-resistant Salmonella edinburgh infection among infants was ascribed to previous unwise routine use of antimicrobics. Strains of staphylococci have become resistant to neomycin and bacitracin. These antimicrobics when used topically may induce microbial resistance.

Penicillin remains the drug of choice for pneumococci. If the patient is sensitive to erythromycin is indicated. Cephaloridine, ampicillin, nafcillin, oxacillin, cephalothin, cloxacillin and tetracycline also are effective in that order. The method of treatment of staphylococcosis was outlined in detail by Finland. Hemolytic streptococci have not become resistant to antimicrobics excepting, in a few instances, to tetracycline. Anyway, tetracyclines are not the agents of choice for treatment. Penicillin G is the most active, cloxacillin, oxacillin, cephalothin, and erythromycin less so, and ampicillin and nafcillin the least. In England, 31 per cent of strains of hemolytic streptococci resisted tetracycline, particularly those present in aural and wound exudates and dermal infections. Indiscriminate use of the drug may have induced resistance. In a survey of Philadelphia hospitals, I ascertained what huge amounts of antimicrobial drugs are dispensed. In an average month in one 500-bed hospital, 12 pounds of penicillin were prescribed and the total cost per month of all antimicrobics was about $16,000 (£5,714). Much effort is wasted by requesting unnecessary tests for microbiological sensitivity. The reported results may be misleading or erroneous especially from an over-burdened laboratory and poor submitted specimens.

Many physicians still are concerned with the "blood-brain-barrier" and the small amount of drug that enters spinal fluid. It is far more important, however, for the agent to attack the microbe in the meninges, not in the spinal fluid, for which intravenous or intramuscular injection is necessary.

Antimicrobial-sensitive bacteria may acquire resistance by growth in the presence of other resistant ones. Apparently, resistance may be "caught" by exposure. Whether the change can occur in vivo is unknown. Sixty-one per cent of 450 strains of Salmonella resisted one or more antimicrobial agents.

The occasional beneficial effect of antimicrobial therapy in addition to the administration of folic acid suggested that infection may play a role in the cause of tropical sprue.

A symposium on antimicrobial drugs was published in the November, 1965 issue of the American Journal of Medicine.

Harmful Effects of Antimicrobial Drugs. Large doses of penicillin caused anemia by destroying erythrocytes. Penicillin and its homologues caused nephropathy. Anaphylactoid shock after oral therapy resulted in severe neurologic residua. After therapy for three months, oxacillin depressed the marrow and caused hepatic dysfunction. Chloramphenicol in dosage more than 50 mg/Kg./day regularly caused toxic amounts to accumulate in the blood. Depression of the bone marrow occurred when 25 µg/ml were attained. In two of 20 patients, daily doses of two to six grams caused toxic changes in the marrow that disappeared when the drug was stopped. Chloramphenicol caused optic atrophy. Tetracycline rarely causes anaphylaxis, but did so in a patient who...
was hypersensitive to penicillin. Tetracycline therapy also may incite candidiasis, photosensitivity, discouloration of teeth, and if decomposed, may cause severe toxicity. Deteriorated tetracycline caused severe nephropathy and nephrogenic diabetes insipidus. As for any other antimicrobial, tetracyclines should be prescribed in amount and duration not exceeding that necessary to control infection. Sodium cephalothin caused an anaphylactoid reaction after its first intramuscular injection in a patient who was hypersensitive to penicillin. Colistimethate caused respiratory depression and muscular weakness. Orally administered neomycin was the probable cause of audio- and nephro-toxicity. As a result of topical application, 26 per cent of 1,538 patients were found to be sensitized to neomycin. Question was raised if antimicrobial therapy during early pregnancy in 85 women caused 12 malformed infants and 13 abortions. Among 26 victims of systemic vasculitis, antimicrobial drugs were the cause in 16. Long-acting sulfonamide drugs probably caused 116 cases of the Stevens-Johnson syndrome (mucocutaneous fever).

Viral Infections of the Respiratory Tract

Influenza. Despite an official optimistic forecast for 1964-65, influenza viruses A and A2 caused intense local outbreaks in the United States and in Europe, and even affected vaccinated persons. The antigenic nature of the viruses changes so rapidly that specific vaccines can not be prepared quickly enough. For the 1965-66 season, another recently isolated A2 strain will be added to A, A1, A2 and B strains now used. Each component added to a vaccine diminishes the amount and effectiveness of the others and one antigen may interfere with another. Interferon was present in the nasopharyngeal secretions of volunteers infected with A2 virus.

Volunteers were infected with a strain of influenza virus derived from horses. Pretreatment with an inactivated influenza virus failed to interfere with subsequent experimental infection with A2 virus. Persons with high specific antibody titer were infected with the virus, and some with low titer or none at all resisted experimental infection.

Adenovirus. Adenovirus Type 4 fed to persons caused symptomless enteric infection without involvement of the respiratory tract. Antibody appeared in the blood of all vaccinees. The procedure successfully immunized against infection during an epidemic. Thirty-two of 132 men in the control group contracted adenoviral infections. Infection did not spread to antibody-free persons in close contact with vaccinees.

Serologic studies of 269 recruits in Norway disclosed a high incidence of infection with adenovirus 4, but little or no respiratory disease. Evidently, the epidemic was largely inapparent. A severe epidemic first mistaken for measles affected about 80 children in an institute. Nineteen children had viral pneumonia, 12 had enteritis, 15 had encephalitis, and four died.

Rhinovirus. Nine serotypes of rhinovirus were isolated from 19 different victims of the common cold. A group of four new types appeared in 1964. Viruses of different types were extant in a season, but for short periods a single type predominated. From the same group of students with colds, two herpes simplex viruses and one adenovirus were isolated. The latter caused severe febrile illness. For unknown reasons, rhinoviruses like mycoplasmas cause disease less often in infants and children than in adults. They were isolated from 16 pneumonic infants and children and from those without pneumonia. Volunteers inoculated with one rhinovirus were inoculated with another strain two to 16 weeks later. Those inoculated two weeks later with either virus were not ill. Evidently protection was afforded by both the homologus and heterologus infection, but not after 16 weeks. The hope of preparing an effective vaccine is dimmed by the great variety of serotypes; a vaccine specific for one strain of rhinovirus protected volunteers against the homologus one, but not against others. Immunity lasted 12 to 18 months. Mineral oil or other adjuvants failed to increase immunogenicity. Interferon failed to have a protective effect when given to volunteers infected with rhinovirus, Coxsackie A21, and parainfluenza 1 viruses.

Reoviruses, so far, have been regarded as unimportant causes of respiratory tract infection. Studies of 406 persons, however, disclosed evidence of infection with Type 2 in 88 per cent and with Type 1 in 49 per cent. Either the infection was mainly inapparent or the diagnosis of overt disease seldom was made.

Respiratory Syncytial Virus. R.S viruses, for some reason, attack infants and children more often and more severely than older persons. In Holland, 28 per cent of 88 children were infected. Complement-fixing antibody appeared in four of six with bronchiolitis and in one third of those with pneumonia. All recovered and antibody in the blood decreased rapidly. One
wonders how bronchiolitis can be distinguished clinically from pneumonia. In Finland, RS virus caused 15 per cent of acute infections in children. Bronchiolitis or pneumonia occurred in 22 infants less than one year old. A commercial vaccine is in preparation.

Serum tests indicated that 72 per cent of a German population had been exposed to RS virus. The lowest percentage (37 per cent) was in seven-to-12-month-old infants. After the age of six years, 84 per cent had neutralizing antibody and this may account for the lesser frequency and milder disease as age advances. An immunofluorescent technique is reliable for the typing of RS virus in about 24 hours.

Coxsackie Viruses. Coxsackie B_{5} virus caused an epidemic in a nursery in the summer. Infections varied from inapparent ones to brief illness with fever, enanthem, rhinorrhea and pharyngitis. A_{20} virus caused a mild vesicular eruption of the hands and feet, and a maculopapular rash on the buttocks of 21 children. Two infants died. Two variant forms of A_{21} virus administered by aerosolization to volunteers resulted in a mild, febrile respiratory tract infection. Two strains of Coxsackie A_{21} virus inhaled by volunteers caused febrile bronchitis and two of 16 had pneumonia. One strain of virus caused febrile disease of the upper respiratory tract. In an outbreak of infectious hepatitis, A_{10} virus was present in 45 samples of feces and in the blood of four patients. It may have been a secondary invader or present as a commensal. Coxsackie A and B viruses were suspected as causes of congenital cardiovascular defects.

A study of 1,888 patients with respiratory tract infections in England between 1961 and 1964, disclosed enteroviruses, adenoviruses, rhinoviruses and parainfluenza viruses to be the ones most often isolated. Influenza and herpes simplex viruses were obtained from 447 patients. The microbes were not always the cause of disease. Hemolytic streptococci were present in 1281. In another survey, viruses, chiefly respiratory syncytial virus, probably were the cause in 62 per cent of infections in 151 children. Antimicrobial therapy therefore is not indicated for routine therapy. Pathogenetic bacteria were present as often in pneumonic patients as in healthy children. H. influenzae was not implicated. Staphylococci were the chief hazard.

Varicella virus caused pneumonia in 16 per cent of adults with chickenpox. In most patients, the pneumonia was signless, symptomless, and was discovered by skiagraphy as most viral pneumonias are. Gsell reviewed and summarized knowledge of viral and other non-bacterial "atypical" pneumonias.

Mycoplasma. Although they are not regarded as true viruses, mycoplasmas as causes of disease in man had been known and studied for decades especially by Dienes and Klieneberger, but attracted little attention. After Eaton’s and Liu’s observations relating Mycoplasma pneumoniae to pneumonia, it now is recognized as important. In 1938, some patients with pneumonia then regarded as of viral origin, undoubtedly were infected with Mycoplasma. At the same time, others had only pharyngitis and a few had severe systemic disease also without pulmonic involvement. Various Mycoplasmas inhabit the body including M. hominis, M. pneumoniae, M. orale and M. salivarium. Volunteers who inhaled M. hominis Type I developed a febrile pharyngitis.

Eleven per cent of 614 respiratory tract infections in Prague were caused by M. pneumoniae especially in older children and young adults. M. pneumoniae was isolated from the inflamed ear of a child with a mild respiratory tract infection. Infection involved only three children in an institution, one of whom had pneumonia. Occasionally, the microbe or a related one may be present as a commensal.

In a study of 239 recruits with pneumonia, cold agglutination of erythrocytes occurred in the blood of 172, but other evidence of infection with M. pneumoniae was present in only 41. Perhaps these microbes were not the cause in most cases or the agglutination reaction was provoked by nonpathogenic commensal mycoplasmas. Many authors still include all pneumonias not of the typical pneumococcal lobar form as "primary" atypical pneumonias. Bacterial pneumonias usually are not primary but are secondary to predisposing factors.

A vaccine prepared against M. pneumoniae evoked a rise in the titer of a specific antibody in 25 of 30 vaccinees. Hamsters developed pneumonitis after intranasal inoculation of M. pneumoniae. The microbes superficially located on the bronchial epithelial cells were visualized by applying special techniques.

Other Viral Infections

Knowledge of viruses, their classification and their "troubles" were summarized by Andrewes. Viruses, no doubt, affected man and other living things since remote antiquity. Any "new" ones probably are mutants of old ones or are newly recognized.

Viral infections of the respiratory tract may predispose persons to bacterial pneumonias,
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enteric viruses may favour bacterial intestinal infection, and suggestion was made that Cox-sackie B viral infections may incite acute appendicitis. Cytomegalovirus may cause disease resembling infectious mononucleosis where in the heterophile test gives a negative result. A newly isolated virus designated as the Darien strain and identical to Wyomyia virus found in mosquitoes was isolated from a man with mild febrile illness in Panama. Neutralizing antibody was demonstrated in 10 of 59 inhabitants of the area.

Viruses are multitropic. After vaccination, vaccinia virus caused unilateral genital arthritis. Complications in the form of generalized vaccinia, eczema vaccinatum and autoinoculation occurred in 336 vaccinated persons. These incidents can be avoided by not vaccinating victims of leukemia, agammaglobulinemia and atopic asthma. Therapy with vaccinia immune globulin was helpful.

An improved antimeasles vaccine for children more than a year old induced immunity in 99 per cent of recipients without inducing communicable measles in vaccinees. Vaccination is contraindicated in victims during other infections and in those with leukemia or neoplastic disease, in patients whose resistance is impaired, and during gestation.

Measles may be prevented or modified by the injection of measles immune globulin if given within six days of exposure. A viral inhibiting factor similar to interferon appeared in the blood of 18 children six to 11 days after vaccination. Particles resembling papova viruses were visualized by electronmicroscopy in nuclei of demyelinated neural cells.

Rubella. It was estimated that 30,000 children born during a large epidemic of rubella in the United States in 1964, will be congenitally defective. Besides the known abnormalities, many previously unrecorded ones were described in a symposium published in the American Journal of Diseases of Children, October, 1965. Inapparent maternal rubella may affect the fetus. The virus retards intrauterine and postnatal growth by inhibiting cellular multiplication. The virus was present in apparently normal infants whose mothers had no evidence of rubella infection, and in others whose mothers had had the disease early in gestation. To determine whether maternal infection had occurred, samples of serum may be sent to the Communicable Disease Centre in Atlanta for a diagnostic test.

Complement-fixing antibody appeared soon after the rubella rash faded and persisted for more than eight months. In eight of 12 persons who had had the disease more than 10 years before, antibody was absent, but neutralizing substance was present. The virus was isolated from 32 of 50 specimens of products of conception in women who had rubella in the first or second trimester of pregnancy. Virus persisted as long as 77 days after the rash. Thrombocytopenic purpura occurred in four of nine children. Steroids were administered for the dubious purpose of controlling the fragility of capillaries. The number of platelets was not influenced. Apparently steroids did not worsen a viral disease.

Three of six children with rubella encephalopathy died. The circumstance probably occurs in one of 5,000 cases. Rubella virus, present in the organs of three infants at necropsy, indicated the persistence of a chronic state of infection in the congenital form of the disease. Serologic evidence suggested that Cox-sackie B viruses of infection of mothers may be another cause of congenital defects.

Encephalitis. Two hundred cases of St. Louis encephalitis were observed in Florida in 1962, but, no doubt, many more mild cases and inapparent infections were undetected. Clinically, the spectrum of severity of illness ranged from mild infection in 49; meningitis in 27; non-paralytic encephalitis in 137; and paralysis in 9. Forty-three patients more than 45 years old died. Inapparent infections were a major source of infection of others and these occurred in a ratio of 39 to one case of overt disease. A detailed description of an epidemic was published. In 1964, eight per cent of the population and 29 per cent of the "contacts" were inapparently infected during a major epidemic in Houston, Texas, where the disease had not been observed in recent years. An antimosquito campaign stopped the epidemic.

More epidemics of arthropod-borne encephalitis may be expected. The urbanization of populations and its attendant faults of sanitation favour the breeding of mosquitoes and the attraction of avian carriers of the viruses. In other words, the changing nature of human society creates a new and favourable milieu for the maintenance and dissemination of viral infections.

California virus encephalitis was recognized for the first time in Florida. Six viruses cause encephalitis in North America. In general, the cause of about 50 per cent of reported cases was unknown. ECHO viruses mostly of Type 4 were involved in 26 of 45 encephalitic patients in Scotland. ECHO 25 virus was the chief cause of another outbreak of encephalitis. A.
caused a small outbreak of polio-like paralysis also in Scotland in 1959, and 15 infections in 1963. Corticosteroid treatment in 346 patients with various kinds of acute and post-infectious meningoencephalitis caused a high mortality rate and more neurologic sequels than in untreated patients.

Rabies is a polio-encephalitis as determined in a study of 49 cases. The site of the bite had no relation to the length of the incubation period or to the clinical course. Negri bodies were present in 70 per cent of patients. In rabid dogs, the virus was in the saliva three days before the onset of illness and for two days afterwards. Therefore, recommendation was made to shorten the time of observation of a bitten patient to five rather than 10 days.

In one victim, hysteria was suspected because physicians were not informed of a cat-bite three months previously. A generalized reaction to antirabies serum affected 16 per cent in adults. Fatal post-vaccinal encephalomyelitis occurred in 18 of 65 persons vaccinated with an antirabies vaccine. "Fixed" virus was isolated from the vaccine. Rabies has increased in incidence in Ontario because of an increased number of foxes as sources of infection. Fewer foxes are killed in response to a smaller demand for their fur.

Smallpox. Doubt raised about the need for continued routine vaccination against smallpox provoked controversy at a Pediatric Society meeting. In a study to detect harmful effects, Kempe stated that no deaths from the disease occurred in the United States since 1948, but more than 200 deaths were caused by vaccination. Among 2.3 million primary vaccinees, 1,427 complications or sequels and four deaths occurred. An estimated 15 to 18 persons died after vaccination in 1963. Vaccination is needed for persons who enter endemic regions or for contacts when victims of smallpox import infection and spread it in an area free of the disease. Safer methods of protection should be devised such as chemotherapy or immune gammaglobulin. The matter was discussed at length and recommendations were proposed. A sterile inflammatory flare-up may appear at the site of vaccination years afterward.

Great trouble and expense ensued when a person from Ghana suspected of having smallpox arrived at an airport. About 1,000 persons who were nearby subsequently were sought, found and vaccinated. The alarm was unnecessary; the patient had varicella.

Because there is no evidence that antismallpox vaccination has any effect on recurrent herpes simplex, it should not be used for its treatment.

Herpes Simplex. Herpes simplex infection of the vulva may be accompanied by viremia and hepatic, pneumonic, neural and adrenal involvement. After a primary attack, recurrences may be provoked by menstruation or other disturbance. Infants may be infected during passage through the birth canal and develop encephalitis and retinopathy. The virus caused encephalitis in 52 patients in a 3-year period. In three, it was preceded by labial lesions. A herpetic-like virus was present in fetal and neonatal dogs that died with an acute hemorrhagic disease. Virus passed through the placenta causing death in some dogs, but in others the virus persisted latently like the virus of herpes simplex in man. Three papers in the Journal of the American Medical Association of November 29, 1965 described epidemics of herpes gladiatorum, that is, infection acquired by contact in wrestlers.

Iododeoxyuridine (IDU) applied to facial herpes simplex was said to have reduced the duration of the lesions to three days as compared with nine days in control subjects. The viruses of herpes simplex, zoster and varicella are related as disclosed by cross reaction, neutralization and complement fixation tests.

Hepatitis. Two-thirds of 1,675 patients with hepatitis acquired the disease without exposure to known sources such as jaundiced persons or transfusion of blood or other injections. One hundred patients with hepatitis and an equal number of control subjects were questioned. Twenty-five infections were acquired by the transfusion of blood. Others had a higher consumption of raw clams, and more injections from physicians than the controls, but the source in many instances was obscure. The higher mortality rate from the serum hepatitis than from infectious hepatitis, at times, may be accounted for by the advanced age of the patient and of other underlying disease.

Hepatitis in aged patients often is mistaken for evidence of cancer or other disease. Six of 23 patients died and four others had progressive disease.

Nonicteric serum hepatitis is ten or more times as common as its icteric form. In a 9-year study of 816 patients after transfusion, 33 had jaundice, an incidence of 9.2 cases per 1,000 units of blood. The death-rate was 4.4 per cent. The risk of infection increases with the number of transfusions given. The injection of gamma globulin did not prevent infection, but lessened the relative proportion of icteric cases to non-
icteric ones. The injection of 10 ml. of gamma- and another dose after a month will prevent about three-fourths of icteric serum hepatitis. globulin in the week after blood transfusion. The case-rate was 1 per cent in treated patients and 3.9 per cent in the controls. The supply of gamma globulin is too limited for routine use125. Two teams of investigators failed to note any protection offered by the injection of gamma-globulin126.

In another report, single unit transfusions accounted for 17 per cent of all cases. Transfusion of whole blood appeared to be less hazardous than pooled plasma or fibrinogen. The onset of hepatitis was highest between 30 and 75 days after transfusion. The overall mortality rate was 11 per cent of 538 cases, but 5.5 per cent in victims less than 40 years old127. Eleven cases of hepatitis were observed in persons exposed to chimpanzees128. Several authorities doubted that the viruses of hepatitis have been isolated. Another group of Italian workers reported the isolation of a causative virus129.

Hemorrhagic Fever. Hemorrhagic fever is not new to Thailand but has been observed every year since 1950 when it came to general attention after the Korean conflict. Question still arises as to the relationship of the virus to dengue viruses. In the epidemics, dengue virus of different types and chikungunya virus were present. None of the victims was of European descent, which suggested that previously exposed natives react more severely to reinfection or that a genetic influence is operative130. Yet American troops in Korea had hemorrhagic fever and the mortality rate was 10 per cent. Uremia was the chief cause of death131. Infection probably transmitted by A. aegypti mosquitoes and the possibility of its appearance in the United States was considered132.

A variety of hemorrhagic fever first noted in Argentina in 1958 and later in Bolivia may be related to the Far Eastern infection133. A symposium on the diseases as they occur in the Americas was published in the September, 1965 issue of the American Journal of Tropical Medicine. As mentioned previously in the case of St. Louis encephalitis, an artificial disturbance of mammalian ecology favoured epidemics of Bolivian hemorrhagic fever. During an antimalaria campaign, DDT was used widely. Cats poisoned by DDT died, thus permitting a household invasion of a mouse-like rodent, the source of human infection. Their virus-bearing urine is deposited on food or in water. No insect vector is involved134. In one instance in the United States, infection was transmitted from a stricken physician to his wife135.

Bacillary Infections

Salmonella. In June, 18,000 persons were infected with Salmonella typhimurium in a Californian city. Three debilitated victims died. Bacilli from a well polluted the city’s reservoir and water supply136.

In a nationwide (U.S.A.) surveillance of salmonellosis, S. typhimurium and S. derby were most often isolated from man. S. derby was usually recovered from persons aged 50 to 79 in whom it usually caused short, mild illness. Infection with S. heidelberg was typhoidal, and with S. cholerae-suis it often was septiceemic137. Five infections of the urinary tract caused by Salmonella were described138.

The pattern of typhoid may vary according to geographic, climatologic and immunologic factors and the ethnic origin of its victims, an impression I also gained in Indonesia. In India, among 340 typhoid victims, rose-spots were absent, epistaxis was rare, and cough was the chief early symptom. Circulatory collapse often occurred, but intestinal hemorrhage and perforation seldom did. The death-rate was about 4 per cent139.

Dysentery. In a survey of families in Scotland, among 1,354 cases of diarrhea only 19 per cent were of bacterial origin, and of those Sh. sonnei caused 84 per cent; Esch. coli, 9 per cent, Salmonellae 6 per cent, and Sh. flexneri 0.4 per cent. Eighty per cent of infections were of unknown cause. Coxsackie A9 and ECHO 7 viruses were isolated but without proof of their relationship to diarrehas140. Among 112 children during three years, those less than six months old were chiefly affected. Diarreha was caused by bacteria alone in 25 per cent of cases, by viruses alone in 12 per cent and by mixed bacterial-viral infection in 12 per cent. Various types of adenovirus, Coxsackie, ECHO and myxoviruses were isolated. Eighty-two per cent of viral isolations were made in summer. At present, the causes of 60 per cent of acute diarrheal disease have not been discovered. On the basis of probable cause, only three of 74 cases of infantile diarrhea needed antimicrobial therapy141.

Sonne shigellosis is responsible for most bacillary dysentery in England. Streptomycin is the therapeutic agent of choice, but more expensive drugs such as nalidixic acid and paromomycin are effective, if streptomycin resistance is encountered142. Shigella flexneri
dysentery occurred in eight of 17 persons in contact with a dysenteric pet money. Shigellas rarely are found in the blood stream. In three children with shigellic dysentery, sepsis was caused by *Esch. coli* and *Aerobacter*. Malnutrition often provides opportunity for the invasion of nonpathogenic commensal bacilli. Many strains of Shigella resisted sulfadiazine which no longer should be used for treatment. Ampicillin and colistimethate, kanamycin and neomycin are most effective in vitro and may be of value for oral administration to patients.

Electron microscopic observations disclosed what appeared to be the phagocytosis of commensal bacilli by the intestinal epithelial cells of rats as a physiological process without inflammation. Suggestion was made that shigellas and vibrios similarly may enter the mucosa, cause inflammation, decompose and liberate their toxins. Shigella bacilli fed to guinea pigs penetrated the intact enteric epithelium and reached the tunica propria in a few hours. An exudative inflammatory reaction preceded degenerative changes in the villi with loss of cytoplasmic components and microvilli. Studies in tissue culture disclosed mycoplasmas stuck to cytoplasmic surfaces, their penetration of cells, and areas of necrosis. Electron microscopy has opened a new field in microbiology.

### Other Bacillary Infections

Vaccination against whooping cough failed to prevent an epidemic. The isolation of *Bord. pertussis* serves better to discover the cause of an outbreak than for diagnosis in individual patients. Whooping occurred in only 20 per cent of patients with paroxysmal cough. A previous attack of pertussis gave no immunity.

*Clostridium botulinum* Type F, caused an outbreak of botulism in Denmark. That type has not been found in the United States, but was isolated from marine sediment 1,646 meters deep in the Pacific Ocean near Oregon.

An antianthrax vaccine is available for distribution. One wonders how reliable it is.

*Pseudomonas aeruginosa*, usually disregarded as an unimportant commensal, caused an outbreak of 14 infections in a neurosurgical ward. A contaminated shaving-brush probably was the source. Twenty other specific types of the bacillus were isolated from the environment.

*Listeria monocytogenes* was reported as the cause of an aortic aneurism in an aged diabetic woman. The aneurism may have existed for years and the site subsequently may have been invaded by an opportunistic microbe.

At a recent conference in Washington, *Myco. leprae* was said never to have been cultivated, yet Garbutt reported success in tissue culture. Leprosy became overt in a soldier who had left New Caledonia 20 years ago.

Tetanus immune globulin prepared from human plasma is effective in preventing tetanus when given at the time of injury. It now is available commercially. Immunization with toxoid still is desirable. Six victims of tetanus recovered after therapy with 3,000 to 5,000 international units of human tetanus hyperimmune globulin. A repository type of penicillin injected promptly after injury was said to be of value in preventing tetanus providing the strain of bacillus is sensitive to penicillin. Toxins derived from nine strains of *Cl. tetani* were the same. Evidently, a specific neurotoxin is shared by all strains.

**Tuberculosis.** For 45 years, J. A. Myers led one of the few continuous studies to determine the natural history of untreated tuberculosis. This is no longer possible since the introduction of modern therapy. His observations have established facts that corrected preconceived ideas and theories. One of the contributions was that the primary infection almost always is benign and needs no treatment because the available drugs are not germicidal, antimicrobial-resistant bacilli may emerge, therapy gives a false sense of security, it does not influence the course of infection, and drugs control the few infections that develop later. Specific sensitization and allergy account for the occurrence and nature of subsequent acute and chronic tuberculosis. A step to eradicate tuberculosis is to prevent or postpone the initial infection throughout life for all persons.

An epidemic of a viral respiratory tract infection apparently impaired resistance and favoured an outbreak of tuberculosis involving 82 Eskimos. About 50 per cent of school children had active disease. Phlyctenular keratoconjunctivitis among Eskimos usually is caused by tubercle bacilli and can be prevented by the use of isoniazid.

A small epidemic occurred among 153 Negro school children, 25 of whom were previously nonreactive to tuberculin, but later reacted positively. Another outbreak involved 27 medical students and hospital personnel in a 2-year period. The source was undetected.

In aged persons, the supposed first tuberculosis infection often is a reactivation of previously unrecognized disease rather than a reinfection or a primary infection. The Ghon...
Tuberculosis persists as a hazard to public health. In the United States, an estimated 50,000 new cases and 9,000 deaths occur annually. About 75 per cent of new infections develop in 35 million tuberculin-positive persons, especially among the poor classes, the aged, and the chronically ill. Persons with arrested tuberculosis should be given 300 mg. of isoniazid daily for a year or two. The indications for prophylactic treatment were outlined. On the other hand, prophylaxis with isoniazid was not so successful as previously reported. In Japan, among 1,000 persons who were treated, eight were infected as compared with 11 who received a placebo.

Among 365 men treated for tuberculosis meningitis, the death-rate diminished from 70 per cent to 20 per cent between 1946 and 1958 after isoniazid was used for treatment. Residual effects ensued in 25 per cent and more often in Negros.

During a year's survey, the increase of primary resistance in strains of Myco tuberculosis to streptomycin rose from 3.1% to 5.6%; to para-aminosalicylic acid, from 2.9% to 6.8%; and to isoniazid from 3.9% to 7.8%. Among 196 strains of "atypical" tubercle bacilli, one was sensitive to isoniazid, one to para-aminosalicylic acid and 64 to streptomycin.

"Atypical" Tubercle Bacilli. In Australia, 460 patients shed atypical mycobacteria, but they caused pulmonic or lymph node infections in only 78. Antimicrobial drugs were of little value in therapy. Mycobacterium kansasii (group 1 atypical mycobacteria) caused genual arthritis. Excision of infected tissue and isoniazid therapy were curative. Myco. kansasii caused a granulomatous dermal lesion that has persisted for 22 years. Therapy with streptomycin was partially successful. A nonphotochromogenic mycobacterium caused disseminated infection.

In my laboratory, a strain of Myco. tuberculosis, after prolonged cultivation, gave rise to variant forms, some of which had the characteristics of so-called atypical tubercle bacilli. Question had been raised as to whether such strains were separate and distinct from the classic form or mutants thereof. Probably both views hold.

Victims of sarcoidosis seldom react to the tuberculin test, even after recovery from the disease. The lack of reactivity therefore is not a temporary state but may be a constitutional or an acquired anomaly related to the development of sarcoidosis.

Pasteurellosis. Six or more cases of bubonic plague and one death were diagnosed in Southwestern United States where sylvatic plague has always been endemic in rodents. A bacillus isolated from rabbits in Alaska at first was identified as Past. pestis, but proved to be Past. pseudotuberculosis. In 1932, I called attention to the similarity and possible relationship of the two bacilli just mentioned to Past. tularensis. Past. hemolytica, multicida and pneumotropica also are pathogenic for Man. Past. pseudotuberculosis was said to have caused erythema nodosum in seven children who were cured by antimicrobial therapy.

Cholera. All that is called cholera isn't cholera, as noted by many observers in the past. Other infections, including viral dysentery and malnutrition may cause similar loss of fluid from the enteric tract by altering vascular or epithelial permeability without demonstrable lesions in the mucosa. Lesions, probably toxic in nature, however, were present in the heart, bronchi, muscles, and parenchymatous organs in victims of cholera. Cholera is a unique disease. Vibrios do not enter the system and the cause of the huge losses of fluid is unexplained. Possibly, a circulating toxin released in the bowel wall affects the hypothalamus and results in an autonomic vascular disturbance of the epithelium.

Cholera-like disease in an endemic area of cholera was caused by a vibrio different from classic V. comma. Such microbes may be mistaken for paracolon bacilli. Infection induced the development of a specific agglutinin. The vibrios were not found in healthy persons. Non-vibrio cholera is usually milder than cholera, but differential diagnosis cannot be made clinically. In one study, no known pathogen was recovered from most victims with profuse watery diarrhea. The possibility of viral dysentery was not mentioned. It is probable that clinical cholera is a syndrome of multiple cause, including malnutrition.

El Tor vibrios, usually regarded as of low virulence, caused epidemics of severe cholera that began in Indonesia and later appeared in Iraq, Iran, Afghanistan and the Soviet Union. Undue panic and unnecessary travel restrictions ensued. Mass vaccination was applied even though vaccine is of doubtful value. Infection is not apt to spread further in regions of good sanitation. Persons infected in endemic areas
may, of course, travel elsewhere and sicken in remote places.

The value of anticholera vaccine is controversial, but a new vaccine was said to be effective. Cholera occurred in 6.1 per 1,000 of control victims, but in only 1.7 of vaccinees. Analysis of the symptoms in 325 cases showed that the course of cholera was not significantly altered by vaccination. The effectiveness of vaccine is weak and of short duration.

A single indigenous case of cholera occurred in the United States. None of the persons with whom the patient had had contact was infected. The patient "recovered soon after being placed on antibiotic therapy" (Post hoc, ergo propter hoc?). No antimicrobial has proved value in treatment. Two persons were accidentally infected in a research laboratory in Washington.

**Coccal Infections**

**Pneumonia.** In a group of families, 39 per cent of members were carriers of pneumococci. Types 3 and 19 predominated. Except Type 8, none of the usual types that cause lobar pneumonia was present. Necrotizing pneumonia caused by gram negative bacilli has increased in incidence chiefly in persons whose resistance was impaired and after the use of equipment for inhalation therapy, tracheostomy and tracheal catheters.

After years of disuse, transthoracic needle aspiration of the lung again was recommended to discover the cause of pneumonias underlying other severe disease. In several instances, sputum cultures were misleading. The aspirated material disclosed the pathogen and occasionally led to appropriate antimicrobial therapy.

**Hemolytic Streptococci.** During a six-year study of school children, the average annual carrier-rate was 8.8 per cent. In a low-income group, the rate averaged 19 per cent without seasonal variation. Nontypable Group A streptococci comprised about 83 per cent of strains. Streptococci cause impetigo half as often as staphylococci, but mixed infections probably are common. Serologic evidence of streptococcal infection was detected in 76 of 303 children with impetigo.

Among 1,125 children with acute pharyngitis, *Streptococcus* was present in 342, Types 12 and 4 accounted for 46 per cent. Four children with Type 4 infection had hematuria. Two had nephritis caused by Type 12.

**Rheumatic Fever.** As reported at a meeting, 785 children with non-exudative pharyngitis who had hemolytic streptococci usually of Group A in their throat were not treated with antimicrobics. There were no complications, no rheumatic fever nor nephritis. Among 82 patients averaging 17 years old, penicillin was given prophylactically and 79 others received placebo pills. There were no significant differences in the number of streptococcal infections or the number of rheumatic recurrences in either group. According to another study among 161 patients, one half who received penicillin daily for about two years had no fewer intercurrent streptococcal infections (22 per cent) than those who received a placebo. The attack rate for rheumatic recurrence was 0.7 per cent in the treated group and 1.4 per cent in the control subjects. Evidently, the value of prophylaxis is questionable. The decline in the incidence and severity of rheumatic fever may owe to a decrease in the virulence of Group A streptococci.

The results of a ten-year study of rheumatic fever were published in the *British Medical Journal* of Sept. 11, 1965, in the *Canadian Medical Association Journal* and in *Circulation*. Treatment with three regimens, namely ACTH, cortisone and aspirin gave similar results. The prognosis in patients without initial carditis was excellent, less so for those with carditis whose hearts were normal previously, and was poor for those with pre-existent cardiac injury. The status of the heart at the beginning of treatment, the rate of recurrences of rheumatic fever and the sex of the patient must be considered in the evaluation of any form of therapy. Rheumatic fever is clinically the same whether it occurs in tropical or temperate climates.

Contrary to some opinions, in adults, carditis may occur in the initial attack of rheumatic fever. Polyarthritis was present in 34 of 35 patients and carditis in eight. Chorea, nodules and erythema marginatum did not appear. Two patients died. As had been surmized, streptococci played no role in the occurrence of valvulitis after rheumatic fever begins. Therapy with penicillin during rheumatic fever had no influence on valvular involvement.

**Endocarditis.** The incidence and survival rate for bacterial endocarditis has not improved in 20 years despite the advances in antimicrobial therapy. There has been a relative decrease in the incidence of cardiac disease as an underlying cause and an increase in the number of cases in old persons with calcific and vascular disease. Nonhemolytic streptococci still are the...
chief causes, but the number of staphylococcal infections has increased. Surprisingly, the incidence of gram negative bacillary or mycotic infections did not increase. The over-all cure rate in one series of patients was 40 per cent for acute endocarditis and 87 per cent for subacute disease. A review of the records of 337 victims of subacute bacterial endocarditis observed between 1924 and 1963 disclosed that staphylococci have exceeded streptococci as causes. Post-cardiotomy infection is a new inciting factor and caused four per cent of cases. Congenital cardiac disease provided grounds for bacterial invasion in six per cent of patients in previous years and in 18 per cent now. The mortality rate had been 100 per cent, but between 1950 and 1963, 30 per cent. It was 51 per cent in a recent group largely as a result of cardiac failure or of unknown causes.

Endocarditis caused by Str. fecalis ensued in three patients after urologic manipulation. Endocarditis, inapparent for long periods, may be the source of infection of aneurysms of cerebral blood vessels.

Staphylococci. Staphylococci not conforming to the 22 known types caused serious outbreaks in a hospital. A newly classified strain caused infections chiefly in patients who had received broad spectrum antimicrobial drugs and in elderly and debilitated ones. The outbreak subsided when treatment with neomycin was restricted. Other epidemics in Australia and elsewhere may have been caused by a strain similar to the newly classified one. As had been shown before, in infants the deliberate application of nonpathogenic staphylococci blocked an epidemic caused by a pathogenic strain apparently by bacterial interference.

Coagulate-negative Staphylococcus albus caused wound infection in 53 of 1,200 patients. Recovery occurred without antimicrobial therapy. Five of 12 strains were sensitive to penicillin. Infection is especially serious in postcardiotomy and in debilitated patients.

Gonococcal Arthritis. Gonococcal arthritis seldom occurs in children, yet six cases, five of them in girls, were observed. Seventeen other children had gonococcosis. The source was unknown except for evidence of gonorrhea in the families of three patients. The infection with arthritis has increased in incidence in women and is easily mistaken for rheumatic fever. Pregnancy and menstruation seem to favour its development. Gonorrheal salpingitis, epididymitis, arthritis and sepsis have not decreased in incidence.

Urinary Tract Infection. Among 252 patients with chronic pyelonephritis, bacteriuria ceased in 80 per cent during therapy, but only one-third remained free of infection for three years. Relapses were caused by the same microbe or by reinfection with another. Hypertension, renal failure, and structural anomalies were predisposing factors. Combinations of antimicrobics were less effective therapeutically than single agents. Recurrences responded to treatment as well as the initial infection. Sulfonamides were the least effective drugs. While preimmunization protected against experimental infection, it failed when there was uropathy. Immunity apparently played little role in recovery, but may determine the kind of microbes that cause reinfection. Many infections of the urinary tract become chronic when the causative microbes are not eradicated, despite the introduction of antimicrobial agents. Because bacterial protoplasts resist therapy and survive in infected kidneys, perhaps the old procedure of "forcing" fluids to reduce medullary hypertonicity still has value in therapy. Revised concepts of urinary tract infection in children and its management were reviewed by Allen.

Premature births occurred in 13 per cent of women with renal infection as compared with five per cent in its absence. Among 4,000 women in early pregnancy, six per cent had bacteriuria that often persisted for six months after delivery. Antimicrobial therapy reduced the incidence of pyelonephritis to two of 72 patients as compared with one-third who received a placebo. Among 111 women who had bacteriuria during pregnancy, the condition persisted in 90. Pyelographic abnormalities were present in 61 of 131. Evidently, asymptomatic bacteriuria often persists and may indicate active renal infection. The tetrazolium test was said to be of value as a screening procedure to discover significant bacteriuria in healthy persons, but not as a substitute for bacteriologic examination.

In another study, 4.5 per cent of 481 gravid women had bacteriuria, only six of whom had not had bacteriuria previously. It was present most often in those more than 30 years old, in multiparas and in Negresses. All but a few cases of post-partum infection occurred in patients who had been infected before delivery or who had been catheterized. The infection rate is not surprising since some degree of hydronephrosis occurs temporarily in almost all gravid women. Suprapubic puncture of
the bladder, a procedure that had been discarded, was useful in detecting bacteriuria in women whose urine may be contaminated by infective vaginal discharges. Bladder urine often was sterile when bacteria were present in midstream specimens of urine\textsuperscript{221}. L-forms or protoplasts, as variant forms of bacteria, were detected in the urine of 19 per cent of patients with chronic urinary tract infection. Those forms may revert to the parent strain during antimicrobic therapy and may account for persistent infection\textsuperscript{222}. Syphilis. The incidence of syphilis continues to increase in the United States. Last year nearly 23,000 infectious patients were reported, the highest number since 1950. The inclusion of many unreported cases no doubt would raise the figure. Seventeen per cent of cases were in teen-aged persons. The incidence of late and late latent infection has decreased steadily.

With the assistance of health officials, a physician traced the spread of syphilis from a patient to 45 others in widely scattered places. The chain of infection involved 365 persons during five months. The attack rate in one city was 346 per 100,000 population, which is seven times the usual incidence\textsuperscript{223}. A syphilitic mother transmitted infection to her offspring for nine years. Of her eight children, five had congenital disease and the last child was unaffected. With each succeeding pregnancy, the effect on the fetus was less severe\textsuperscript{224}. The efficacy of penicillin as a therapeutic agent has been questioned. Treponemases persisted in patients treated for late syphilis, but the possibility of re-infection was not eliminated\textsuperscript{225}.

Histoplasmosis. In a 17-month period, 42 persons in South Carolina had erythema multiforme, erythema nodosum or both, probably caused by \textit{H. capsulatum}. A few had abnormal sialographic shadows in the lungs. Most infections occurred near a golf-course under construction from which the spores of the fungus were spread by air\textsuperscript{226}. Destruction of a starling roost caused an epidemic of histoplasmosis. Twenty-eight patients were detected, two died and 29 per cent of children in the community reacted to the histoplasmin test\textsuperscript{227}. Two men acquired histoplasmosis by digging around a bat-infested tree stump. \textit{H. capsulatum} was isolated from three bats and from the soil\textsuperscript{228}. The fungus also was present in bats in Panama\textsuperscript{229}. Evidently, \textit{H. capsulatum} is in the bat's gut, is shed in feces and enters the soil. This may apply to poultry and to other birds as well. Mediastinal involvement caused dysphagia in three patients\textsuperscript{230}. In Montreal, histoplasmosis was transferred from a donor to the recipient of a renal homograft. This is the first reported example of person-to-person transmission of histoplasmosis\textsuperscript{231}. Coccidioidomycosis transmitted in a plaster cast was referred to in the 1965 Review of Infections.

Infective Agents and Neoplasia

As studies progress, the problem becomes more and more complex. An unsolved question is why viruses can be related to oncogenesis in animals, but not conclusively in man\textsuperscript{232}?

Mycoplasmas were isolated from benign tumours in children\textsuperscript{233} and were detected in 19 of 35 patients with lymphomas\textsuperscript{234, 235}. They may be commensals without pathogenicity\textsuperscript{236}. Similarly toxoplasmas have been suspected as causes of neoplasms and evidence of their presence was demonstrated in 71 of 126 patients\textsuperscript{237}. Bacteria of the tribe \textit{Mimae}, formerly known as the Morax-Axenfeld bacillus and by a variety of other names, usually are opportunistic invaders. In one study they were isolated from 65 patients with neoplastic disease. Infections often followed the use of intravascular catheters\textsuperscript{238}. Lymphocytic choriomeningitis virus that contaminates tumours in hamsters is a source of misleading conclusions. The virus also may infect laboratory personnel\textsuperscript{239}. Newcastle disease virus apparently is oncolytic or antineoplastic\textsuperscript{240}.

Miscellaneous

\textit{Pneumocystis carinii} caused pneumonia usually discovered by sphiography in 12 victims of neoplasms\textsuperscript{241}. The infection occurs chiefly in persons debilitated by other conditions, but two healthy persons in a family were infected by contact with another member who died from leukemia and cariniosis\textsuperscript{242}. Therapy with pentamidine isothionate was thought to be curative in a hypogammaglobulinemic child\textsuperscript{243}. Toxoplasma caused lymphadenitis in six otherwise healthy persons. Infection can be recognized by isolating the microbe and proving its activity by serologic tests. Persistent lymphadenitis is the commonest form of acquired infection\textsuperscript{244}. Fourteen per cent of 2,080 recruits had specific antibody in their blood\textsuperscript{245}. Toxoplasmic myocarditis and ventricular fibrillation were fatal in a leukemic patient\textsuperscript{246}.

Septicemia with varieties of bacteria occurred in 52 of 420 leukemic patients chiefly with bacilli and candida. All but four died\textsuperscript{247}.
of leukemia also are subject to infection with the cytomegalic inclusion virus. Diagnosis usually is made postmortem. There is no effective therapy\textsuperscript{248}.

Infectious diseases usually are caused by a single bacterium. In a 10-year review of blood cultures from 633 patients, several bacteria were present in 52 (7.8 per cent). Most of the patients were debilitated. \textit{Esch. coli}, \textit{Staph. aureus}, \textit{Ps. aeruginosa}, \textit{Proteus}, \textit{Klebsiella}, \textit{Str. fecalis}, and anaerobic streptococci were chiefly involved in combinations or in succession. During antimicrobial therapy, one bacterium may be controlled, but a different resistant one may become invasive\textsuperscript{249}.

During a 3-week period, an unusual outbreak of pneumonia was fatal for 12 of 80 adult patients in a psychiatric hospital. Several staff members were also affected. The cause was not known. Klebsiella was suspected, but these usually are secondary opportunistic invaders and infection rarely is contagious\textsuperscript{250}. \textit{Acanthamoeba} apparently caused four rapidly fatal cases of pyogenic meningitis in Australia. Infection may have occurred by the olfactory route\textsuperscript{251}.

Among 315 persons in Montana, about 50 per cent were inapparently infected with Q fever. No overt illness was observed in the enzootic region\textsuperscript{252}. The incidence of Rocky Mountain spotted fever is increasing in the south-eastern United States, probably because of conditions favourable for ticks and infected animals on abandoned farms. The actual incidence of the disease no doubt is greater than the number of recognized and reported cases\textsuperscript{253}. An unusual outbreak of typhus affected more than 26 children in eastern Switzerland\textsuperscript{254}.

Trichinellosis has decreased from about 18 per cent to less than four per cent in the United States because of better feeding of swine and the modern processing of pork\textsuperscript{255}. Thiabendazole given to pigs tended to destroy the larvae\textsuperscript{256}.

A review of the history and new developments in the United States about leptospirosis and an analysis of 483 cases appeared in the October 14 and 21 issues of the New England Journal of Medicine. Infection with \textit{L. pomona} often is mistaken for other diseases, Agglutination tests of 29,000 samples of serum gave positive results in 0.5 per cent. Persons exposed to contaminated water, livestock handlers and meat processors chiefly are at risk\textsuperscript{257}.

Studies were made over a long period on technicians employed in microbiologic laboratories who had been immunized with a variety of vaccines and antitoxins. Among 76 persons, no illness attributable to the procedures were discovered, but 19 had abnormal blood-globulins and other elements. Since 1902 it was known that long-continued immunization of horses often resulted in hyperglobulinemia and amyloidosis. Similar increases of globulins also induce amyloidosis in immunized persons. In the technicians studied, there was no evidence of amyloidosis, probably because of the small amounts of antigens injected and their wide temporal spacing\textsuperscript{258}.

Three reports should eliminate much unnecessary therapy for trivial disorders. Treatment with tetracyclines had no effect on acne. Placebos occasionally seemed to hasten healing\textsuperscript{259}. Bacteriophage-lysed vaccine failed to influence staphylococcal furunculosis\textsuperscript{260}. Bacterial-vaccine therapy was less effective than placebos in reducing the incidence of wheezing, infections, and infectious episodes in patients with "infectious" asthma\textsuperscript{261}. Questions still remain whether or not the bacteria are present as normal flora, and whether asthma is caused by allergy to bacteria.

Remains of bacteria two billion years old were visualized by electron microscopy in rocks from Ontario\textsuperscript{62}. Fossils of algae were present in pre cambrian limestone in Australia\textsuperscript{263}. Contaminant bacteria also were cultivated from meteorites\textsuperscript{264} and from coal\textsuperscript{265}. The problem was discussed critically by Urey\textsuperscript{266}.

The threat of using biological weapons for warfare received further attention,\textsuperscript{267} but one wonders what microbe could be disseminated successfully against an enemy, and which would not harm an aggressor as well. Nevertheless, the danger must be anticipated even though preimmunization is impracticable and there are no vaccines or other preventive measures against many infections.

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