Annual Review

INFECTIOUS 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 as effective 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 outlined^{7a}. 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 patients⁷. The drug has no particular advantage over other agents⁸. 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 resistance⁹. 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*, *Ancylostoma*, *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 infections¹⁸. 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 fever¹⁹. 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 nephritis²⁰.

Antimicrobial agents are of no value for prophylaxis against bacterial invasion during acute viral respiratory tract infections^{21, 22} nor in unconscious patients²³. As examples of unnecessary prophylaxis and therapy, "vigorous" antimicrobial therapy was applied in a patient with esophageal stricture caused by an escharotic²⁴ and in a patient with massive epistaxis. Prophylactically administered agents rarely prevent bacterial superinvasion, and that which does occur may be even more difficult to treat²². 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 flora²⁵.

A protracted outbreak of multiple drug-resistant *Salmonella edinburgh* infection among infants was ascribed to previous unwise routine use of antimicrobics²⁶. Strains of staphylococci have become resistant to neomycin and bacitracin. These antimicrobics when used topically may induce microbial resistance²⁷.

Penicillin remains the drug of choice for pneumococcoses. If the patient is sensitive thereto, erythromycin is indicated. Cephaloridine, ampicillin, nafcillin, oxacillin, cephalothin, cloxacillin and tetracycline also are effective in that order²⁸. The method of treatment of staphylococcosis was outlined in detail by Finland²⁹. 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 least³⁰. 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 resistance³¹. 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 microbial sensitivity. The reported results may be misleading or erroneous especially from an over-burdened laboratory³² 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 agents³³.

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 sprue³⁴.

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 erythrocytes³⁵. Penicillin and its homologues caused nephropathy^{35a}. Anaphylactoid shock after oral therapy resulted in severe neurologic residua³⁶. After therapy for three months, oxacillin depressed the marrow and caused hepatic dysfunction³⁷. 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 stopped³⁸. Chloramphenicol caused optic atrophy³⁹. Tetracycline rarely causes anaphylaxis, but did so in a patient who

was hypersensitive to penicillin⁴⁰. Tetracycline therapy also may incite candidiasis, photosensitivity, discolouration of teeth, and if decomposed, may cause severe toxicity. Deteriorated tetracycline caused severe nephropathy⁴¹ and nephrogenic diabetes insipidus⁴². 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 penicillin⁴³. Colistimethate caused respiratory depression and muscular weakness⁴⁴. Orally administered neomycin was the probable cause of audio- and nephrotoxicity⁴⁵. As a result of topical application, 26 per cent of 1,538 patients were found to be sensitized to neomycin^{45a}. Question was raised if antimicrobial therapy during early pregnancy in 85 women caused 12 malformed infants and 13 abortions⁴⁶. Among 26 victims of systemic vasculitis, antimicrobial drugs were the cause in 16⁴⁷. Long-acting sulfonamide drugs probably caused 116 cases of the Stevens-Johnson syndrome (mucocutaneous fever)^{47a}.

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 enough⁴⁸. For the 1965-66 season, another recently isolated A₂ strain will be added to A, A₁, A₂ and B strains now used⁴⁹. 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 virus⁵⁰.

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 infection⁵¹.

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 infections⁵². 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 inapparent⁵³. 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 died⁵⁴.

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 illness⁵⁵. 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 pneumonia⁵⁶. Volunteers inoculated with one rhinovirus were inoculated with another strain two to 16 weeks later. Those reinoculated two weeks later with either virus were not ill. Evidently protection was afforded by both the homologous and heterologous infection, but not after 16 weeks⁵⁷. 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 homologous one, but not against others. Immunity lasted 12 to 18 months. Mineral oil or other adjuvants failed to increase immunogenicity⁵⁸. Interferon failed to have a protective effect when given to volunteers infected with rhinovirus, Coxsackie A₂₁ and parainfluenza 1 viruses⁵⁹.

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 cent⁶⁰. 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 rapidly⁶¹. One

wonders how bronchiolitis can be distinguished clinically from pneumonia. In Finland, RS virus caused 15 per cent of acute infections in children⁶². 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 antibody⁶³ 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 hours⁶⁴.

Coxsackie Viruses. Coxsackie B₃ virus caused an epidemic in a nursery in the summer. Infections varied from inapparent ones to brief illness with fever, enanthem, rhinorrhea and pharyngitis⁶⁵. A₂₆ 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 A₂₁ virus administered by aerosolization to volunteers resulted in a mild, febrile respiratory tract infection⁶⁷. Two strains of Coxsackie A₂₁ virus inhaled by volunteers caused febrile bronchitis and two of 16 had pneumonia. One strain of virus caused febrile disease of the upper respiratory tract⁶⁸. In an outbreak of infectious hepatitis, A₁₀ virus was present in 45 samples of feces and in the blood of four patients⁶⁹. It may have been a secondary invader or present as a commensal. Coxsackie A and B viruses were suspected as causes of congenital cardiovascular defects⁷⁰.

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 128⁷¹. 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. Pathogenic bacteria were present as often in pneumonic patients as in healthy children. *H. influenzae* was not implicated. Staphylococci were the chief hazard⁷².

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 are⁷³. Gsell reviewed and sum-

marized knowledge of viral and other non-bacterial "atypical" pneumonias⁷⁴.

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 involvement⁷⁵. Various *Mycoplasmas* inhabit the body including *M. hominis*, *M. pneumoniae*, *M. orale* and *M. salivarium*. Volunteers who inhaled *M. hominis* Type 1 developed a febrile pharyngitis⁷⁶.

Eleven per cent of 614 respiratory tract infections in Prague were caused by *M. pneumoniae* especially in older children and young adults⁷⁷. *M. pneumoniae* was isolated from the inflamed ear of a child with a mild respiratory tract infection⁷⁸. Infection involved only three children in an institution, one of whom had pneumonia⁷⁹. 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 41⁸⁰. 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 vaccinees⁸¹. Hamsters developed pneumonitis after intrasal inoculation of *M. pneumoniae*. The microbes superficially located on the bronchial epithelial cells were visualized by applying special techniques⁸².

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 antiquity⁸³. 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,

enteric viruses may favour bacterial intestinal infection, and suggestion was made that Coxsackie B viral infections may incite acute appendicitis⁸⁴. Cytomegalovirus may cause disease resembling infectious mononucleosis wherein the heterophile test gives a negative result⁸⁵. 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 area⁸⁶.

Viruses are multitropic. After vaccination, vaccinia virus caused unilateral genua arthritides⁸⁷. 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 helpful⁸⁸.

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 exposure⁸⁹. A viral inhibiting factor similar to interferon appeared in the blood of 17 of 18 children six to 11 days after vaccination⁹⁰. Particles resembling papova viruses were visualized by electronmicroscopy in nuclei of demyelinated neural cells⁹¹.

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 gestation⁹². 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 present⁹³. 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 pregnancy⁹⁴. Virus persisted as long as 77 days after the rash^{95, 96}. 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 influenced⁹⁷. Apparently steroids did not worsen a viral disease.

Three of six children with rubella encephalopathy died⁹⁴. 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 disease⁹². Serologic evidence suggested that Coxsackie B₁ virus infection of mothers may be another cause of congenital defects⁹⁸.

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 undetected⁹⁹. 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 died¹⁰⁰. Inapparent infections were a major source of infection of others and these occurred in a ratio of 39 to one case of overt disease¹⁰¹. A detailed description of an epidemic was published¹⁰². In 1964, eight per cent of the population and 29 per cent of "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 epidemic¹⁰³.

More epidemics of arthropod-borne encephalitis may be expected. The urbanization of populations and its attendant faults of sanitation favour the breeding of mosquitos 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 Florida¹⁰⁴. 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 Scotland¹⁰⁵. ECHO 25 virus was the chief cause of another outbreak of encephalitis¹⁰⁶. A.

caused a small outbreak of polio-like paralysis also in Scotland in 1959, and 15 infections in 1963¹⁰⁷. 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 patients¹⁰⁸.

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^{108a}. 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 days¹⁰⁹. In one victim, hysteria was suspected because physicians were not informed of a cat-bite three months previously¹¹⁰. A generalized reaction to antirabies serum affected 16 per cent in adults¹¹⁰. Fatal post-vaccinal encephalomyelitis occurred in 18 of 65 persons vaccinated with an antirabies vaccine. "Fixed" virus was isolated from the vaccine¹¹². 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 vaccination¹¹³. 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 proposed¹¹³. A sterile inflammatory flare-up may appear at the site of vaccination years afterward¹¹⁴.

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 varicella¹¹⁵.

Because there is no evidence that antismallpox vaccination has any effect on recurrent

herpes simplex, it should not be used for its treatment¹¹⁶.

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 canal¹¹⁷ and develop necrotizing encephalitis and retinopathy¹¹⁸. The virus caused encephalitis in 52 patients in a 3-year period. In three, it was preceded by labial lesions¹¹⁹. A herpes-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 man¹²⁰. 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 subjects¹²¹. The viruses of herpes simplex, zoster and varicella are related as disclosed by cross reaction, neutralization and complement fixation tests¹²².

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 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 disease¹²³. Hepatitis in aged patients often is mistaken for evidence of cancer or other disease. Six of 23 patients died and four others had progressive disease¹²⁴.

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* often was typhoidal, and with *S. cholerae-suis* it often was septicemic¹³⁷. 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 diarrheas¹⁴⁰. Among 112 children during three years, those less than six months old were chiefly affected. Diarrhea 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 money¹⁴³. Shigellas rarely are found in the blood stream. In three children with shigellar dysentery, sepsis was caused by *Esch. coli* and *Aerobacter*. Malnutrition often provides opportunity for the invasion of nonpathogenic commensal bacilli¹⁴⁴. 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 patients¹⁴⁵.

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 toxins¹⁴⁶. *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 microvilli¹⁴⁷. Studies in tissue culture disclosed mycoplasmas stuck to cytoplasmic surfaces, their penetration of cells, and areas of necrosis¹⁴⁸. 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 immunity¹⁴⁹.

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 Oregon¹⁵⁰.

An antianthrax vaccine is available for distribution¹⁵¹. 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 environment¹⁵².

Listeria monocytogenes was reported as the cause of an aortic aneurism in an aged diabetic woman¹⁵³. 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 culture¹⁵⁴. Leprosy became overt in a soldier who had left New Caledonia 20 years ago¹⁵⁵.

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 desirable¹⁵⁶. Six victims of tetanus recovered after therapy with 3,000 to 5,000 international units of human tetanus hyperimmune globulin¹⁵⁷. 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 penicillin¹⁵⁸. Toxins derived from nine strains of *Cl. tetani* were the same. Evidently, a specific neurotoxin is shared by all strains¹⁵⁹.

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 persons¹⁶⁰.

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 disease¹⁶¹. Phlyctenular keratoconjunctivitis among Eskimos usually is caused by tubercle bacilli and can be prevented by the use of isoniazid¹⁶².

A small epidemic occurred among 153 Negro school children, 25 of whom were previously nonreactive to tuberculin, but later reacted positively¹⁶³. Another outbreak involved 27 medical students and hospital personnel in a 2-year period. The source was undetected¹⁶⁴.

In aged persons, the supposed first tuberculous infection often is a reactivation of previously unrecognized disease rather than a reinfection or a primary infection. The Ghon

complex was present in 72 per cent of 66 aged patients¹⁶⁵.

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 ill¹⁶⁶. Persons with arrested tuberculosis should be given 300 mg. of isoniazid daily for a year or two¹⁶⁷. The indications for prophylactic treatment were outlined¹⁶⁸. 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 placebo¹⁶⁹.

Among 365 men treated for tuberculous 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 Negroes¹⁷⁰.

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 streptomycin¹⁷¹.

"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 therapy¹⁷². *Mycobacterium kansasii* (group 1 atypical mycobacteria) caused genual arthritis. Excision of infected tissue and isoniazid therapy were curative¹⁷³. *Myco. kansasii* caused a granulomatous dermal lesion that has persisted for 22 years. Therapy with streptomycin was partially successful¹⁷⁴. A nonphotochromogenic mycobacterium caused disseminated infection^{174a}.

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 bacilli¹⁷⁵. Question had been raised as to whether such strains were separate and distinct from the classic form or mutants thereof. Probably both views hold¹⁷⁶.

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 sarcoidosis¹⁷⁷.

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 rodents¹⁷⁸. A bacillus isolated from rabbits in Alaska at first was identified as *Past. pestis*, but proved to be *Past. pseudotuberculosis*¹⁷⁹. In 1932, I called attention to the similarity and possible relationship of the two bacilli just mentioned to *Past. tularensis*¹⁸⁰. *Past. hemolytica*, *multicida* and *pneumotropica* also are pathogenic for Man¹⁸¹. *Past. pseudotuberculosis* was said to have caused erythema nodosum in seven children who were cured by antimicrobial therapy¹⁸².

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 cholera¹⁸³. 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 persons¹⁸⁴. 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 diarrhea¹⁸⁵. 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 Union¹⁸⁶. 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 vaccinees¹⁸⁷. Analysis of the symptoms in 325 cases showed that the course of cholera was not significantly altered by vaccination¹⁸⁸. The effectiveness of vaccine is weak and of short duration¹⁸⁹.

A single indigenous case of cholera occurred in the United States. None of the persons with whom the patient had had contact was infected¹⁹⁰. 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 present¹⁹¹. 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 catheters¹⁹².

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 therapy¹⁹³.

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 strains¹⁹⁴. 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 impetigo¹⁹⁵.

Among 1,125 children with acute pharyngitis, *Str. hemolyticus* 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 12¹⁹⁶.

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 group¹⁹⁷. 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 subjects¹⁹⁸. 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 climates¹⁹⁹.

Contrary to some opinions, in adults, carditis may occur in the initial attack of rheumatic fever. Polyarthritides was present in 34 of 35 patients and carditis in eight. Chorea, nodules and erythema marginatum did not appear. Two patients died²⁰⁰. 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 involvement²⁰¹.

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 increase²⁰². 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 causes²⁰³.

Endocarditis caused by *Str. fecalis* ensued in three patients after urologic manipulation²⁰⁴. Endocarditis, inapparent for long periods, may be the source of infection of aneurisms of cerebral blood vessels²⁰⁵.

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 restricted²⁰⁶. Other epidemics in Australia and elsewhere may have been caused by a strain similar to the newly classified one²⁰⁷. As had been shown before, in infants the deliberate application of nonpathogenic staphylococci blocked an epidemic caused by a pathogenic strain apparently by bacterial interference²⁰⁸.

Coagulase-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 patients²⁰⁹.

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 patients²¹⁰. The infection with arthritis has increased in incidence in women and is easily mistaken for rheumatic fever. Pregnancy and menstruation seem to favour its development²¹¹. Gonorrheal salpingitis, epididymitis, arthritis and sepsis have not decreased in incidence²¹².

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 factors²¹³. 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 reinfection²¹⁵. 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 therapy²¹⁶. Revised concepts of urinary tract infection in children and its management were reviewed by Allen²¹⁷.

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 infection²¹⁸. 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 examination²¹⁹.

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 Negroes. All but a few cases of post-partum infection occurred in patients who had been infected before delivery or who had been catheterized²²⁰. 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 urine²²¹.

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 antimicrobial therapy and may account for persistent infection²²².

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 incidence²²³. 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 severe²²⁴.

The efficacy of penicillin as a therapeutic agent has been questioned. Treponemes persisted in patients treated for late syphilis, but the possibility of re-infection was not eliminated²²⁵.

Histoplasmosis. In a 17-month period, 42 persons in South Carolina had erythema multiforme, erythema nodosum or both, probably caused by *H. capsulatum*. A few had abnormal skiagraphic shadows in the lungs. Most infections occurred near a golf-course under construction from which the spores of the fungus were spread by air²²⁶. 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 test²²⁷. Two men acquired histoplasmosis by digging around a bat-infested tree stump. *H. capsulatum* was isolated from three bats and from the soil²²⁸. The fungus also was present in bats in Panama²²⁹. Evidently, *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 patients²³⁰. 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 histoplasmosis²³¹. 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 man²³²?

Mycoplasmas were isolated from benign tumours in children²³³ and were detected in 19 of 35 patients with lymphomas^{234, 235}. They may be commensals without pathogenicity²³⁶. Similarly toxoplasmas have been suspected as causes of neoplasms and evidence of their presence was demonstrated in 71 of 126 patients²³⁷. Bacteria of the tribe *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 catheters²³⁸. Lymphocytic choriomeningitis virus that contaminates tumours in hamsters is a source of misleading conclusions. The virus also may infect laboratory personnel²³⁹. Newcastle disease virus apparently is oncolytic or antineoplastic²⁴⁰.

Miscellaneous

Pneumocystis carinii caused pneumonia usually discovered by skiagraphy in 12 victims of neoplasms²⁴¹. 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 cariniosis²⁴². Therapy with pentamidine isothionate was thought to be curative in a hypogammaglobulinemic child²⁴³.

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 infection²⁴⁴. Fourteen per cent of 2,080 recruits had specific antibody in their blood²⁴⁵. Toxoplasmic myocarditis and ventricular fibrillation were fatal in a leukemic patient²⁴⁶.

Septicemia with varieties of bacteria occurred in 52 of 420 leukemic patients chiefly with bacilli and candida. All but four died²⁴⁷. Victims

of leukemia also are subject to infection with the cytomegalic inclusion virus. Diagnosis usually is made postmortem. There is no effective therapy²⁴⁸.

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. *Esch. coli*, *Staph. aureus*, *Ps. aeruginosa*, *Proteus*, *Klebsiella*, *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 invasive²⁴⁹.

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 contagious²⁵⁰. *Acanthamoeba* apparently caused four rapidly fatal cases of pyogenic meningitis in Australia. Infection may have occurred by the olfactory route²⁵¹.

Among 315 persons in Montana, about 50 per cent were inapparently infected with Q fever. No overt illness was observed in the enzootic region²⁵². 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 cases²⁵³. An unusual outbreak of typhus affected more than 26 children in eastern Switzerland²⁵⁴.

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 pork²⁵⁵. Thiabendazole given to pigs tended to destroy the larvae²⁵⁶.

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 *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 risk²⁵⁷.

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 spacing²⁵⁸.

Three reports should eliminate much unnecessary therapy for trivial disorders. Treatment with tetracyclines had no effect on acne. Placebos occasionally seemed to hasten healing²⁵⁹. Bacteriophage-lysed vaccine failed to influence staphylococcal furunculosis²⁶⁰. Bacterial-vaccine therapy was less effective than placebos in reducing the incidence of wheezing, infections, and infectious episodes in patients with "infectious" asthma²⁶¹. 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 Ontario⁶². Fossils of algae were present in precambrian limestone in Australia²⁶³. Contaminant bacteria also were cultivated from meteorites²⁶⁴ and from coal²⁶⁵. The problem was discussed critically by Urey²⁶⁶.

The threat of using biological weapons for warfare received further attention,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.

REFERENCES

1. EICKHOFF, T. C., KISLAK, J. W., and FINLAND, M. (1965): Clinical Evaluation of Nafcillin in Patients with Severe Staphylococcal Disease, *New Engl. J. Med.*, **272**, 699.
2. KISLAK, J. W., EICKHOFF, T. C., and FINLAND, M. (1965): Cloxacillin: Activity in Vitro and Absorption and Urinary Excretion in Normal Young Men, *Amer. J. med. Sci.*, **249**, 636.
3. NYDAL, B. C., and HALL, W. H. (1965): The Treatment of Staphylococcal Infection with Nafcillin with a Discussion of Staphylococcal Nephritis, *Ann. intern. Med.*, **63**, 27.
4. MANDRIQUEZ, L., et al. (1965): Clinical Trials with Ampicillin in Typhoid Fever and Paratyphoid A, *Brit. med. J.*, **ii**, 152.
5. PROTIVINSKY, R. (1965): Chemotherapy of Chronic Bronchitis: Experiences with Ampicillin, *Münch. med. Wschr.*, **107**, 1950.

6. Ampicillin Seen as Choice Initial Meningitis Drug, (1965): *Antibiot. News*, **2**, 5.
- 6a. PETERSDORF, R. G., and TURK, M. (1966): The New Penicillins and Their Proper Use, *Ann. intern. Med.*, **64**, 207.
7. TURK, M., et al. (1965): Laboratory and Clinical Evaluation of a New Antibiotic—Cephalothin, *Ann. intern. Med.*, **63**, 199.
8. Evaluation of a New Antibiotic: Sodium Cephalothin (Keflin), (1965): Council on Drugs, *J. Amer. med. Ass.*, **194**, 182.
9. BENNER, E. J., et al. (1965): Natural and Acquired Resistance of *Klebsiella-Aerobacter* to Cephalothin and Cephaloridine, *Proc. Soc. exp. Biol. (N.Y.)*, **119**, 536.
10. GOTOFF, S. P., and LEPPER, M. H. (1965): Treatment of Salmonella Carriers with Colistin Sulfate, *Amer. J. med. Sci.*, **249**, 399.
11. A New Antibiotic. Lincocycin (Lincocin) (1965): Council of Drugs, *J. Amer. med. Ass.*, **194**, 545.
12. JACKSON, H., et al. (1965): Group A β -Hemolytic Streptococcal Pharyngitis—Result of Treatment with Lincocycin, *J. Amer. med. Ass.*, **194**, 1189.
13. A New Bacterial Agent for Infections of the Genitourinary Tract. Nalidixic Acid (Neg Gram), Council on Drugs, (1965): *J. Amer. med. Ass.*, **192**, 628. OKUN, H., and HARLIN, H. C. (1965): Study of Nalidixic Acid; *Invest. Urol.*, **2**, 409.
14. MOST, H., et al. (1965): The Treatment of Strongyloides and Enterobius Infections with Thiabendazole, *Amer. J. Trop. Med. Hyg.*, **14**, 379. FRANZ, K. H., SCHNEIDER, W. J., and POHLMAN, M. H. (1965): Clinical Trials with Thiabendazole Against Intestinal Nematodes Infecting Humans, *ibid.*, **14**, 383.
15. BOTERO, D. (1965): Treatment of Human Intestinal Helminthiasis with Thiabendazole, *Amer. J. trop. Med. Hyg.*, **14**, 618.
16. Borrelidin and Vivomycin, Annot. (1965): *Lancet*, **i**, 1152.
17. CHAVARRIA, A. P., KOTCHER, E., and LIZANO, C. (1965): Preliminary Evaluation of Cycloguanil Pamoate in Dermal Leishmaniasis, *J. Amer. med. Ass.*, **194**, 1142.
18. CAMPBELL, P. C. (1965): Large Doses of Penicillin in the Prevention of Surgical Wound Infections, *Lancet*, **ii**, 805.
19. FRANK, P. F., STOLLERMAN, G. H., and MILLER, L. F. (1965): Protection of a Military Population from Rheumatic Fever. Routine Administration of Benzathine Penicillin G to Healthy Individuals, *J. Amer. med. Ass.*, **193**, 775.
20. PERLMAN, L. V., et al. (1965): Poststreptococcal Glomerulonephritis. A Ten-Year Follow-Up of an Epidemic, *J. Amer. med. Ass.*, **194**, 63.
21. DAVIS, S. D., and WEDGWOOD, R. J. (1965): Antibiotic Prophylaxis in Acute Viral Respiratory Diseases, *Amer. J. dis. Child.*, **109**, 544.
22. Antibiotic Sugar Pills. (1965): Editorial, *New Engl. J. Med.*, **273**, 825.
23. MACKINTOSH, T. B., and MATTHEW, H. (1965): Do Unconscious Poisoned Patients Need Prophylactic Penicillin? *Curr. med. Dig.*, **32**, 881.
24. DANZIG, L. S., and LOEBEL, A. S. (1965): Clintest-Tablet Ingestion and Stricture of the Esophagus, *J. Amer. med. Ass.*, **192**, 1092.
25. FARRAR, W. E., and KENT, J. H. (1965): Enteritis and Coliform Bacteria in Guinea Pigs Given Penicillin, *Amer. J. Path.*, **47**, 629.
26. HIRSCH, W., et al. (1965): Salmonella Edinburgh Infection in Children, *Lancet*, **ii**, 828.
27. Staphylococci Resistant to Neomycin and Bacitracin, Lead. Art. (1965): *Lancet*, **ii**, 421.
28. KISLAK, J. W., et al. (1965): Susceptibility of *Pneumococcus* to Nine Antibiotics, *Amer. J. med. Sci.*, **250**, 264.
29. FINLAND, M. (1965): Staphylococcal Infections and Antistaphylococcal Antibiotics, *Med. Tms. (N.Y.)*, **93**, 101 (Feb.).
30. EICKHOFF, T. C., and FINLAND, M. (1965): In Vitro Susceptibility of Group A Beta Hemolytic Streptococci to 18 Antibiotics, *Amer. J. med. Sci.*, **249**, 261.
31. ROBERTSON, M. H. (1965): Beta Hemolytic Streptococci in Southwest Essex with Particular Reference to Tetracycline Resistance, *Brit. med. J.*, **ii**, 569.
32. Testing of Sensitivity to Antibiotics, (1965): Lead. Art., *Lancet*, **i**, 641.
33. "Infective" Resistance to Antibiotics. (1965): Lead. Art., *Lancet*, **i**, 1149. Transferable Antibiotic Resistance (1965): Lead Art., *Brit. med. J.*, **i**, 1325.
34. SHEEHY, T. W., et al. (1965): Tropical Sprue in North Americans, *J. Amer. med. Ass.*, **194**, 1069.
35. VAN ARSDEL, P. P., and GILLILAND, B. C. (1965): Anemia Secondary to Penicillin Treatment: Studies on Two Patients with "Non-Allergic" Serum Hemagglutinins, *J. Lab. clin. Med.*, **65**, 277.
- 35a. SCHRIER, R. W., BULGER, R. J., and VAN ARSDEL, P. P. (1966): Nephropathy Associated with Penicillin and Homologues, *Ann. intern. Med.*, **64**, 116.
36. FOX, A. M. (1965): Anaphylactoid Shock Induced by Oral Penicillin and Resulting in Gerstmann's Syndrome, *Brit. med. J.*, **ii**, 206.
37. FREEDMAN, M. A. (1965): Oxacillin Toxicity, *Rocky Mtn. med. J.*, **62**, 34.
38. SCOTT, J. L., et al. (1965): A Controlled Double Blind Study of the Hematologic Toxicity of Chloramphenicol, *New Engl. J. Med.*, **272**, 1137.
39. Chloramphenicol Blindness, (1965): Lead. Art., *Brit. med. J.*, **i**, 1511.
40. FELLNER, M. J., and BAER, R. L. (1965): Anaphylactic Reaction to Tetracycline in a Penicillin-Allergic Patient, *J. Amer. med. Ass.*, **192**, 997.
41. MAVROMATIS, F. (1965): Tetracycline Nephropathy, *J. Amer. med. Ass.*, **193**, 191.
42. CASTELL, D. O., and SPARKS, H. A. (1965): Nephrogenic Diabetes Insipidus due to Demethylchlorotetracycline Hydrochloride, *ibid.*, **193**, 237.
43. KABINS, S. A., EISENSTEIN, B., and COHEN, S. (1965): Anaphylactoid Reaction to an Initial Dose of Sodium Cephalothin, *J. Amer. med. Ass.*, **193**, 165.
44. PARISI, A. F., and KAPLAN, M. H. (1965): Apnea During Treatment with Sodium Colistimethate, *J. Amer. med. Ass.*, **194**, 298.

298. GOLD, G. M., and RICHARDSON, A. P. (1965): Myasthenic Reaction to Colistimethate, *J. Amer. med. Ass.*, **194**, 1151.
45. GREENBERG, L. H., and MOMARY, H. (1965): Audiotoxicity and Nephrotoxicity Due to Orally Administered Neomycin, *J. Amer. med. Ass.*, **194**, 827.
- 45a. Neomycin Skin Reactions Frequent Among Danes, (1965): *Med. World News*, **7**, 22.
46. CARTER, M. P., and WILSON, F. (1965): Antibiotics in Early Pregnancy and Congenital Malformations, *Develop. Med. Child. Neurol.*, **7**, 353.
47. MCCOMBS, R. P. (1965): Systemic "Allergic" Vasculitis, Clinical and Pathological Relationships, *J. Amer. med. Ass.*, **194**, 157.
- 47a. Sulfonamide Warning Issued (1966): *A.M.A. News*, **9**, 1.
48. Flu Deaths Rise Despite Vaccine, (1965): *Med. World News*, **6**, 38.
49. Another Strain Added to Influenza Vaccine, (1965): *A.M.A. News*, **8**, 14.
50. JAO, R., WHELOCK, E. F., and JACKSON, G. G. (1965): Interferon Study in Volunteers Infected with Asian Influenza, Program, *Amer. Soc. Clin. Invest.*, May 2, 1965, p. 45.
51. New Research on Influenza: Studies with Normal Volunteers, (1965): Clinical Staff Conference, National Institutes of Health, *Ann. intern. Med.*, **62**, 1307.
52. EDMONSTON, W. P., *et al.* (1965): Selective Intestinal Infection with Type 4 Adenovirus and Its Specific Protective Effect Against Epidemic Disease, Program, *Amer. Soc. Clin. Invest.*, May 2, p. 27. *Med. News, J. Amer. med. Ass.*, **191**, 34.
53. ORSTAVIK, I., FLUGSRUD, L., and HARBOE, A. (1965): The Adenoviruses: A Survey of the Viruses and Serological Investigations Among Norwegian Soldiers, *T. norske Laegeforen*, **85**, 766.
54. STENGER, K., KAFFANKE, V., and SCHAUERHAMMER, G. (1965): Severe Adenovirus Epidemic with Encephalopathy, *Medizin. Kinderheilk*, **113**, 438.
55. PHILLIPS, C. A., *et al.* (1965): Rhinoviruses Associated with Common Colds in a Student Population, *J. Amer. med. Ass.*, **192**, 277.
56. PORTNOY, B., ECKERT, H. L., and SALVATORE, M. A. (1965): Rhinovirus Infection in Children with Acute Lower Respiratory Disease: Evidence Against Etiologic Importance, *Pediatrics*, **35**, 899.
57. FLEET, W. F., CROUCH, R. B., CATE, T. R., and KNIGHT, V. (1965): Hemologous and Heterologous Resistance to Rhinovirus Common Cold, *Amer. J. Epidem.*, **82**, 185.
58. Prevention of Colds by Vaccination Against a Rhinovirus, (1965): Report by the Scientific Committee on Common Cold Vaccines, *Brit. med. J.*, **i**, 1344.
59. Experiments with Interferon in Man. Committee Report (1965): *Lancet*, **i**, 505.
60. SCHMIDT, J., TAUSCHNITZ, C., and KUHN, O. (1965): Occurrence of Hemagglutination-Inhibiting Antibodies Against REO Viruses Types 1 and 2, *Z. Hyg. Infekt-Kr.*, **150**, 269.
61. DIERCKX, L., VAN ZAANE, D. J., and VAN DER VEEN, J. (1965): Acute Respiratory Disorders in Children Caused by Respiratory Syncytial Virus, *Ned. T. Geneesk.*, **109**, 300.
62. BERGLUND, B., VIHMA, L., and WICKSTROM, J. (1965): Respiratory Syncytial Virus Studies on Children Hospitalized During an Outbreak of Respiratory Illness in Finland, *Amer. J. Epidem.*, **81**, 271.
63. SCHMIDT, J., TAUSCHNITZ, C., and KUHN, O. (1965): Neutralizing Antibodies Against RS Virus in the Population, *Z. Hyg. Infekt-Kr.*, **150**, 330.
64. SCHIEBLE, J. H., LENNETTE, E. H., and KASE, A. (1965): An Immunofluorescent Staining Method for Rapid Identification of Respiratory Syncytial Virus, *Proc. Soc. exp. Biol. (N.Y.)*, **120**, 203.
65. ROBERTS, A. N., RENDTORFF, R. C., and HALE, B. D. (1965): Association of Coxsackievirus B3 with Epidemic Respiratory Illness in an Orphanage Nursery, *Amer. J. Epidem.*, **82**, 123.
66. RICHARDSON, H. B., and LEIBOVITZ, A. (1965): "Hand, Foot, and Mouth Disease" in Children, *J. Pediatr.*, **67**, 6.
67. LANG, D. J., *et al.* (1965): Response of Volunteers to Inoculation with Hemagglutinin-positive and Hemagglutinin-Negative Variants of Coxsackie A21 Virus, *J. clin. Invest.*, **44**, 1125.
68. COUCH, R. B., *et al.* (1965): Production of Illness with a Small-Particle Aerosol of Coxsackie A21, *J. clin. Invest.*, **44**, 535.
69. EMBIL, J. A., VAN ROOYEN, C. E., and NAGLER, F. P. (1965): Coxsackie A10 Virus Infection among Infectious Hepatitis Contacts, *Canad. med. Ass. J.*, **93**, 740.
70. Coxsackie Held cause of Cardiac Damage, (1965): *Antibiot. News*, **2**, 1.
71. A Collaborative Study of the Aetiology of Acute Respiratory Infections in Britain (1965): *Brit. med. J.*, **ii**, 319.
72. ELDERKIN, F. M., *et al.* (1965): Aetiology and Management of Bronchiolitis and Pneumonia in Childhood, *Brit. med. J.*, **ii**, 722. Lead Art., *ibid*, p. 714.
73. WEBER, D. M., and PELLECCIA, J. A. (1965): Varicella Pneumonia. Study of Prevalence in Adult Men, *J. Amer. med. Ass.*, **192**, 572.
74. GSELL, O. (1965): Atypischen Pneumonien, ihre Klinische und atologische Differenzierung, *Regensburg. Jb. ärztl. Fortbild.*, **13**, 1.
75. REIMANN, H. A. (1964): Viral and Mycoplasma Pneumonias, *Dis. Chest.*, **46**, 158.
76. MUFSON, M. A., *et al.* (1965): Exudative Pharyngitis Following Experimental *Mycoplasma hominis* Type 1 Infection, *J. Amer. med. Ass.*, **192**, 1146.
77. SOBESLAVSKY, O. (1965): The Ecology of Mycoplasma Pneumonia Infections, *J. Hyg. Epidem.*, (Praha), **9**, 86.
78. SOBESLAVSKY, O., *et al.* (1965): The Etiological Role of Mycoplasma Pneumoniae in Otitis Media in Children, *Pediatrics*, **35**, 652.
79. BAERNSTEIN, H. D., *et al.* (1965): Mycoplasma pneumonia (Eaton atypical pneumonia agent) in Children's Respiratory Infections, *J. Pediatr.*, **66**, 829.
80. GRIFFIN, J. P., and CRAWFORD, Y. E. (1965): Mycoplasma Pneumoniae in Primary Atypical Pneumonia, *J. Amer. med. Ass.*, **193**, 1011.

81. JENSEN, K. E., *et al.* (1965): An Inactivated Mycoplasma Pneumoniae Vaccine, *J. Amer. med. Ass.*, **194**, 248.
82. DAJANI, A. S., CLYDE, W. A., and DENNY, F. W. (1965): Experimental Infection with Mycoplasma Pneumoniae (Eaton's Agent), *J. exp. Med.*, **121**, 1071.
83. ANDREWES, C. H. (1965): Viruses and Noah's Ark, *Bact. Rev.*, **29**, 1; (1965): The Troubles of a Virus, *J. gen. Microbiol.*, **40**, 149.
84. TOBE, T. (1965): Inapparent Virus Infection as a Trigger of Appendicitis, *Lancet*, **ii**, 1343.
85. KLEMOLA, E., and KAARIAINEN, L. (1965): Cytomegalovirus as a Possible Cause of a Disease Resembling Infectious Mononucleosis, *Brit. med. J.*, **ii**, 1099.
86. SRIHONGSE, S., and JOHNSON, C. M. (1965): Wyomia Subgroup of Arbovirus: Isolation from Man, *Science*, **149**, 863.
87. SILBY, H. M., *et al.* (1965): Acute Monarticular Arthritis after Vaccination: Report of a Case with Isolation of Vaccinia Virus from Synovial Fluid, *Ann. intern. Med.*, **62**, 347.
88. SUSMAN, S., and GROSSMAN, M. (1965): Complications of Smallpox Vaccination, Effects of Vaccina Immune Globulin Therapy, *J. Pediat.*, **67**, 1169.
89. Current Status of Measles Immunization (1965): *J. Amer. med. Ass.*, **194**, 1237.
90. PETRALLI, J. K., MERIGAN, T. C., and WILBUR, J. R. (1965): Circulating Interferon after Measles Vaccination, *New Engl. J. Med.*, **273**, 198.
91. ZU RHEIN, G., CHOU, S. (1965): Viruslike Particles and Demyelination, *Science*, **148**, 1477.
92. PHILLIPS, C. A., *et al.* (1965): Persistence of Virus in Infants with Congenital Rubella and in Normal Infants with a History of Maternal Rubella, *J. Amer. med. Ass.*, **193**, 1027.
93. SEVER, J. L., *et al.* (1965): Rubella Complement Fixation Test, *Science*, **148**, 385.
94. SHERMAN, F. E., MICHAELS, R. H., and KENNY, F. M. (1965): Acute Encephalopathy (Encephalitis) Complicating Rubella, *J. Amer. med. Ass.*, **192**, 675.
95. MONTIFF, G. R. G., *et al.* (1965): Postmortem Isolation of Rubella Virus from Three Children with Rubella-Syndrome Defects, *Lancet*, **i**, 723.
96. MONIFF, G. R. G., *et al.* (1965): Isolation of Rubella Virus from Products of Conception, *Amer. J. Obstet. Gynec.*, **91**, 1143.
97. ADKINS, A. T., and FERNBACK, D. J. (1965): Thrombocytopenic Purpura Following Rubella, *J. Amer. med. Ass.*, **193**, 243.
98. NAEYE, R. L., and BLANC, W. (1965): Pathogenesis of Congenital Rubella, *J. Amer. med. Ass.*, **194**, 1277.
99. BOND, J. O., *et al.* (1965): The 1962 Epidemic of St. Louis Encephalitis in Florida, *Amer. J. Epidemiol.*, **81**, 392.
100. QUICK, D., *et al.* (1962): The 1962 Epidemic of St. Louis Virus in Florida, III. A Survey for Inapparent Infections in an Epidemic Area, *ibid.*, 405.
101. QUICK, D. T., THOMPSON, J. M., and BOND, J. O. (1965): IV. Clinical Features of Cases Occurring in the Tampa Bay Area, *ibid.*, 415.
102. Epidemic St. Louis Encephalitis in Houston, 1964. A Co-operative Study, *J. Amer. med. Ass.*, **193**, 139. St. Louis Encephalitis, Editorial, *ibid.*, 150.
103. PHILLIPS, C. A., and MELNICK, J. L. (1965): Community Infection with St. Louis Encephalitis Virus. Serologic Study of the 1964 Epidemic in Houston, *J. Amer. med. Ass.*, **193**, 207.
104. QUICK, D. T., *et al.* (1965): California Encephalitis Virus Infection: A Case Report, *Amer. J. trop. Med. Hyg.*, **14**, 456.
105. SPUDIS, E. V., and CRAMBLETT, H. G. (1965): Echo 4 Meningoencephalitis, *Arch. Neurol. (Chic.)*, **12**, 404.
106. BELL, E. J., GRIST, N. R., and RUSSELL, S. J. M. (1965): Echovirus 25: Infections in Scotland, 1961-64, *Lancet*, **ii**, 464.
107. GRIST, N. R. (1965): Further Studies of Coxsackie A7 Virus Infections in the West of Scotland, *Lancet*, **ii**, 261.
108. BOE, J. SOLBERG, C. O., and SAETER, T. (1965): Corticosteroid Treatment for Acute Meningoencephalitis: A Retrospective Study of 346 Cases, *Brit. med. J.*, **i**, 1094.
- 108a. DUPONT, J. R., and EARLE, K. M. (1965): Human Rabies Encephalitis, *Neurology (Minneapolis)*, **15**, 1023.
109. VAUGHN, J. B., GERHARDT, P., and NEWELL, K. W. (1965): Excretion of Street Rabies Virus in the Saliva of Dogs, *J. Amer. med. Ass.*, **193**, 363.
110. RIDELY, A. S., and DUDGEON, J. W. (1965): A Case of Rabies, *Brit. med. J.*, **i**, 1596.
111. KARLINER, J. S., and BELAVAL, G. S. (1965): Incidence of Reaction Following Administration of Antirabies Serum, Study of 526 Cases, *J. Amer. med. Ass.*, **193**, 359.
112. Postvaccinal Rabies in Brazil (1965): *Trop. Med. and Hyg. News*, **14**, 8.
113. KEMPE, C. H., and BENENSON, A. S. (1965): Smallpox Immunization in the United States, *J. Amer. med. Ass.*, **194**, 161.
114. DIAMOND, M. T., and JOFFE, B. (1965): Reaction at Old Vaccination Site, *J. Amer. med. Ass.*, **194**, 1325.
115. Smallpox Case Diagnosis False (1965): *A.M.A. News*, **8**, 1.
116. STONE, O. J. (1965): Recurrent Herpes Simplex Primum Nil Nocete, *J. Amer. med. Ass.*, **192**, 648.
117. YEN, S. S. C., REAGAN, J. W., and ROSENTHAL, M. S. (1965): Herpes Simplex of Female Genitalia, *Obstet. and Gynec.*, **25**, 479.
118. YOUNG, G. F., KNOX, D. L., and DODGE, P. R. (1965): Necrotizing Encephalitis in a Young Infant, *Arch. Neurol. (Chic.)*, **13**, 15; COGAN, D. G., *et al.*: Herpes Simplex Retinopathy in an Infant, *Arch. Ophthalmol.*, **72**, 641.
119. LEIDER, W., *et al.* (1965): Herpes Simplex Encephalitis. Its Possible Association with Reactivated Latent Infection, *New Engl. J. Med.*, **273**, 341.
120. STEWART, S. E., *et al.* (1965): Herpes-Like Virus Isolated from Neonatal and Fetal Dogs, *Science*, **148**, 1341.
121. JUEL-JENSEN, B. E., and MACCALLUM, F. O. (1965): Herpes Simplex Lesion of Face Treated with Idoxuridine Applied by Spray Gun: Results of a Double-Blind Controlled Trial, *Brit. med. J.*, **i**, 901.

122. ROSS, C. A., SHARPE, J. H. S., and FERRY, P. (1965): Antigenic Relationship of Varicella-Zoster and Herpes Simplex, *Lancet*, ii, 708.
123. GRADY, G. F., CHALMERS, T. C. and the Boston Inter-Hospital Liver Group, Viral Hepatitis in a Group of Boston Hospitals, I. (1965): *New Engl. J. Med.*, **272**, 657. II *ibid*, 662.
124. FENSTER, L. F. (1965): Viral Hepatitis in the Aged, *Gastroenterology*, **49**, 262.
125. MYRICK, G. S., WARD, R., and MCCOLLUM, R. W. (1965): Modification of Post-Transfusion Hepatitis by Gamma Globulin, *New Engl. J. Med.*, **273**, 59.
126. Gamma-Globulin "Ineffective" against Hepatitis. (1965): *Med. News, J. Amer. med. Ass.*, **194**, 31. Gamma Globulin Fails in Serum Hepatitis, *Med. World News*, **6**, 154.
127. MOSLEY, J. W. (1965): The Surveillance of Transfusion-Associated Viral Hepatitis, *J. Amer. med. Ass.*, **193**, 1007.
128. Chimpanzees Pose Hepatitis Problem, *Mod. Med. (Minneap.)*, **33**, 78.
129. The Virus of Infectious Hepatitis Identified. (1965): *J. Amer. med. Ass.*, Internat. News, **194**, 203.
130. HALSTEAD, S. B., and YAMARAT, C. (1965): Recent Epidemics of Hemorrhagic Fever in Thailand, *Amer. J. publ. Hlth.*, **55**, 1386.
131. KIM, D. (1965): Clinical Analysis of 11 Fatal Cases of Hemorrhagic Fever, *Amer. J. Med.*, **39**, 218.
132. Dengue Hemorrhagic Fever. Possible Menace to the United States. (1965): *Trop. Med. and Hyg. News*, **14**, 8.
133. Hemorrhagic Fever in Argentina. (1965): *Lancet*, i, 564.
134. Bolivian Hemorrhagic Fever. (1965): *Trop. Med. and Hyg. News*, **14**, 3.
135. DOUGLAS, R. G., WIEBENGA, N. H., and COUCH, R. B. (1965): Bolivian Hemorrhagic Fever Probably Transmitted by Personal Contact. *Amer. J. Epidem.*, **82**, 85.
136. Salmonella Whodunit Unsolved, *Med. World News*, **6**, 43, 1955.
137. SANDERS, E., *et al.* (1965): Salmonellosis in the United States, *Amer. J. Epidem.*, **81**, 370.
138. MITCHELL, R. G. (1965): Urinary Tract Infections Caused by Salmonellae, *Lancet*, i, 1092.
139. PATHANIA, N. S., and SACHAR, R. S. (1965): Typhoid and Paratyphoid Fevers in Punjab (India): A Study of 340 Cases, *Amer. J. trop. Med. Hyg.*, **14**, 419.
140. GILLES, R. R.: Longitudinal Family Studies in Scotland, The Milbank Memorial Fund Quarterly, R. M. Acheson Edit., **43**, 244, Milbank Fund, 1965.
141. CRAMBLETT, H. G., and SIEWERS, C. M. F. (1965): Etiology of Gastroenteritis in Infants and Children, *Pediatrics*, **35**, 885.
142. MOORHEAD, P. J., and PARRY, H. E. (1965): Treatment of Sonne Dysentery, *Brit. med. J.*, ii, 913.
143. ROBINSON, D. T., ARMSTRONG, E. C., and CARPENTER, K. P. (1965): Outbreak of Dysentery Due to Contact with a Pet Monkey, *Brit. med. J.*, i, 903.
144. HALTALIN, K. C., and NELSON, J. D. (1965): Coliform Septicemia Complicating Shigellosis in Children, *J. Amer. med. Ass.*, **192**, 441.
145. HALTALIN, K. C., and NELSON, J. D. (1965): In Vitro Susceptibility of Shigellae to Sodium Sulfadiazine and to Eight Antibiotics, *J. Amer. med. Ass.*, **193**, 705.
146. REIMANN, H. A. (1965): Microbic Phagocytosis by Enteric Epithelial Cells, *J. Amer. med. Ass.*, **192**, 1130.
147. TAKEUCHI, A., *et al.* (1965): Experimental Bacillary Dysentery. An Electron Microscopic Study of the Response of the Intestinal Mucosa to Bacterial Invasion, *Amer. J. Path.*, **47**, 1011.
148. HUMMELER, K., ARMSTRONG, D., and TOMASINI, N. (1965): Cytopathic Mycoplasmas Associated with Human Tumors, *J. Bact.*, **90**, 511.
149. WILSON, A. T., *et al.* (1965): Whooping-Cough: Difficulties in Diagnosis and Ineffectiveness of Immunization, *Brit. med. J.*, ii, 623.
150. EKLUND, M. W., and POYSKY, F. (1965): Clostridium botulinum Type F from Marine Sediments, *Science*, **149**, 306.
151. Vaccine Against Anthrax, Lead. Art., *Brit. med. J.*, ii, 717.
152. AYLIFFE, G. A. J., *et al.* (1965): Hospital Infection with Pseudomonas Aeruginosa in Neurosurgery, *Lancet*, ii, 365.
153. NAVARRETE-REYNA, A., ROSENSTEIN, D. L., and SONNENWIRTH, A. C. (1965): Bacterial Aortic Aneurism Due to Listeria Monocytogenes, *Amer. J. clin. Path.*, **43**, 438.
154. Mycobacterium leprae Cultured. (1965): *Med. News*, London, July 9.
155. World War Veteran Develops Leprosy after 20 Years, *Mod. Med. (Minneap.)*, **33**, 45.
156. A New Agent for Prophylaxis of Tetanus. Tetanus Immune Globulin (Hyper-Tet). Council on Drugs. (1965): *J. Amer. med. Ass.*, **192**, 471.
157. VOSS, R., *et al.* (1965): Therapy of Tetanus with Use of Human Tetanus Antitoxin in the Form of Gamma-Globulin (Tetanus Hyperimmune Globulin) *Munch. Med. Wschr.*, **107**, 854.
158. BLATTNER, R. J. (1965): The Role of Penicillin in the Prevention of Tetanus; *J. Pediatr.*, **66**, 975.
159. HARDEGREE, M. C., and WANNAMAKER, L. W. (1965): An Electrophoretic Study of the Neurotoxin(s) of Nine Strains of Clostridium Tetani, *Proc. Soc. exp. Biol. (N.Y.)*, **118**, 692.
160. MYERS, J. A. (1965): The Natural History of Tuberculosis in the Human Body. Forty-Five Years of Observation, *J. Amer. med. Ass.*, **194**, 1086.
161. CAREY, S. L. (1965): A Unique Epidemic of Tuberculosis: Eskimo Point, 1963, *Amer. Rev. resp. Dis.*, **91**, 479.
162. PHILIP, R. N., and COMSTOCK, G. W. (1965): Phlyctenular Keratoconjunctivitis among Eskimos in Southwestern Alaska, *Amer. Rev. resp. Dis.*, **91**, 194.
163. BATES, J. H., POTTS, W. E., and LEWIS, M. (1965): Epidemiology of Primary Tuberculosis in an Industrial School, *New Engl. J. Med.*, **272**, 714.
164. ALPERT, M. E., and LEVISON, M. H. (1965): An Epidemic of Tuberculosis in a Medical School, *ibid*, 718.
165. STEAD, W. W. (1965): Pathogenesis of Pulmonary Tuberculosis Among Older Persons,

- Amer. Rev. resp. Dis.* **91**, 811.
166. Reemphasis on Tuberculosis. (1965): Editor. *J. Amer. med. Ass.*, **192**, 1088.
 167. Criteria for Prophylaxis in Active Tuberculosis. (1965): Editor. *J. Amer. med. Ass.*, **192**, 1088.
 168. FUCHS, G. F. (1965): Criteria for Prophylaxis in Inactive Tuberculosis, *Arch. environm. Hlth.*, **10**, 937.
 169. BUSH, O. B., et al. (1965): Isoniazid Prophylaxis in Contacts of Persons with Known Tuberculosis, *Amer. Rev. resp. Dis.*, **92**, 732.
 170. FALK, A. (1965): Tuberculosis Meningitis in Adults: Long-Term Study of 365 Patients, *Amer. Rev. resp. Dis.*, **91**, 823.
 171. HOBBS, G. L., et al. (1965): Primary Drug Resistance: Continuing Study of Tubercle Bacilli in Veteran Population within the United States, *Amer. Rev. resp. Dis.*, **91**, 575.
 172. CURRUTHERS, K. J. M., and EDWARDS, F. G. B. (1965): Atypical Mycobacteria in Western Australia, *Amer. Rev. resp. Dis.*, **91**, 887.
 173. GODWIN, M. C. (1965): Infection of Knee Joint with Mycobacterium Kansasii, *J. Amer. med. Ass.*, **194**, 88.
 174. MAYBERRY, J. D., MULLINS, J. F., and STONE, O. J. (1965): Cutaneous Infection Due to Mycobacterium Kansasii, *J. Amer. med. Ass.*, **194**, 1135.
 - 174a. KOENIG, M. J., COLLINS, R. D., and HEYSSEL, R. M. (1966): Disseminated Mycobacteriosis Caused by Battey Type Mycobacteria, *Ann. intern. Med.*, **64**, 145.
 175. REIMANN, H. A., and MA, P. P. C. (1965): Dissociants of M. Tuberculosis and Atypical Mycobacteria, *Amer. Rev. resp. Dis.*, **92**, 193.
 176. KRAUS, O. (1963): Die Stellung der sogenannten "Anonymen" Mykobakterien, *Beitr. Klin. Tuberk.*, **127**, 626.
 177. Most Postsarcoidosis Patients Stay Tuberculin-Negative. (1965): *Med. World News*, **6**, 9.
 178. New Mexico Plague. (1965): *A.M.A. News*, Sept. 13, p. 1.
 179. QUAN, S. F., et al. (1965): Isolation of a Strain of *Pasteurella Pseudotuberculosis* from Alaska Identified as *Pasteurella pestis*: An Immunofluorescent False Positive, *Amer. J. trop. Med. Hyg.*, **14**, 424.
 180. REIMANN, H. A. (1932): Further Studies on P. Pseudotuberculosis, *Amer. J. Hyg.*, **16**, 206.
 181. HUBBERT, W. T. (1965): Human Pasteurellosis, *Trop. Med. and Hyg. News*, **14**, 4.
 182. BOISSIERE, H., et al. (1965): Erythema Nodosum from Pasteurella Pseudotuberculosis, *Sem. Hôp. Ann. Pédiat.*, **41**, 1239.
 183. Cholera Study Underscores Cytotoxicity, *Antibiot. News*, **2**, 1, 1965.
 184. MCINTYRE, O. R., et al. (1965): Diarrhea Caused by Non-Cholera Vibrosis, *Amer. J. trop. Med. Hyg.*, **14**, 413.
 185. LINDENBAUM, J., et al. (1965): Non-Vibrio Cholera, *Lancet*, **i**, 1081.
 186. MUKERJEE, S., BASU, S., and BHATTACHARYA, P. (1965): A New Trend in Cholera Epidemiology, *Brit. med. J.*, **ii**, 837.
 187. FEELEY, J. C., and PITTMAN, M. (1965): Laboratory Assay of Cholera Vaccine: Used in Field Trial in East Pakistan, 1963, *Lancet*, **i**, 449.
 188. OSEASOHN, R. O., BENENSON, A. S., and FAHIMUDDIN, M. (1965): Field Trial of Cholera Vaccine in Rural East Pakistan, *ibid*, 450.
 189. Epidemic Cholera. (1965): Lead. Art., *Brit. med. J.*, **ii**, 832.
 190. First Cholera Case Since 1911 Reported. (1965): *Trop. Med. and Hyg. News*, **14**, 3.
 191. SUHS, R. H., and FELDMAN, H. A. (1965): Pneumococcal Types Detected in Throat Cultures from a Population of "Normal" Families, *Amer. J. med. Sci.*, **250**, 424.
 192. Gram-negative Pneumonia. (1965): *Mod. Med. (Minneapolis)*, **33**, 52.
 193. GHERMAN, C. R., and SIMON, H. J. (1965): Pneumonia Complicating Severe Underlying Disease, *Dis. Chest.*, **48**, 297.
 194. QUINN, R. W. (1965): Carrier Rates for Hemolytic Streptococci in School Children: A Six-Year Study, *Amer. J. Epidemiol.*, **82**, 1.
 195. MARKOWITZ, M., et al. (1965): Streptococcal Impetigo, *Pediatrics*, **35**, 393.
 196. HIGGINS, P. M., et al. (1965): Acute Nephritis and Streptococcal Sore Throat: A Prospective Study in General Practice, *Brit. med. J.*, **ii**, 1156.
 197. Accepted RF Therapy Concepts Subjected to New Look, (1965): *Antibiot. News* (1965) **2**, 4.
 198. Prophylaxis for Rheumatic Fever. (1965): *Mod. Med. (Minneapolis)*, **33**, 75.
 199. SCHEFFERMAN, M. M., et al. (1965): Acute Rheumatic Fever in Puerto Rico, *Amer. J. Dis. Child.*, **110**, 239.
 200. ADDATO, I. J., et al. (1965): Rheumatic Fever in the Adult, *J. Amer. med. Ass.*, **194**, 1043.
 201. VAISMAN, S., et al. (1965): Failure of Penicillin to Alter Rheumatic Valvulitis, *J. Amer. med. Ass.*, **194**, 1284.
 202. UWAYDA, M. M., and WEINBERG, A. N. (1965): Bacterial Endocarditis—A Changing Pattern, *New Engl. J. Med.*, **273**, 1231.
 203. RABINOVICH, S., et al. (1965): A Long-Term View of Bacterial Endocarditis. 337 Cases 1924 to 1963, *Ann. intern. Med.*, **63**, 185.
 204. LLOYD-STILL, J. D. (1965): Bacterial Endocarditis and Urology, *Brit. med. J.*, **i**, 768.
 205. ROACH, M. R., and DRAKE, C. G. (1965): Ruptured Cerebral Aneurisms Caused by Microorganisms, *New Engl. J. Med.*, **273**, 240.
 206. LAVINE, D., et al. (1965): Staphylococcus of a Newly Recognized Bacteriophage Type, *J. Amer. med. Ass.*, **192**, 935.
 207. SMITH, J. A., WILLIS, A. T., and O'CONNOR, J. (1965): New Epidemic Strains of Staphylococcus Aureus, *Lancet*, **ii**, 772.
 208. LIGHT, I. J., SUTHERLAND, J. M., and SCHOTT, J. E. (1965): Control of a Staphylococcal Outbreak in a Nursery. Use of Bacterial Interference, *J. Amer. med. Ass.*, **193**, 700.
 209. WILSON, T. S., and STUART, R. D. (1965): Staphylococcus Albus in Septicemia, *Canad. med. Ass. J.*, **93**, 8.
 210. FINK, C. W. (1965): Gonococcal Arthritis in Children, *J. Amer. med. Ass.*, **194**, 237.
 211. Gonococcal Arthritis Rising in Woman (1965): *Med. World News*, **6**, 1965.
 212. BJÖRNBERG, A., and GISSLEN, H. (1965): Gonococcal Sepsis, *Nord. Med.*, **73**, 338.
 213. KINCAID-SMITH, P., and BULLEN, M. (1965): Bacteriuria in Pregnancy, *Lancet*, **i**, 395.
 214. MCCABE, N. R., and JACKSON, G. G. (1965): Treatment of Pyelonephritis, *New Engl. J. Med.*, **272**, 1037.

215. SANFORD, J. P., and BARNETT, J. A. (1965): Immunologic Responses in Urinary-Tract Infections, *J. Amer. med. Ass.*, **192**, 587.
216. ANDRIOLE, V. T., and EPSTEIN, F. H. (1965): Prevention of Pyelonephritis by Water Diuresis: Evidence for Role of Hyper-tonicity in Promoting Renal Infection, *J. clin. Invest.*, **44**, 73.
217. ALLEN, T. D. (1965): Pathogenesis of Urinary Tract Infection in Children, *New Engl. J. Med.*, **273**, 1421.
218. CARLETON, H. G., BAKER, T. H., and RICHARDS, H. L. (1965): Bacteriuria in Pregnancy, *Amer. J. Obstet. Gynec.*, **92**, 227.
219. NETER, E. (1965): Evaluation of the Tetra-zolium Test for the Diagnosis of Significant Bacteriuria, *J. Amer. med. Ass.*, **192**, 769.
220. WHALLEY, P. J., MARTIN, F. G., and PETERS, P. C. (1965): Significance of Asymptomatic Bacteriuria, Detected during Pregnancy, *J. Amer. med. Ass.*, **193**, 879.
221. BEARD, R. W. (1965): Diagnosis of Urinary Infection by Suprapubic Bladder Puncture, *Lancet*, **ii**, 610.
222. GUTMAN, L. T., *et al.* (1965): Significance of Bacterial Variants in Urine of Patients with Chronic Bacteriuria, *J. clin. Invest.*, **44**, 1945.
223. BALL, R. W. (1965): Outbreak of Infectious Syphilis in South Carolina, *J. Amer. med. Ass.*, **193**, 13.
224. FIUMARA, N. J. (1965): A Legacy of Syphilis, *Arch. Derm.*, **92**, 676.
225. Treponema Pallidum and Penicillin, Editorial, (1965): *J. Amer. med. Ass.*, **192**, 55.
226. SELLERS, T. F., PRICE, W. N., and NEWBERRY, W. M. (1965): An Epidemic of Erythema Multiforme and Erythema Nodosum Caused by Histoplasmosis, *Ann. intern. Med.*, **62**, 1244.
227. D'ALESSIO, D. J., *et al.* (1965): A Starling Roost as the Source of Urban Epidemic of Histoplasmosis in an Area of Low Incidence, *Amer. Rev. resp. Dis.*, **92**, 725.
228. KLITE, P. D., and YOUNG, R. V. (1965): Bats and Histoplasmosis. A Clinico-epidemiologic Study of Two Human Cases, *Ann. intern. Med.*, **62**, 1263.
229. KLITE, P. D., and DIERCKS, F. H. (1965): Histoplasma Capsulatum in Fecal Contents and Organs of Bats in the Canal Zone, *Amer. J. trop. Med. Hyg.*, **14**, 433.
230. FIFER, W. R., WOELLNER, R. C., and GORDON, S. S. (1965): Mediastinal Histoplasmosis, *Dis. Chest*, **47**, 518.
231. Homograft Transmits Donor's Histoplasmosis, *Med. World News*, **6**, 80.
232. Cancer and Viruses (1965): Editorial, *J. Amer. med. Ass.*, **192**, 54.
233. ARMSTRONG, D., *et al.* (1965): Cytopathogenic Mycoplasmas Associated with Two Human Tumors, *J. Bact.*, **90**, 418.
234. DMOCHOWSKI, L., *et al.* (1965): Viruses and Mycoplasma (PPLO) in Human Leukemia, *Cancer*, **18**, 1345.
235. FALLON, R. J., *et al.* (1965): Further Studies of Agents Isolated from Tissue Cultures Inoculated with Human Leukemic Bone-Marrow, *Brit. med. J.*, **ii**, 388.
236. Mycoplasma Find a Defender, (1965): *Med. World News*, **6**, 67.
237. Human Tumor Trail Points to Toxoplasma, *Med. World News*, **6**, 165.
238. GREENE, G. S., JOHNSON, R. J., and SHIVELY, J. A. (1965): Mima: Opportunistic Pathogens, *J. Amer. med. Ass.*, **194**, 1065.
239. LEWIS, A. M., *et al.* (1965): Lymphocytic-Choriomeningitis Virus in Hamsters and Humans, *Science*, **150**, 363.
240. CASSEL, W. A., and GARRETT, R. E. (1965): New Castle Disease Virus as Antineoplastic Agent, *Cancer*, **18**, 863.
241. ESTERLY, J. A. (1965): Pneumocystis Carinii Pneumonia, *Arch. Path.*, **80**, 433.
242. WATANABE, J. M., *et al.* (1965): Pneumocystis carinii. Pneumonia in a Family, *J. Amer. med. Ass.*, **193**, 685.
243. ROBBINS, J. B., *et al.* (1965): Successful Treatment of Pneumocystis Carinii Pneumonitis in a Patient with Congenital Hypogammaglobulinemia, *New Engl. J. Med.*, **272**, 708.
244. JONES, T. C., KEAN, B. H., and KIMBALL, A. C. (1965): Toxoplasmic Lymphadenitis, *J. Amer. med. Ass.*, **192**, 1.
245. FELDMAN, H. (1965): A Nationwide Serum Survey of United States Military Recruits, 1962. VI. Toxoplasma Antibodies, *Amer. J. Epidem.*, **81**, 385.
246. WERTLAKE, P. J., and WINTER, T. S. (1965): Fatal Toxoplasmic Myocarditis in an Adult Patient with Acute Lymphatic Leukemia, *New Engl. J. Med.*, **273**, 438.
247. BODEY, G. P., NIES, B. A., and FREIREICH, E. J. (1965): Multiple Organism Septicemia in Acute Leukemia, *Arch. intern. Med.*, **116**, 266.
248. BODEY, G. P. *et al.* (1965): Cytomegalic Inclusion Disease, *Ann. intern. Med.*, **62**, 899.
249. HOCHSTEIN, H. D. *et al.* (1965): Recovery of More than 1 Organism in Septicemias, *New Engl. J. Med.*, **273**, 468.
250. "Very Unusual" Outbreak of Pneumonia Reported (1965): *Med. News. J. Amer. med. Ass.*, **193**, 37.
251. FOWLER, M., and CARTIER, R. F. (1965): Acute Pyogenic Meningitis Probably Due to *Acanthamoeba* sp.: A Preliminary Report *Brit. med. J.*, **ii**, 740.
252. LUOTO, L., CASEY, M. L. and PICKENS, E. G. (1965): Q Fever Studies in Montana, *Amer. J. Epidem.*, **81**, 356.
253. ATTWOOD, E. L., LAMB, J. T., and SONENSHINE, D. E. (1965): A Contribution to the Epidemiology of Rocky Mountain Spotted Fever in the Eastern United States, *Amer. J. trop. Med. Hyg.*, **14**, 831.
254. Swiss Typhus, (1965): Abstract, *A.M.A. News*, **8**, 3.
255. MOST, H. (1965): Trichinellosis in the United States. Changing Epidemiology During the Past 25 Years, *J. Amer. med. Ass.*, **193**, 871.
256. CAMPBELL, W. C. and CUCKLER, A. C. (1965): Thiabendazole Treatment in Invasive Phase of Experimental Trichinosis in Swine, *Ann. trop. Med. Parasit.*, **56**, 500.
257. TJALMA, R. A., and GALTON, M. M. (1965): Incidence of Leptospirosis, *Amer. J. trop. Med. Hyg.*, **14**, 387.
258. PEELER, R. N., KADULL, P. J. and CLUFF, L. E. (1965): Intensive Immunization of Man. Evaluation of Possible Adverse Consequences, *Ann. intern. Med.*, **63**, 44.

259. CROUNSE, R. G. (1965): The Response of Acne to Placebos and Antibiotics, *J. Amer. med. Ass.*, **193**, 906.
260. BRYANT, R. E., SANFORD, J. P. and ALCOZE, T. (1965): Treatment of Recurrent Furunculosis with Staphylococcal Bacteriophage-Lysed Vaccine, *J. Amer. med. Ass.*, **194**, 11.
261. FONTANA, V. J. *et al* (1965): Bacterial Vaccine and Infectious Asthma, *J. Amer. med.*, **193**, 895.
262. SCHOPF, J. W. *et al* (1965): Electron Microscopy of Fossil Bacteria Two Billion Years Old, *Science*, **194**, 1365.
263. BARGHOORN, E. S., and SCHOPF, J. W.: Microorganisms from the Late Precambrian of Central Australia, *ibid.*, **150**, 337.
264. ORO, J. and TORNABENT, T.: Bacterial Contaminants of Some Carbonaceous Meteorites, *ibid.*, **150**, 1046.
265. EHLERS, STILES, D. W., and BIRLE, J. D.: Fossil Bacteria in Pyrite, *ibid.*, **148**, 1719.
266. UREY, H. C. (1966): Biological Material in Meteorites: A Review, *ibid.*, **151**, 157.
267. SIDEL, V. W., and GOLDWYN, R. M. (1965): Chemical and Biologic Weapons—A Primer, *New Engl. J. Med.*, **274**, 21.
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