ANNUAL REVIEW

Infectious Diseases

Annual review of significant publications

HOBART A. REIMANN
M.D.

The Hahnemann Medical College and Hospital, Philadelphia, U.S.A. 19102

Introduction

Beneficial and harmful effects of antimicrobial therapy and the introduction of new agents, as usual, were subjects of interest in 1967. Most attention, however, was given to viruses and viroses, but with the exception of mycoplasmal infection, reports dealing with involvement of the respiratory tract were fewer than in previous years. As new features, the probable viral cause of infectious mononucleosis was discovered and DNA (deoxyribonucleic acid) was synthesized. Because predicted serious epidemics of influenza A₂ did not occur, little opportunity was offered to test the prophylactic value of amantadine. The cause of 'viral' hepatitis remains enigmatic and the relation of viruses to neoplasms in man still is unclear. Venereal diseases continue to increase in incidence. Iatrogenic and noscomial infections caused further concern.

Antimicrobial drugs

In the United States, 865 tons of penicillin G and 75 tons of semisynthetic penicillins were made in 1964 at sales value of \$127 million (£53 million). Sales of tetracyclines amounted to \$100 million (£41.5 million) a year.¹ Antimicrobics comprised more than 50% of all medicinals in written prescriptions.² In hospitals, antimicrobics were ordered oftener than any other drugs excepting analgesics. Some patients received twelve antimicrobial agents. 'The extraordinary frequency and variability of antibiotic drug practice points out the need and importance of further studies'³ which is mild critique, to say the least. An estimated 6% of the population now is sensitive to penicillin. Penicillin caused allergic reactions in 10-39% of known sensitized patients. All penicillins and occasionally cephalosporins are immunologically cross-reactive.⁴ The removal of protein and peptide residues of penicillin

eliminated the allergic reactions incident thereto.⁵ Harmful iatrogenic results of therapy will not diminish until medical personnel are better informed about bacteriology and proper antimicrobial therapy.⁶

In tests on 25,000 strains of bacteria, synthetic penicillins inhibited 99% of staphylococci and penicillin G only 45%. Infection caused by tetracycline-resistant pneumococci and group A streptococci have increased. Gram-negative bacilli also increased in incidence and are more resistant to antimicrobics than Gram-positive bacteria.⁷

Ampicillin is effective against pneumococci, hemolytic streptococci, meningococci, gonococci, non-penicillinase-producing staphylococci, enterococci, *H. influenzae*, and against many strains of *Esch. coli*, *Salmonella*, *Shigella* and *Proteus mirabilis*. *Klebsiella*, *Aerobacter* and *Pseudomonas* are resistant.⁸ Strains of staphylococci resistant to methicillin appeared. One resisted, in addition, penicillin, erythromycin, kanamycin, chloramphenicol, tetracycline and cephalothin.⁹ Ampicillin was effective in treating listeriosis as reported in two papers in the 16 June 1967, issue of *Deutsche Medizinische Wochenschrift*, but not for typhoid.¹⁰ A severe methicillin-resistant staphylococcal infection was successfully controlled with vancomycin.¹¹ Vancomycin is ototoxic and nephrotoxic. As yet staphylococci have not become resistant to it but may if the drug is widely used. The report of a conference on broad-spectrum penicillins and other antimicrobics was published.¹²

Streptomycin-dependent bacteria also depend upon unrelated drugs which act similarly on the ribosome to induce the requirement.¹³ Kanamycin and neomycin have the broadest range of activity against Gram-negative bacilli. Kanamycin being less toxic is preferred for initial treat-

ment, pending the results of sensitivity tests. A safer drug should be substituted if the tests so indicate. Kanamycin was consistently effective *in vitro* against *Klebsiella*, especially in combination with cephalothin.¹⁴ *Pseudomonas* resists kanamycin and is combatted with polymyxin B (Aerosporin) or polymyxin E (Colistimethate) together with kanamycin or ampicillin.¹⁵ Topically applied neomycin failed to eradicate bacteria from dermal lesions.¹⁶ For superficial wound infections, dressings soaked with acetic acid inhibited the growth of *Pseudomonas*.¹⁷

Klebsiella and *Esch. coli* often resisted more than three antimicrobics. Experimentally, *Klebsiella* transferred multiple antimicrobial resistance to a susceptible strain of *Esch. coli*.¹⁸ The transmitting or R factor also may involve *Salmonella* and *Shigella* especially in hospitals.¹⁹

Antimicrobial prophylaxis

Conflicting opinions persist. For the treatment of severely burned patients, the following regimen in maximal tolerated dosage was applied: chloramphenicol to suppress Gram-negative bacilli, penicillin for streptococci and clostridias, methicillin for staphylococci. Polymyxin, lincomycin, gentamycin and cephalothin were added on occasion and γ -globulin was given to 'potentiate the antimicrobial effects'. Chloramphenicol, neomycin, polymyxin and mycostatin were applied topically. No evidence of toxicity, no deaths, and no superinvasion of bacteria were recorded. Intensive prophylaxis, it was said, 'may' have merit,²⁰ but admittedly, the mortality-rate was no better than at other 'burn centers'. According to Meade, chemoprophylaxis is of no value in preventing infection in burned patients. Therapy may simply select out the organism which may eventually infect the patient.²¹ Weinstein said 'most experience indicated that if the purpose of prophylaxis is to prevent invasion of any, other than a single species, organism that happens to be present... and this frequently involves the use of broad-spectrum antimicrobial drugs or combinations—then the chances for failure are very close to 100 percent'.²¹

Antimicrobics should not be administered orally preparatory to surgery on the intestinal tract unless anterior resection with extraperitoneal anastomosis is to be done. Staphylococcal enteritis occurred oftener in patients who received antimicrobics than after mechanical preparation.²² Penicillin given during cardiac catheterization failed to prevent bacteremia.²³ Antimicrobial prophylaxis during cardiac surgery still is widely used, but its value is unproved.^{24, 24a}

Continuous antimicrobial prophylaxis failed to influence the course of chronic bronchitis in Holland.²⁵

New antimicrobial drugs

According to two papers in the January 1968 issue of *Archives of Internal Medicine*, the value of cephaloridine was similar to that of other agents. The usual side-effects of superinfection with resistant bacteria, nephro- and hemotoxicity ensued. It was effective for pneumococcal pneumonia,²⁶ and more active against staphylococci than methicillin. *Pseudomonas* and indole-producing *Proteus* were resistant, but for other Gram-negative bacilli, cephaloridine was equal to cephalothin.²⁷ The proceedings of a conference on the drug were published in a supplement to this Journal.²⁸

Therapeutically hetacillin is inferior to ampicillin from which it is derived.²⁹ Carbenicillin, a penicillin relative, affects especially *Pseudomonas* and *Proteus*.³⁰ Gentamycin, a relative of neomycin and kanamycin, has a similar spectrum of antimicrobial activity, and the same ototoxicity as discussed editorially and in four papers in the 27 May 1967 issue of *British Medical Journal*. Some pseudomonal infections were treated successfully, others were not. The maximum dosage usually is 240 mg daily.

Spiramycin (Rovamycin) was said to be effective as a prophylactic against staphylococcal infection after prostatectomy.³¹ In monkeys infected with penicillin-resistant staphylococci, cloxacillin and, surprisingly, oleandomycin which is bacteriostatic, were superior to erythromycin for therapy.³² More than fifty newly-named antimicrobics were discussed in a book.³³ How many of them will survive the test of time?

Harmful effects of antimicrobial drugs

Daily dosage of 40–60 million units (24 to 36 g) of penicillin controlled Gram-negative bacillary infections, but caused transient neurotoxicity.³⁴ Encephalopathy ensued in uremic patients after 30 million units (18 g).³⁵ Three elderly patients with suspected Gram-negative bacilemia and decreased renal function died from neurologic disturbance after the intravenous injection of similar huge amounts. In a fourth nonfatal case, convulsions ceased when therapy was stopped.³⁶ One may wonder how often death from therapy is regarded as death from disease. Mental disturbance alone was thought to be an immediate pseudoanaphylactic response which differs from anaphylactic shock and circulatory failure. It did not seem to indicate cessation of therapy.³⁷ In an unusual case, an immediate

anaphylactoid reaction was followed 2 weeks later by 'serum sickness'³⁸

Acute renal failure ensued during therapy with methicillin,³⁹ polymyxin B,⁴⁰ kanamycin, bacitracin, neomycin, and colistin. Early use of hemodialysis meliorated the harm.⁴¹ Kunin published a guide to the safer use of antimicrobics during renal failure. Harm from nephrotoxicity is reversible if therapy is stopped soon enough.^{42, 42a}

Tetracycline given intravenously caused fatty change in the liver of six non-pregnant women.⁴³ Two icteric patients who had received large doses of tetracycline postoperatively died from hemorrhage possibly the result of disturbance of the clotting mechanism.⁴⁴ Oleandomycin, novobiocin, chloramphenicol, amphotericin, sulfonamides and isoniazid have been implicated as causes of hepatic disturbance.⁴⁵ In ten patients, pneumonia followed within a few hours of therapy with nitrofurantoin. Chills, fever and leukocytosis with eosinophilia disappeared when the drug was stopped.⁴⁶

Reports of 408 cases of chloramphenicol-associated hemal depression were reviewed. Regrettably, the drug had been administered mostly to patients with the 'common cold' for which no antimicrobial is needed, for pneumonia for which other drugs are available, and for lower genitourinary tract infections. Gonorrhea, the commonest of the latter, is better treated with other drugs. Marrow toxicity occurs after large or small doses or short or long courses. The risk of its occurrence is low but the risk of fatality is great. Evidence of damage usually appears after therapy ceases, and leukocyte counts made during therapy are of little value in predicting toxicity.⁴⁷ A positive direct Coombs' test reaction was noted in 75% of patients who received cephalothin especially in azotemic ones.⁴⁸ Cephalothin induced thrombocytopenia in a patient sensitive to penicillin.⁴⁹

During a 2-month period, of eight patients who underwent open-heart surgery five developed respiratory tract infection with *Ps. aeruginosa* type 10 and three died. All had received ampicillin and methicillin prophylactically.⁵⁰ Granulomatous hepatic and pulmonic lesions discovered by biopsy followed dosage of 2 g of sulfadimethoxine given for sore throat.⁵¹ Sulfonamide drugs on successive occasions incited attacks of hiccough without other evidence of toxicity.⁵² Antimicrobial therapy may mask acute otitic infection while complications progress unrecognized.⁵³ Because of the universal use of antimicrobics, *Monilia* has displaced *Trichomonas* as the cause of vaginitis.⁵⁴ A 15%

incidence of dermal eruptions during infectious mononucleosis, increased to 45% during antimicrobial therapy.⁵⁵

Viral infections

Respiratory tract infections

Among infants, acute pharyngitis usually was of viral origin. Between ages 6 and 8 years hemolytic streptococci caused illness in more than half. *Mycoplasma pneumoniae* affected adolescents only. Etiologic diagnosis rarely can be made clinically; epidemiologic factors, the age of patients, the season and current prevalence of identified microbial infections are more helpful. Recognition of hemolytic streptococci as causes is of special value. Even so, streptococci were present at the same rate in 6-year-old well children.⁵⁶ They also may be present during viral infections. Respiratory syncytial virus caused most infections, especially pneumonia in children less than 1 year old. Parainfluenza viruses 1 and 3 caused less severe illness, and mycoplasmal infection usually was mild. Streptococci and pneumococci rarely caused pneumonia in children.⁵⁷ In older children, 17% of respiratory tract infections were caused by viruses and bacteria together, and in 20% by more than one virus at once.⁵⁸ Viral respiratory tract infections did not seem to predispose to the invasion or dissemination of meningococci.⁵⁹

Rhinovirus

Besides changes in weather, factors such as cosmic rays or light cycles may influence seasonal epidemics of acute respiratory tract disease.⁶⁰ In agreement with the early studies of Andrewes, exposure to cold and chilling failed to increase the incidence of infection or its severity in volunteers inoculated with rhinovirus.⁶¹ In my personal experience, chilling induced severe respiratory tract infections in at least two instances.

From young children with afebrile colds, twenty-six rhinoviruses mostly of types 16, 38, and a new H group serotype 54 were recovered. The isolation-rate was 3.5% as compared with 15% in adults with respiratory tract infections.⁶² In a hospital, seventy-three infants and children were infected with rhinoviruses chiefly of the 'H' strain. Eight had viral pneumonia.⁶³ Rhinovirus illness usually lasted about 1 week in young adults. The development of antibody in most patients probably is a factor in preventing reinfection.⁶⁴ Rhinoviruses do not survive in the intestinal tract.⁶⁵ Rhinovirus often incites exacerbations of chronic bronchitis.⁶⁶ Osler's

description of the common cold in 1892 has never been surpassed.⁶⁷

Respiratory syncytial virus seemed to be the chief cause of death among sixteen of twenty-two infants. Nine of these had congenital abnormalities. Bacterial infections were fatal in six.⁶⁸

Influenza

Influenza A₂ virus caused severer illness than B virus among Eskimo children. During several outbreaks, respiratory syncytial, parainfluenza 3, adenoviruses 2 and 5, rhinovirus and herpes simplex virus also were isolated. Occasionally two viruses were present in one patient. About 50% of synchronous A and B infections were pneumonic.⁶⁹ An A₂ virus affected about 60% of dental students and some patients who had visited a dental clinic. Prior vaccination against influenza was not effective.⁷⁰ Dentists are liable to infection with aerosolized virus exhaled by patients.

According to present information, amantadine hydrochloride is useful only for the prevention of influenza A₂, but its premature commercial availability may lead to indiscriminate use against any viral infection, and its possible adverse reactions are unknown.^{71, 71a} The drug seemed to worsen the effects of rubella, and was not recommended for general use pending further information.⁷²

Parainfluenza virus was present in the air near a sick child and infection evidently can be airborne.⁷³ Paramyxoviruses in the pharynx are easily detectable and diagnosis is possible within 1 hr by applying electron-microscopic technique.⁷⁴

Adenovirus

Physicians hesitate to ascribe fatal pneumonia to viral origin and generally use the phrase 'associated with' rather than 'caused by'. Death in an adult was associated with adenovirus 4⁷⁵ and in a child with Reovirus 3.⁷⁶ Adenovirus 7 caused fatal pneumonia and pericarditis in an infant.⁷⁷ Adenovirus 3 and *Mycoplasma pneumoniae* caused unilateral deafness in two instances.⁷⁸

Newly recognized viruses

Eight hitherto unknown viruses were isolated from patients with acute upper respiratory tract infections. By electron-microscopy some of them resembled avian bronchitis virus but were distinct from myxoviruses.⁷⁹ A newly isolated virus, Fermon, probably of the picorna group was obtained from children with viral pneumonia.⁸⁰ An agent regarded as Ryan virus isolated from

patients with respiratory tract infections later was identified as an ameba (*Hartmannella*), the clinical significance of which is uncertain.⁸¹ Specific antibody was present in 20% of patients.⁸² Amebas of that group were isolated from the pharynx of healthy persons especially children.⁸³ As mentioned later, amebas also caused encephalitis. These reports resurrect Kofoid's views of amebic infections 35 years ago.

Another 'new' virus resembling the avian bronchitis agent isolated from the throat of a patient caused mild infection in inoculated volunteers. Blood from 29% of persons in Britain contained neutralizing antibody.⁸⁴

Herpes simplex

Herpes simplex virus heretofore considered as relatively unimportant gained much attention. Disseminated herpes simplex infection occurs more often than believed especially in children whose resistance is impaired. In South Africa ninety-three cases were recognized.⁸⁵ Diagnostic methods were described.⁸⁶ The frequent presence of herpes virus in the throat needs further investigation as to its possible role in causing pharyngitis and pneumonia. The virus could be isolated and identified in 4 days. Accurate diagnosis obviates unwarranted antimicrobial medication.⁸⁷ Idoxyuridine is believed to cure herpetic keratoconjunctivitis, but if it also hastens recovery from chemically-induced keratitis,⁸⁸ perhaps its action is nonspecific and not antiviral.

Infectious mononucleosis

Recent investigations revealed unsuspected viral relationships and the long-sought cause of infectious mononucleosis. Cytomegalovirus, a relative of herpes simplex virus, caused mononucleosis-like disease⁸⁹ and hepatitis.⁹⁰ By serendipity, the Henles educed evidence that a herpes-like virus, related to the virus obtained from Burkitt's sarcoma, causes infectious mononucleosis. The virus was visualized by immunofluorescent technique in patients and specific antibody was present in 80% of a population.⁹¹ It must be determined if the three viruses mentioned actually are causes of the respective diseases or commensal. Indirect immunofluorescence in biopsy specimens localized a specific heterophile reactive antigen in the kidneys.⁹²

Recurrent attacks of erythema multiforme after herpetic lesions of the face suggested that hypersensitivity to herpes simplex virus resulted in the generalized vesicobullous eruption.⁹³ Herpes simplex virus inoculated intravenously in pregnant rabbits induced viremia and killed 30% of the fetuses.⁹⁴

Slow viruses

Herpes simplex virus, rubella virus and cytomegalovirus can penetrate the placenta and incite chronic infection as 'slow' viruses. Rubella virus persisted in the lens of an infant for 3 years after infection.⁹⁵ Failure to produce interferon in culture, and insensitivity to the antiviral action of interferon in the circulation, may account for the persistence of cytomegalovirus.⁹⁶ Failure to terminate the excretion of rubella virus may be due to a defect of the cellular immune-function of lymphocytes injured by the virus.⁹⁷ As in human infants with congenital rubella, rubella virus inoculated into newborn ferrets caused chronic inapparent infection detectable for a year.⁹⁸ Current knowledge of slow viruses was summarized in a book.⁹⁹

The causal agent of scrapie was said to be smaller than any known virus. It survives rapid freezing and thawing, boiling for 30 min and exposure in 10% formalin, but is inactivated by urea. No particles were visualized by electron-microscopy. It may be either a microbe or non-living matter.¹⁰⁰

Encephalitis

Herpes simplex came to attention as an important cause of encephalitis.¹⁰¹ It accounted for about 10% of cases.¹⁰² In one study the virus was recovered from the brains of five patients, four of whom died.¹⁰³ In another report, diagnosis also was established by isolation of the virus from the brains of four children. One who recovered had received idoxyuridine.¹⁰⁴ Dermal or mucosal lesions seldom aided diagnosis; biopsy was needed. In other victims described in the 13 May 1967 issue of *British Medical Journal*, recovery occurred in two patients treated with idoxyuridine, but serious physical and mental impairment ensued. Among forty-nine other cases, thirty-four were fatal. If 30% of untreated patients recover, the therapeutic value of idoxyuridine is questionable.

Fifteen per cent of patients died during the Texas epidemic of St Louis encephalitis. One-third of them had other underlying disease.¹⁰⁵

The mortality-rate in general is much lower if all mild and unrecognized cases are included statistically. ECHO virus causes meningo-encephalitis, transverse myelitis and probably other neurologic diseases.¹⁰⁶ Central European encephalitis caused by an arbo virus is less severe than the Russian spring-summer disease.¹⁰⁷ Although rabies is considered to be fatal invariably, Rumanian physicians state that with modern methods of therapy some patients recover.¹⁰⁸ This remains to be proved. Recom-

mendations for the prevention of rabies were outlined.¹⁰⁹ Vaccine prepared in chick or duck embryo cells induced neutralizing antibody in volunteers. Immunization before infection was recommended for veterinarians and others especially exposed to rabies.¹¹⁰

Electron microscopy disclosed inclusion bodies, like those associated with myxovirus, in the brain in two instances of subacute inclusion-body encephalitis. One of the patients had been exposed to canine distemper.¹¹¹ Viruses reach the central nervous system via neural, olfactory and especially the hematogenous routes. The existence of a 'blood-brain barrier' is doubtful.¹¹²

Amebas of the genus *Hartmannella* and *Naegleria* acquired during swimming caused fatal encephalitis.¹¹³

In 1966, the incidence of paralytic poliomyelitis in the U.S.A. was the third lowest recorded. During an epidemic in Texas, sixty-six unvaccinated children were stricken, bringing the total number to 102 cases. Five instances of paralytic disease occurred as vaccine-associated cases in vaccinees, and four instances of the disease occurred in contacts of vaccinees.¹¹⁴

Measles

Measles virus may attack the kidneys. By immunofluorescent procedure, measles antigen was observed in the mucosa of the bladder, and in cells of the tubules and epithelium of Bowman's capsule. Exfoliated giant cells and cells with inclusion bodies appeared in the urine.¹¹⁵

Antibody against measles virus was detected in victims of multiple sclerosis.¹¹⁶ One study confirmed Adams' observation,¹¹⁷ another did not.¹¹⁸ Suggestion of a delayed auto-immune reaction as a cause was made.^{117, 117a} Some forms of chronic encephalitis may be caused by latent measles virus.^{119, 120} The subject was discussed at a conference.¹²¹ Similarly, Dawson's encephalitis may ensue from infection with a 'slow virus'.^{117a}

Mumps

An epidemic of mumps involved 119 of 212 natives in an area of Alaska free from infection for 60 years. Six persons who had had mumps in 1907 were not reinfected, suggesting the existence of durable immunity. Hyperimmune γ -globulin administered prophylactically to fifty-six susceptible persons failed to provide immunity and was not recommended for prevention.¹²²

The attack rate of mumps in children vaccinated with an attenuated live virus was 2% as compared with 61% in control subjects. Protection lasted as long as 8 months and may be perm-

anent.^{123, 124} There is question as to the need for mass vaccination of children for so mild an infection. In rare instances, mumps causes serious orchitis^{124a} and still rarer neurologic disturbances. Mumps caused spinal paralysis in two sisters.¹²⁵

Illingworth called attention to the futility of enforced bed-rest, dietary restriction, medication and quarantine for children with rubeola, rubella, varicella and mumps.¹²⁶

Coxsackie

A large outbreak caused by A₉ virus affected a community in 1963. About 88% of susceptible persons developed antibody to the virus indicating a high degree of communicability. Exanthem, fever, coryza and meningitis occurred.¹²⁷ B₉ virus was usually prevalent in Britain in 1965 affecting chiefly the respiratory and intestinal tract of children. After age 10, neural and muscular disturbance predominated.¹²⁸

Coxsackie viral myocarditis occurred in twenty patients, thirteen of whom had infection of the respiratory tract. Transient cardiomegaly appeared in eleven, leukocytosis in fifteen and recurrence followed in eight.¹²⁹ From fifty-five hearts examined post-mortem, antigens for Coxsackie viruses were demonstrated in the myocardium of seventeen and in the mitral valve of three. Chronic, focal interstitial lesions were seen.¹³⁰ B virus caused pneumonia in infants.¹³¹ Although the incidence of spontaneous abortions increased in Hungary after a large epidemic caused by Coxsackie B₃ virus, the incidence of stillbirths and premature births did not.¹³² Virus A₁₆ was implicated in forty children with 'hand, foot and mouth disease'. In two instances, the presence of herpes simplex virus caused diagnostic perplexity.^{133, 133a}

Miscellaneous viral infections

ECHO type 30 virus caused an epidemic in England.¹³⁴ ECHO 9 virus caused fatal myocarditis.¹³⁵

Complications of varicella or herpes zoster in pregnant women may not be so serious as feared. Of eleven victims, only one had nephritis and hepatitis. Seven women delivered normal full-term infants; three others with neonatal varicella recovered.¹³⁶ Serologic evidence of past or present cytomegaloviral infection was detected in half of forty-two children of migrants, aged 1-13 years. One-third of those less than 4 years old had viruria.¹³⁷ Evidence of cytomegaloviral infection was present in 52%¹³⁸ and in 73%¹³⁹ of patients who had had renal transplants. For leukemic children under intensive chemotherapy,

flouxuridine given with prednisone seemed to cure cytomegaloviral infection.¹⁴⁰

A veterinarian contracted foot-and-mouth disease type C.¹⁴¹ A serious epizootic of foot-and-mouth disease affected cattle in England.¹⁴² Vesicular stomatitis caused mild influenza-like illness in persons in contact with sick animals. Diagnosis was possible only by serologic methods.¹⁴³ A newly recognized disease in Germany among handlers of African monkeys was said to resemble a pox-like infection and hemorrhagic fever.¹⁴⁴ Marburg virus was the cause.¹⁴⁵

More than 1500 instances of infections acquired in laboratories resulted in thirty-nine deaths. Arboviruses especially of Group B accounted for 126 cases in 1967. Infections followed contact with infected animals and inhalation of aerosolized viruses. Many inapparent and mild infections no doubt are unrecognized.¹⁴⁶

An attack-rate of 50% characterized an epidemic of dengue in Puerto Rico.¹⁴⁷ Chikungunya virus and dengue type 2 virus were present in blood from a patient with dengue-like disease. Antibody to both viruses increased.¹⁴⁸ The lesions of Bolivian hemorrhagic fever chiefly involved the reticulo-endothelial organs with hyperplasia and edema. Hemorrhage and congestive changes are common to viral hemorrhagic diseases including yellow fever.¹⁴⁹ Filaments resembling myxovirus in nuclei and cytoplasm of degenerating muscle tissue during chronic polymyositis may be a cause of the disease.¹⁵⁰

A variety of viruses, especially of the exanthems, interfere with the clotting of blood. They affected platelets, injured endothelium and caused hemolysis and disseminated intravascular coagulation.^{151, 152}

The May 1967 issue of *British Medical Bulletin* contains sixteen articles on aspects of medical virology. Reviews of viral infections of the joints¹⁵³ and of the kidneys¹⁵⁴ were published. The scientific aspects of the synthesis of DNA *in vitro* were presented.¹⁵⁵

Viruses and tumors

Particles resembling herpes virus in cultured lymphoma cells were able to infect, to reproduce and to kill the cells *in vitro* and *in vivo*. The agent caused encephalitis in inoculated animals. Similar particles also were present in other cancer cells and in normal human leukocytes. To cause leukemia, the virus probably is activated when helped by unknown factors.¹⁵⁶ Inclusion bodies found in leukemic marrow cells in a patient resembled those present in a variety of other diseases and probably are not of viral origin.¹⁵⁷

Electron microscopy disclosed viral particles in cells from patients with Burkitt's lymphoma. The virus appeared to originate in nuclei and emerge from cells by budding.¹⁵⁸ A herpes-type virus obtained from cultured Burkitt cells induced a persistent chromosomal lesion and often enabled a continuous growth of hematopoietic cells.¹⁵⁹ A related virus probably causes infectious mononucleosis as mentioned previously. An unknown virus was isolated from Burkitt lymphoma cell cultures superinfected with a sarcoma virus. Its causal relationship was undetermined.¹⁶⁰ The problem of viral oncogenesis was discussed editorially¹⁶¹ and an extensive review of research on viruses and cancer was published.¹⁶²

Rous in his Nobel lecture stated 'No virus has yet been found that indubitably actuates tumors in man. Yet this is not to say that viruses play no part in initiating them occasionally'.¹⁶³ According to Dameshek, there is no evidence that viruses cause leukemia in man.¹⁶⁴

Vaccines

An attenuated anti-smallpox vaccine awaits field trial. It does not replace the standard vaccine, but seemed to be safer to use in eczematous children. Fever ensued at times.¹⁶⁵ Warts disappeared after anti-smallpox vaccination in all but one of 165 instances probably as a result of viral antagonism or the action of interferon.¹⁶⁶ Such success was not attained by others, and reaction may be severe.¹⁶⁷ Two years after anti-poliomyelitis vaccination, 96% of children had antibody titers of 8 or more to three types of virus. Antibody to types 2 and 3 declined most except after booster doses.¹⁶⁸

A symposium of fourteen papers about immunization procedures appeared in the October 1967 issue of the *Archives of Environmental Health*. The problems and value of vaccines against seventeen viral diseases were discussed.¹⁶⁹ Official recommendations about the use of measles vaccine were published.¹⁷⁰

Unwanted effects of vaccination

Vaccinia after anti-smallpox vaccination in Britain affected an estimated 5 million persons and caused four deaths between 1951 and 1960.¹⁷¹ A person who reacted violently to vaccination was the source of an epidemic of vaccinia involving twenty-two people and 450 cows. Milker's nodules were suspected at first.¹⁷² Anti-smallpox vaccination for the illogical treatment of recurrent herpetic lesions caused death from vaccinia necrosum.¹⁷³

Reaction to live measles vaccine after previous injection of inactivated vaccine suggested discon-

tinuance of the latter which is of less value anyway.¹⁷⁴ Severe measles with pneumonia and unusual eruptions as a result of altered reactivity, affected children 5-6 years after receiving inactivated measles vaccine.¹⁷⁵ Vaccination also caused thrombocytopenic purpura.^{176, 177}

In Dakar, 243 cases of encephalitis and twenty-three deaths, chiefly among children, followed vaccination with antiyellow fever vaccine. The risk was about two cases per 1000.¹⁷⁸ The tragedy recalls the occurrence of hepatitis after similar vaccination during World War II. Paralytic poliomyelitis caused by a vaccine-like strain of virus affected a child¹⁷⁹ and a man¹⁸⁰ who had had contact with orally vaccinated children. While vaccination might control outbreaks of foot-and-mouth disease in cattle, it will not eradicate infection, but actually may favor its perpetuation.¹⁸¹ Among twenty persons who received the Semple rabbit-brain vaccine after exposure to a rabid leopard, thirteen developed lethargy and other unpleasant symptoms 4 days after vaccination began, and nineteen noted erythema, induration and tenderness at the site of injection. Axillary lymphadenopathy occurred in seven and two were severely ill.¹⁸²

Sir Graham Wilson's book discusses the hazards of vaccination, particularly *en masse*.¹⁸³ Lederberg pointed out possible harmful genetic effects in man after inoculation with live viruses.

Interferon

A double-stranded RNA injected into mice induced the appearance of interferon which protected them against infection with viruses.¹⁸⁵ The discovery of interferon raised unfulfilled hopes of its action to prevent or cure viral infections. A substance antagonistic to interferon was discovered which stimulates viruses. The predominant action of either interferon or 'stimulon' may determine the occurrence or the outcome of a viral infection.¹⁸⁶ Merigan discussed the problems involving interferon and referred to four other reviews of the matter.¹⁸⁷

Mycoplasma pneumoniae

Nearly one-half of students admitted to an infirmary had acute respiratory infection. Of 136 with pneumonia, *M. pneumoniae* was the cause in 52%, but in only about 2% did it cause upper respiratory tract infection. Over a 12-year period, the incidence of pneumonias increased cyclically every 4 or 5 years.¹⁸⁸ *Mycoplasma pneumoniae* caused an outbreak of respiratory tract disease in Scotland that persisted from January to June 1965. Symptoms in some victims persisted for weeks. Most were ambulatory, three of forty

had pneumonia and four had myringitis.¹⁸⁹ At the same time in West Virginia, among 208 patients with acute respiratory tract disease, sixty-seven were infected with *M. pneumoniae* and of these thirty-seven had pneumonia, five had myringitis and two had otitis media. All recovered. The mean age of victims was 46 years. The infection was suspected but unproved in forty-two other patients. Thirty-four patients had other associated diseases. The average duration of disease was 28 days in non-pneumonic patients and 41 days for the pneumonias. For diagnosis the agglutination test for *M. pneumoniae* was not so sensitive as the complement fixation or immunofluorescent procedures, but it is more reliable than the cold-agglutinin test.¹⁹⁰ Therapy with antimicrobics did not give striking results. Fatal infection, acute hemolytic anemia and multiple thrombosis occurred in an aged patient. *M. pneumoniae* was cultivated from the lung and bronchial lymph nodes.¹⁹¹

An epidemic of *M. pneumoniae* infection in autumn affected 90% of children in an institution, especially the mongoloids. About 64% of adult attendants were infected. The incidence of pneumonia was 28% in the sick children and 7% in the adults.¹⁹² In another study, *M. pharyngis* and *M. salivarium* were present in the throat of many healthy children. *M. pneumoniae*, however, was present in twenty-seven of forty-six children and caused pneumonia in five.¹⁹³ In family studies for 8 months, 50% of members initially had positive cultures. After 8 weeks, the figure rose to 90%. Pneumonia occurred in fourteen, milder disease in eighteen and inapparent infection in six. Tetracycline failed to influence the course of disease and did not eradicate the microbe.¹⁹⁴ The microbe rarely causes otitis media.¹⁹⁵ The causal relation of *M. pneumoniae* to erythema multiforme exudativum was demonstrated culturally and serologically in a patient.¹⁹⁶

Erythromycin was the most active of twenty-one antimicrobics against *M. pneumoniae* *in vitro*. Penicillin was inactive.¹⁹⁷ The microbe persisted in the respiratory tract in infected volunteers after therapy with either tetracycline or erythromycin and disease recurred in one instance.¹⁹⁸ Inactivated vaccine evoked antibody in ten of nineteen volunteers. After a challenge inoculation only one of the ten became sick while respiratory tract infection developed in seven of nine who failed to develop antibody, and in ten of thirteen unvaccinated persons.¹⁹⁹

A newly-described mycoplasma probably caused spontaneous abortion and inflammation of the fetal membranes. It was present in the urine of both wife and husband.²⁰⁰

Viral hepatitis

Five patients contracted viral hepatitis 49–103 days after exposure to chimpanzees.²⁰¹ The attack-rate of viral hepatitis among missionaries abroad was 1.6% to 5.5% a year.^{202, 202a} The virus persists in insufficiently steamed clams.²⁰³ Serum hepatitis occurred among competitors in cross-country races in Sweden. Infection presumably was acquired through scratches and wounds bathed with polluted water. The outbreak ceased when hygienic principles were observed and recurred when they were discontinued.²⁰⁴ An outbreak of serum hepatitis affected twenty-seven narcotic addicts after the use of contaminated syringes and needles.²⁰⁵ Cytomegalovirus was present in the urine of two patients with cholestatic hepatitis.²⁰⁶ Whether it was the cause or a commensal cannot be said. Toxoplasma caused hepatitis in two adults. The microbe was demonstrated immunofluoroscopically in cells in necrotic areas. Specific antibody appeared in the blood.²⁰⁷ No virus particles, no antigen and no cytopathologic effects were observed in a wide variety of cell-cultures inoculated with serum from patients with infectious hepatitis.²⁰⁸ A different approach and different methods are needed to discover the cause.

Bacillary infections

Tuberculosis

Knowledge of tuberculosis acquired since the bacillus first was seen by Robert Koch 87 years ago was reviewed by Myers who himself devoted nearly a half century to studies and control of the disease.²⁰⁹ His efforts reduced the incidence of tuberculin reactors in Minnesota from 60% in 1921 to about 3% in 1967. In contrast, today in Saigon, 85% of adults are reactors. Eventually to eradicate the disease, reactors discovered by the tuberculin test must be controlled and effort made to rid them of the bacilli. This has not been accomplished, and for several reasons may never be.

Confusion exists as to whether hypersensitivity to tuberculo-protein is beneficial or hazardous. In itself it probably is neither, but is an indication of the presence of infection. Reactors to tuberculin are already infected and their chance of developing chronic tuberculosis is greater than for non-reactors.²⁰⁹ Non-reactors may of course be primarily infected and become reactors.^{210, 211} Vaccination with BCG was advocated²¹² but it induces hypersensitivity and thus destroys the value of the skin test to discover infected persons. The weak immunity afforded by vaccination does not rid the body of tubercle bacilli.

Chemoprophylaxis with isoniazid was recommended officially for persons with apparently inactive tuberculosis, for ex-patients, for those with significant roentgenographic pulmonic changes who react to tuberculin, and for reactors whose roentgenograms show no lesions, especially if reaction to the dermal test changes from negative to positive.²¹³ Prophylaxis with isoniazid reduced the incidence of tuberculosis about 60% in a heavily infected population in Alaska.²¹⁰ After nearly 3000 tuberculin-positive schoolchildren received isoniazid for a year only one case of tuberculosis occurred, as compared with twenty-five cases among 1192 untreated reactors. The cost of treatment per person was \$80.²¹⁴

Several 'micro-epidemics' occurred on shipboard among naval personnel. Isoniazid given prophylactically to reactors caused reversion in most of the recent converters, but not in those with established disease.²¹⁵ Both good and bad long-range effects must be considered. Because the drug is suppressive, infection may be perpetuated and will obstruct eradication.

Therapy

Pyrazinamide, ethionamide, cycloserine, kanamycin, viomycin, capriomycin and ethambutol were considered as 'second-line' anti-tuberculosis drugs when the usual ones are not given. Each may cause serious toxic effects and should be applied only if the physician has had experience with their use and has facilities available to detect toxicity.²¹⁶ Methylprednisone injected intrathecally for sciatica(!) incited tuberculous meningitis.²¹⁷

Vaccination with BCG was said to prevent leprosy. Four years after vaccination began, nineteen cases occurred among 8000 vaccinees and 143 cases in the control group.²¹⁸

Atypical tubercle bacilli

In recent years, the reduction in the number of people who react positively to the standard tuberculin test to less than 15% of a population made it possible to detect widespread inapparent infection with other mycobacteria. According to Smith, atypical mycobacteria now cause more infections in young persons than *M. tuberculosis*. From 15% to 50% of recruits reacted to antigens of three atypical tubercle bacilli. Atypical forms reside in soil like *Histoplasma* and *Coccidioides*. They were thought not to be transmitted from person to person,^{212, 219} but the question arose on shipboard whether or not conversion of tuberculin reactions in some previous non-reactors was caused by inapparent infection with atypical mycobacteria acquired by contact with a carrier.²²⁰

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The medical significance of *Mycobacteria* other than *M. tuberculosis* still is unclear and their classification is uncertain. Of 291 strains examined, 240 belonged to Group I, three to Group II, fourteen to Group III, nineteen to Group IV and fifteen were unclassifiable. Group I bacilli were the most sensitive to isoniazid. There seemed to be no geographic predominance of distribution.²²¹ Low-catalase strains of *M. kansasii* were not associated with disease in man, Group II scotochromogens, Group III non-photochromogens often were and the remaining subgroups of scotochromogens rarely were.²²²

Salmonellosis

Outbreaks of salmonellosis originated from pies made with frozen eggs contaminated with different types of salmonellas²²³ and from powdered milk.^{223a} Salmonellosis occurred in nineteen of 5000 patients with neoplastic disease. Bacteremia occurred in seven and pneumonia, meningitis, peritonitis and urinary tract infection in six others.²²⁴ Salmonellosis, a common complication of schistosomiasis in Egypt, is essentially a urinary tract infection manifested by long, remittent fever.²²⁵

Carmine dye, used as a stool marker, contaminated with *Salmonella cubana* caused infections in patients in hospitals as reported in two papers in the 13 April 1967 issue of *New England Journal of Medicine*. *Salmonella typhi* was present in the blood but not in the feces or urine of twelve patients who did not have typhoid. Evidently in carriers, salmonellas from a residual focus of infection may be shed into the blood as well as the feces.²²⁶

Dysentery

More than 500 persons who drank an orange-juice beverage were stricken with nausea, vomiting, diarrhea, headache and fever presumably caused by a virus.²²⁷ An attack-rate of 17% characterized an epidemic of diarrheal disease in a small community. Households were affected. The water supply was suspected as the source, but no bacteria could be incriminated as the cause.²²⁸ The possibility of air-borne viral dysentery was not mentioned. No causal agent could be identified in jejunal, ileal, or fecal specimens from twenty-nine other adults with acute diarrhea. The chief change was an increased number of bacteria in the jejunum.²²⁹

During a small outbreak of *Sh. flexner* dysentery, bacilli resistant to five antimicrobics were excreted. The resistance was transferred to an antimicrobial-sensitive strain.²³⁰ Coxsackie, ECHO and adenoviruses were present in stools of more than 10%, *Shigella* and *Salmonella* in

3% and *Esch. coli* in 16% of infants with severe diarrhea.²³¹

Whooping cough, at times, is caused by parainfluenza viruses and other microbes. When *B. pertussis* is causal, the term pertussis is preferred. Secondary bacterial complications rarely occurred in 140 cases.²³²

Tetanus

Nearly three-quarters of known instances of tetanus in New York City occurred in narcotic addicts, mostly in young Negroes in whom the case fatality rate was 87% compared with 38% in non-addicted patients.²³³ As had long been suspected, the therapeutic use of antitetanus serum was of no value once the disease is fully developed.^{234, 235} Yet, it was said to be beneficial for neonatal tetanus.²³⁶ The therapeutic effect of hyperbaric oxygen was disappointing.^{236a} Tetanus toxoid provides immunity lasting 15–20 years. 'Booster' injections should not be given annually. Except in an emergency, a reinforcing dose is recommended at 10-year intervals for previously immunized persons. Otherwise, the population at large will by hypersensitized to toxoid without adding to protection against tetanus.²³⁷

Plague

During an outbreak of plague in Vietnam in 1965, *Past. pestis* was present in the throat of fifteen of 114 healthy persons.²³⁸ Carriers exist and undiagnosed mild attacks occur which if included statistically increase the incident-rate and lower the usually stated mortality rate. Several patients with bubonic plague were in Saigon hospitals during my presence in April 1967. An American, previously vaccinated, contacted plague and recovered. Vaccination was thought to have conferred some protection²³⁸ but its value is questionable. Three cases of meningeal plague occurred in children in New Mexico.²⁴⁰ As recorded in three papers in the December 1967, *Public Health Reports*, six Navaho children had plague during an epizootic among prairie dogs.

Tularemia affected 536 persons in Missouri between 1949 and 1965. Ticks were the vectors in 26% of cases, contact with rabbits occurred in 13% and in the rest the source was unknown.²⁴¹

Cholera

Cholera as a unique infectious disease resembles the effects of a hydragogic purgative without inflammation of the enteric mucosa. Suggestion was made that 'cholera', a product of *V. comma* apart from its endotoxin, does not

cause epithelial denudation, does not inhibit the 'sodium pump', nor increase permeability of the membrane, but stimulates epithelial cells to secrete the usual fluid in abnormally large amount.²⁴²

V. comma resident in the gall bladder of convalescent patients may account for the carrier state and serve as a source of infection.²⁴³ Phillips received a deserved award for his contributions to the knowledge of cholera, but Chinese physicians in 1945 already showed that the mortality-rate could be reduced to nearly zero by prompt therapy.²⁴⁴

Melioidosis, endemic in Australia, Southeast Asia and nearby islands,²⁴⁵ has a spectrum of severity ranging from inapparent to fatal disease. It appears as pneumonia, septicemia, localizes in joints, skin, liver, and bones and may become chronic. The death-rate is not so high as believed. A survey disclosed specific antibody in 15% of natives. Eight deaths occurred among thirty-five American victims who were or had been in Vietnam.²⁴⁶ Nine had mild pneumonia. As in tuberculosis or histoplasmosis, transient cavitation may ensue.²⁴⁷ Therapy was recommended with dangerously high dosage of kanamycin, chloramphenicol and novobiocin.²⁴⁸

Brucellosis (Mediterranean Fever) affects 20% of bison in Yellowstone Park.²⁴⁹

L forms of *H. influenza* were present in sputum of patients treated with penicillin. When treatment was stopped, L forms reverted to the usual bacillary forms.²⁵⁰

Coccal infections

Streptococci

Among 4000 victims of scarlet fever, 171 had second attacks during a 4-year period. Reinfection presumably depended on the kind of penicillin administered during the first attack.²⁵¹ An anti-streptococcal vaccine is under trial, but if scarlet fever leaves transient immunity, what can be expected of a vaccine? As yet, no coccal infection can be prevented by vaccination. Identification of streptococci made from throat cultures in physicians' private offices often is faulty.²⁵²

Hemolytic streptococci caused ninety-five cases of pneumonia among recruits, without preceding viral respiratory tract infections. Empyema, pericarditis and abscesses occurred. Nephritis ensued in one case, but rheumatic fever was not observed.²⁵³ In a community, a second epidemic of acute nephritis caused by type-49 streptococci recurred after 17 years.²⁵⁴ After many previously unsuccessful attempts, acute glomerulonephritis

similar to that in man was induced by inoculating rabbits with a nephritogenic strain of streptococci.²⁵⁵ An immunosuppressant component of Group A streptococci was discovered.²⁵⁶

Staphylococci

Tests of antimicrobial sensitivity on 442 strains of staphylococci obtained from children not in hospitals disclosed high-resistance to penicillin in 90%. The majority also resisted bacitracin, tetracycline, kanamycin and streptomycin. Evidently antimicrobial-resistant staphylococci are not confined to hospitals.²⁵⁷ 'Toxic epidermal necrosis' may be caused by a unique toxic effect of staphylococcus type 71.²⁵⁸

The death-rate from pneumococcal meningitis ranges between 10% and 65%. The presence of associated disease is of graver import than advanced age.²⁵⁹ Pneumococcal bacteremia caused a self-limiting febrile disease in three infants.²⁶⁰ Six instances of pneumococcal peritonitis occurred in patients with postnecrotic cirrhosis.²⁶¹

Meningococcosis has a range of severity varying from mild to fatal disease. During a study of 112 cases, the death rate was 7%. Adrenal insufficiency plays no role in accompanying shock. Corticosteroids were of no value in treatment. Penicillin is the drug of choice for therapy. Ampicillin, tetracycline, erythromycin and cephalothin also are effective. No single antimicrobial nor combination is satisfactory for mass prophylaxis or for treating carriers. Early diagnosis and treatment are more effective.²⁶²

Pneumonias

Three papers on pneumonia appeared in the December 1967 issue of the *American Review of Respiratory Disease*. Pseudomonal pneumonia, as described in seven patients with severe predisposing disease, is a distinct entity. It was characterized by firm necrotic lesions with many bacilli and monocytic cell predominance, but minimal inflammation. Features of pneumonias caused by *Proteus*, *Pseudomonas* and *Bacteroides* were described in three respective papers in the February issue of the *Annals of Internal Medicine*. In most instances, the infections occurred in debilitated patients. Information of *Pneumocystis carinii* pneumonia was reviewed. No distinctive roentgenographic shadows distinguish viral pneumonias from those caused by *Mycoplasma*. Psittacosis is easily confused with bacterial pneumonias. Pericarditis, arthritis and hepatitis occur.²⁶³

Endocarditis

An editorial called attention to the changing

nature and increased incidence of endocarditis in old age, during other chronic diseases and after cardiac surgery. It often is caused by penicillin-resistant staphylococci, enterococci and occasionally by *Brucella*, *Candida*, *Histoplasma*, *Coxiella* and others. Although penicillin given prophylactically to 'cover' exodontia or tonsillectomy may be important, long-term antimicrobial therapy favors the replacement of sensitive streptococci by resistant microbes. Against general advice to use bactericidal agents, sulfonamides instead were recommended for prophylaxis against rheumatic fever since they suppress infection with hemolytic streptococci without suppressing the less sensitive *Str. viridans* in the mouth.²⁶⁴ The incidence of bacterial endocarditis in rheumatic children who received prophylactic antimicrobics was about the same as in the pre-antimicrobial era. Evidently, therapy did not increase the risk.²⁶⁵ Penicillin-, ampicillin- and cephaloridine-resistant *Streptococcus viridans* was present in the saliva of children who had received penicillin.²⁶⁶

Surgical replacement of infected cardiac valves during subacute bacterial endocarditis was performed in three patients. The procedure was recommended when antimicrobial therapy fails and for intractable cardiac failure.²⁶⁷ Combined cephalothin and streptomycin were not superior to penicillin for treating enterococcal endocarditis.²⁶⁸ Penicillin alone or with streptomycin is the drug of choice, but seventy-one (18%) of 400 patients were sensitive to penicillin. Urgency in fifty-six of these required administration of penicillin and twenty-two had an allergic reaction in contrast to three who previously had had no reaction. As a rule, unless survival is dubious, nonpenicillin agents should be used.²⁶⁹

Rare instances of endocarditis caused by an *Actinobacillus*,²⁷⁰ by a chromogenic mycobacterium,^{270a} and by *H. capsulatum*²⁷¹ were observed. Reports of endocarditis caused by *Moraxella*,²⁷² and others caused by *Esch. coli* and *Salmonella* appeared in the October 1967 issue of *Archives of Internal Medicine*.

A second victim of *C. neoformans* endocarditis was cured by treatment with amphotericin B for 35 days. No evidence of nephrotoxicity nor recurrence of infection followed.²⁷³ A murine adenovirus caused endocarditis in inoculated mice similar to that caused by Cocksackie A₄ virus. Adenovirons and inclusion bodies were visualized in nuclei of endothelial cells.²⁷⁴

Twenty-nine of fifty hearts of children examined post mortem had interstitial myocarditis. Cocksackie virus B antigen present in twelve suggested a causal relation. Probably cases previously named idiopathic myocarditis now

can be specifically diagnosed. The lesion may be a cause of sudden death of infants.²⁷⁵

Venereal infections

Gonorrhea

Because of its increasing incidence, gonorrhea was said to be out of control and excepting colds, is the most prevalent infectious disease in the United States. An estimated 3–4 million infections occur annually but less than 10% are reported officially.²⁷⁶ In New York City the rate among teenage persons has increased 264% since 1955, and 9% more than last year.²⁷⁷ Gonorrheal pharyngitis was described for the first time.²⁷⁸

In Canada, 27% of gonococcal strains isolated from patients had developed resistance to penicillin, some of them to 1.0 unit/ml.²⁷⁹ Cephalosporin may be a substitute for therapy. In different areas of the United States, the percentage of penicillin-resistant strains increased from 11% in 1962 to 60% in 1966.²⁸⁰

Three articles about treating gonorrhea among military personnel appeared in the 6 November 1967 issue of *Journal of the American Medical Association*. In naval service, failure followed therapy with penicillin in 29% of cases, whereas tetracycline was 'always' successful. Postgonococcal urethritis affected about two-thirds of the patients, but less often after tetracycline had been given. *Mycoplasma* often was the cause. Tetracycline was said to be effective in treating nongonococcal urethritis.

Nearly 90% of cases of gonorrhea and syphilis are not reported to public health authorities by private physicians. Physicians usually were unwilling to do so lest the patients be embarrassed. Hence source and contact are undetected and infection continues to be spread.²⁸¹ The availability of antimicrobics and recently of contraceptive medication was said to favor promiscuity and contribute to the increased incidence of venereal diseases.

Spirochetes, demonstrated by immunofluorescence, were present without evidence of abnormalities in the liver, aqueous humor and spinal fluids of patients with late seronegative syphilis.²⁸² Motile spirochetes resembling *Tr. pallidum* were present in the aqueous humor of patients who had had syphilis years before and apparently had been adequately treated.²⁷³

A vaccine against syphilis is under investigation.²⁸⁴ So far, vaccines have been successful in preventing some viral infections, less so for rickettsioses and one or two bacillary diseases, and least or not at all against cocci or fungi. It will be surprising if treponemal, protozoal or mycotic infections can be prevented by vaccination.

Other infections

Malaria

Falciparum malaria in Vietnam is characterized by high fever, headache, myalgia, gastrointestinal and pulmonic involvement. Recrudescences ensued in 95% of victims after therapy with chloroquine or quinine alone or in combination. Pyrimethamine gave better results, but the best were achieved with sulfadiazine and diaminodiphenylsulfone.²⁸⁵ In other studies, colchicine-quinine reduced the recurrence rate.²⁸⁶ About 1.6% of 1200 patients with malaria developed the cerebral form. With proper therapy, all recovered without residual harm.²⁸⁷ Malaria must be suspected in febrile illnesses in south-east Asia and northern South America.²⁸⁸

Most military personnel who developed malaria on return from Vietnam, did so after several weeks. In 83% of cases, *Pl. vivax* was the cause.²⁸⁹ Recent progress and problems of malaria were reviewed by Neva. Control is possible but eradication still is a distant goal.²⁹⁰

Mycoses

Histoplasmosis

The ecology of histoplasmosis was discussed. Podzolic soil, bird manure, proper conditions of temperature, humidity, and winds are necessary for the existence of *H. capsulatum* in nature.²⁹¹ The highest incidence of disease and deaths occurs in age groups less than 1 year and between 46 and 64 years.²⁹¹ Thirteen of seventeen bats in Alabama harbored *H. capsulatum*. Guano collectors, speleologists and cleaners of avian roots are at risk.²⁹² In 1963, histoplasmosis was observed in 147 patients with nine deaths in Montreal. Many undiagnosed mild infections probably occurred. The source seemed to be in soil at a bird-roost.²⁹³ In different regions of Colombia, South America, from zero to 74% of the population reacted to the histoplasmin skin test.²⁹⁴ Lingual ulceration was observed in a patient with disseminated histoplasmosis. The lesion disappeared after administration of amphotericin in a total amount of 2530 mg for 5 months.²⁹⁵ Histoplasmosis presumably caused choroiditis in 190 patients.²⁹⁶

Asymptomatic or inapparent cryptococcal infection is not uncommon and often results from the inhalation of dust especially in areas occupied by pigeons. The dermal test with cryptococcin gave positive results in 32% of pigeons fanciers, and 4% of others.²⁹⁷ Candidemia without evidence of actual infection needs no therapy except to remove resistance-impairing factors if possible. If invasion and ill-

ness occur or if iatrogenic factors exist, therapy with amphotericin is needed.²⁹⁸

Only eight of 160 patients with cephalic mucormycosis survived. Most victims had been debilitated previously and 42% were diabetic.²⁹⁹ Maddy reviewed the epidemiology and ecology of deep mycoses of man and animals.³⁰⁰

Nosocomial infections

Reports about nosocomial and iatrogenic infections emphasize the growing importance of the problem often resulting from mismanagement, but also from the unavoidable use of resistance-suppressant agents and procedures. In one hospital, septicemia with Gram-negative bacilli increased six-fold after the 'golden age' of antimicrobial therapy ended in 1955.³⁰¹ Immunosuppressive therapy has increased the incidence of infections with *Pneumocystis carinii*.³⁰² Six patients with underlying disease who received immunosuppressive drugs had *Pn. carinii* pneumonia. Diagnosis was made antemortem in only one instance by pulmonic biopsy. Treatment with pentamidine seemed to be therapeutically effective.³⁰³ ^{303a} *Pseudomonas* is a hazard in surgical practice.³⁰⁴ Gram-negative bacillæmia, staphylococcal and fungal infections were major causes of death in leukemic patients. The incidence of infection increases in proportion to the duration of leukemia and the use of therapeutic agents.³⁰⁵

Gram-negative bacilli have replaced staphylococci as causes of hospital-acquired infections particularly of the respiratory and urinary tracts. In one hospital, Gram-negative bacilli accounted for two-thirds of cases.³⁰⁶ Elsewhere, eighty-two cases of pneumonia caused by *Klebsiella- enterobacter*, *Esch. coli*, *Pseudomonas*, *Bacteroids*, *Proteus*, *H. influenza* and *Achromobacter* accounted for 4% of all pneumonias in 30 months. *Esch. coli* infection in twenty victims, mostly chronically ill and more than 50 years old, gave a death-rate of 60%. Kanamycin was the therapeutic agent of choice.³⁰⁷ Nine of sixteen debilitated patients with *Serratia marcescens* septicemia died.³⁰⁸ Kanamycin at present is the drug of choice for treatment. *Listeria monocytogenes* caused bacteremia or meningitis in sixteen patients with lymphomas. Antimicrobics inhibited the bacilli *in vitro*, but had little or no therapeutic effect.³⁰⁹ Systemic mycosis involved twenty-three of fifty-seven patients who had had renal transplantation and immunosuppressive therapy.³¹⁰ Among ninety-six heroin addicts, forty-two had hepatitis; twenty-one, cellulitis or thrombophlebitis; seventeen, pneumonia, eight had endocarditis and one had tetanus.³¹¹ Nine

of eleven others with pulmonic infections had septicemia and two died.³¹²

About one in 1500 patients died from nosocomial infections in a hospital.³¹³ Post-operative 'Gram-negative' shock occurred eighteen times often in diabetic patients than in others.³¹⁴ A prosthetic device replacing the aortic valve was the nidus of infection with *Histoplasma capsulatum*.³¹⁵

Miscellaneous items

According to Freeman, about 80% of patients with chronic urinary tract infection have relapses after apparently successful antimicrobial treatment. In a 13-month period relapse occurred in only 21% who were given methenamine mandelate continuously. In those who received nitrofurantoin or sulfamethizole, 42 and 55% had recurrences, and 87% in placebo-treated patients. *Esch. coli*, *Klebsiella*, *Aerobacter* and *Pseudomonas* were implicated. Mixed infection was present in 15%.³¹⁶ Urine often inhibits growth or is bactericidal for *Esch. coli* and other Gram-negative bacilli, for enterococcus and *Staph. albus*.³¹⁷

Toxoplasmosis was acquired by thirty-eight adult patients, and the parasite was isolated from the lymph nodes of ten. Lymphadenopathy, fever and malaise were the chief features, but myocarditis, encephalitis and chorioretinitis occurred. The disease usually is self-limiting.³¹⁸ A pathologist acquired toxoplasmosis at necropsy on a patient with underlying Hodgkin's disease.³¹⁹

Protoplasts of *Str. fecalis*, *Str. pyogenes* and *Esch. coli* were killed by serum while their bacterial forms were resistant. In contrast, protoplasts of *P. mirabilis* resisted serum, but the bacterial forms did not.³²⁰

Accidental inoculation, tick bites and possibly airborne transmission caused Rocky Mountain spotted fever in five laboratory workers in an 11-year period. Four had been vaccinated previously.³²¹ Since 1950, 2700 cases of laboratory-acquired infections and 107 deaths were recorded. Arbo viruses accounted for 428 cases and sixteen deaths.³²²

Squirrels infected with *L. grippotyphosa* were the source of leptospirosis in four persons.³²³ Electron-microscopy disclosed what appeared to be pathogenic spirochetes invading colonic mucosa.³²⁴ Similar observations suggested that some microbes enter the mucosa without causing harm.³²⁵ Schistosome cercarias penetrated the skin of mice but failed to develop into adult worms if 14, 15-epoxygeranylgeranoil had been applied prophylactically.³²⁶ Filtration removed hundreds of schistosome flukes from the blood

of patients after their dislodgement from the liver with antimony tartrate.³²⁷ Thiabendazole seemed to cure severe infection with strongyloides.³²⁸

Among 100 febrile American servicemen in South Vietnam, diagnosis was achieved in seventy-four. Dengue, chikungunya infection, scrub typhus and falciparum malaria predominated. Melioidosis, leptospirosis, cholera and plague were not encountered in the group observed.^{329, 329a}

Serologic evidence of infection with a variety of microbes pathogenic for man was found in fish from polluted waters.³³⁰ Filamentous bacteria grew at temperature of 91.5°C in hot springs in Yellowstone Park. The upper limit of temperature at which microbes survive and grow is unknown.³³¹

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