ANNUAL REVIEW

Infectious diseases

Annual review of significant publications

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Introduction

Publications in 1966 indicated the continued search for new and better antimicrobial drugs, but also emphasized many harmful effects from their logical application and especially from their indiscriminate use. Alarm again was raised about the increasing incidence of nosocomial and iatrogenic infections caused by antimicrobial-resistant Gram-negative bacilli, by latent viruses and fungi. More facts accrued about the multitropism of viruses usually regarded as selective of one tissue or organ. Progress was made in the preparation of vaccines against a number of viral diseases and antiviral chemical agents for their prevention and treatment are under investigation. The aetiological relation of viruses to cancer and lymphomas in man remains unclear. The Asian epidemic of cholera provided opportunity for extensive investigation. War in south-eastern Asia induced a resurgence of interest in exotic infections.

Antimicrobial agents

The indiscriminate application of antimicrobics continues. An investigation in eighteen hospitals disclosed that 26% of patients received antibiotics, in one instance 40%. Patients in a 500-bed hospital paid \$20,000 (£6944) in 1 month for antimicrobics which accounted for 60% of the total charge for drugs. Twelve pounds (5.5 kg) of penicillin were dispensed monthly! Because so few infections are amenable to antimicrobial therapy, an estimated 90% of it is unnecessary.¹ Eight tons of penicillins were prepared in 1964, and 2000 semisynthetic ones have been investigated.

It is of interest that 75 years ago quinine was regarded as the 'wonder' drug and was used as indiscriminately for respiratory tract infections and for fevers in general as antimicrobics are used now. Menthol in an oily nasal spray, antipyrin,

acetanilid and phenacetin, now known to be dangerous, were and still are widely used for treatment.² Because bodily temperature higher than the norm is unfavourable to viruses, antipyretic drugs rarely should be prescribed for fever.

Reports of the failure of antimicrobial prophylaxis for surgical wound infections continue to appear,³ but seem to be generally unheeded. No differences accrued in the number of postoperative infections among 150 surgical patients whether or not patients received methicillin or chloramphenicol.⁴ The same applies to prophylaxis for extensive burns.⁵

In a 5-year study, British observers found little benefit either prophylactically or therapeutically from the administration of antimicrobics to victims of chronic bronchitis.⁶ This is not surprising if viruses often are causes. In one study of fifteen patients for 2 years, seventy-five periods of illness were associated with viruses, 23% of which were rhinoviruses.⁷ 'Anticold' nostrums that contain antimicrobics were suppressed by the U.S. Federal Drug Administration.⁸

A useful outline of measures used to select appropriate antimicrobics, the manner of their application and precautions against adverse reactions was published.⁹ If it is adopted much needless therapy would be avoided.

New antimicrobics

Among newly introduced antimicrobics are ferrimycin, verrucarin, moenomycin, kasugamycin, sugordomycin,¹⁰ hetacillin, doxycycline, hedamycin, leucomycin, rifamycin,andomycin, garamycin, hamycin and lysostaphin.¹¹ One wonders how many are different and superior to ones now in use, and which ones will survive the test of time. Several authorities doubt that those now at hand will be superseded. The bewildering number of antimicrobics makes it difficult for a physician to decide which one to use for what infection, how much to use and how.

Ampicillin is bactericidal and resembles cephalothin and tetracycline in its effects. It is active

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against enterococci and *Proteus*, but not against penicillin-resistant staphylococci, *Klebsiella* or *Pseudomonas*.¹² It was as effective as penicillin for the treatment of bacterial pneumonias,¹³ for pneumococcal, meningococcal and *H. influenzae* meningitis.¹⁴ Cloxacillin, another semisynthetic penicillin, acts like oxacillin and against penicillin-resistant staphylococci.¹⁵

For several reasons, including its greater action against gonococci,¹⁶ cephaloridin is superior to cephalothin.¹⁷ It was effective against all Gram-positive coccal infections, excepting enterococci, against penicillin-resistant staphylococci, most strains of coliforms and some strains of *Proteus*. Large dosage was nephrotoxic.^{18, 19} Cephalothin may cause allergic reactions in patients sensitive to penicillins.^{20, 21} Cephalosporin cured endocarditis in penicillin-sensitive patients.²²

Kanamycin attacks Gram-negative bacilli excepting *Pseudomonas*, and is useful for tuberculosis that resists other agents. Some staphylococci have become resistant. Thirty tons of kanamycin were used in 8 years, but it is being supplanted by semisynthetic penicillins.²³ Gentamycin is bactericidal and more active than streptomycin and kanamycin against *Pseudomonas* and also is active against neomycin-, bacitracin- and kanamycin-resistant staphylococci.²⁴

Penicillin, erythromycin, ampicillin and lincomycin were equally effective in the treatment of haemolytic streptococcal infections in children and in eliminating cocci from the throat. Ten to 30 days after therapy, recurrent infection or the carrier state ensued in about 20% of patients.²⁵ Drugs of choice for *E. coli* infections are ampicillin and tetracycline; for nonmotile *Klebsiella*, cephalothin and kanamycin; for motile *Aerobacter*, kanamycin and chloramphenicol; for *Proteus mirabilis*, ampicillin and kanamycin; for indole-positive *Proteus*, kanamycin; and for *Pseudomonas*, colistin and polymyxin B.²⁶ According to Foster's advice, kanamycin or neomycin is best for *E. coli* infections; tetracycline or chloramphenicol for *Aerobacter* and neomycin or kanamycin for resistant *Proteus*.²⁷ Evidently, at present, opinions differ.

Candicin, whose antifungal spectrum resembles amphotericin B, was effective in the treatment of candidal vaginitis and tolfanate for the treatment of cutaneous infections.²⁸

At the December conference arranged by the New York Academy of Sciences, ampicillin was said to increase more slowly, attain a lower level, and persist longer in the blood than penicillin because of lesser renal excretion. Ampicillin changes to hetacillin *in vivo* and neither are effective against coliforms, aerobic streptococci or

Bacteroides. Ampicillin is as effective as chloramphenicol for typhoid and is of value in treating enterococcal endocarditis, meningococcal meningitis and shigellosis. Hetacillin cured pneumococcal pneumonia, but was ineffective for *Klebsiella*, *Pseudomonas* and penicillinase-producing staphylococci. Ampicillin, cephalothin and cephaloridine were of equal value for urinary tract infections. Kanamycin, though toxic, probably is the best single drug for Gram-negative bacillary infections. Lincomycin was not mentioned. Corticosteroid therapy is of doubtful value for the treatment of shock in Gram-negative bacillary sepsis.

Unwanted effects of antimicrobics

Reactions to drugs occurred in about 11% of patients in a hospital.²⁹ Elsewhere, 20% of patients had iatrogenic disease either from therapy or diagnostic procedures. *Pseudomonas* infections followed the use of cephalothin and *Klebsiella* infections occurred after therapy with ampicillin. In a 10-year period, 109 instances of staphylococcal enteritis occurred among patients who received antimicrobics prophylactically, chiefly chloramphenicol, during abdominal surgery. Vancomycin given orally was recommended for its treatment.³⁰ Despite the use of antimicrobics or because they were used, the incidence of bacterial infections of the newborn increased in a hospital. The predominant causes were Gram-negative bacilli.³¹ Gram-negative bacillary septicemia increased seven-fold in a decade in Cincinnati hospitals, mostly in children and in persons more than 60 years old. The death-rate was 67%. Elsewhere the incidence of Gram-negative bacillary pneumonias, as found post-mortem, rose from 0.8% in 1952 to 7.9% in 1963. The increase was attributed to antimicrobial therapy and contaminated apparatuses for inhalation therapy, especially in debilitated patients.³² Candidiasis also has increased in incidence from the use of antimicrobics.³³

About 8% of patients treated with penicillin reacted adversely to it and from 100 to 300 deaths from anaphylaxis occur yearly in the United States.^{21, 29} Antibody to penicillin appeared in the blood in 1-8% of patients treated with the drug. Huge doses caused haemolytic anaemia in several instances³⁴ and severe neural disturbances in others.³⁵ Accidental arterial entry of penicillin injected into buttocks caused transverse myelitis, occlusion of arteries of a leg and gangrene in infants.³⁶ Penicilloyl-polylysine used as a dermal test caused a severe reaction in one patient³⁷ and gave positive results in 22% of others.²¹

Prolonged administration of chloramphenicol caused visual impairment in victims of cystic

fibrosis as described in three papers in the January 1966 issue of the *Journal of Pediatrics*, and optic neuritis in others.³⁸ Kanamycin is ototoxic and nephrotoxic.²³ Prolonged oral administration of neomycin in volunteers caused malabsorption and steatorrhea.³⁹ Applied locally, it increased the incidence of allergic dermatitis.⁴⁰ Isoniazid and para-aminosalicylic acid may cause sideroblastic anaemia by interfering with the metabolism of pyridoxine.

Genetic transfer of drug-resistance among Gram-negative enteric bacilli was first observed in Japan⁴¹ and later in England⁴² and in the United states.^{43, 44} Various antimicrobial-resistant strains of enterobacteria have their resistant genes on an episome and transfer this factor to sensitive bacilli by conjugation in mixed culture. Surprisingly, antimicrobial-resistant *Salmonella* transferred resistance factors to recipient strains of *E. coli*.⁴⁵ Transduction of antimicrobial resistance also occurs among staphylococci.⁴⁶ Extensive clinical and agricultural use of antimicrobics and the resultant widespread increase of the transferable R factors threaten the emergence of serious therapeutic problems.⁴⁴

Nosocomial infections

Bacteria and other microbes once regarded as harmless are important causes of 'hospital' infections. They are invasive because of impaired resistance of patients resulting from corticosteroid therapy, overuse of antimicrobics, instrumentation and for other reasons. Staphylococcus, *Salmonella* and Gram-negative bacilli chiefly are implicated. Acute staphylococcic arthritis occurred in elderly victims of rheumatoid arthritis, four of whom had received prolonged steroid therapy.⁴⁷ *Pseudomonas* infected patients after intraocular⁴⁸ and urologic operations⁴⁹ and others from contaminated respiratory apparatus⁵⁰ and catheters.⁵¹ *Aerobacter* (now called *Enterobacter*) caused nine infections in a 5-month period in patients with chronic diseases. Excepting streptomycin, the bacilli resisted antimicrobics, as did *E. coli* and *Klebsiella*.⁵³ Type 25 *Klebsiella* caused sepsis as a contagious infection in six children during 8 days.⁵⁴ *Serratia marcescens* (*B. prodigiosus*, now included in the tribe *Klebsiella* as genera *Serratia*⁵²) from a contaminated plastic bottle caused infections in infants,⁵⁵ and often was isolated from patients treated with antimicrobics and from debilitated ones. It was resistant to most antimicrobics.^{56, 57} Thrombocytopenia, said to be a diagnostic sign of Gram-negative bacillary disease,⁵⁸ is unspecific and occurs during many other infections.¹¹³

Cytomegalic inclusion disease was present in eight of twenty-five patients who had received

renal homotransplants and immunosuppressive drugs.⁵⁹ Of 111 other patients fifty-five died. Pneumonia was present in forty-one and was associated with *Pneumocystis carinii* in ten. In nine of these, other microbes also were present.⁶⁰ Fatal strongyloidiasis occurred in patients receiving corticosteroids.⁶¹

The control of hospital-acquired infections was the subject of a symposium published by the U.S. Department of Health, Education and Welfare, Communicable Disease Center, Atlanta, Georgia, 4-5 September 1963, pp. 1-203.

Viral respiratory tract infections

Respiratory tract infections comprise 58% of acute diseases in the United States.⁶² Viruses caused 50% of respiratory tract infections of 286 students. Of these, rhinoviruses caused 17%; para-influenza, 13%; influenza, 11%; respiratory syncytial, 4% and coxsackie viruses, 3%.⁶³ Herpes simplex virus caused respiratory tract infections with pneumonia in six patients.⁶⁴ Ryan virus, newly isolated from patients with respiratory tract and systemic infection, may be related to herpes viruses.⁶⁵

A normal or subnormal number of circulating leucocytes is generally regarded as characteristic of viral infection. However, among infants with respiratory tract infections caused chiefly by RSV, para-influenza and adenoviruses, the median leucocyte count was 14,000/mm³ and in asymptomatic patients, 9000.⁶⁶

Rhinovirus

Specific antibody appeared in the blood of victims of rhinovirus infection after 14-17 days, and in nasal, salivary and lacrimal secretions after 24 days.⁶⁷ A rhinovirus and a para-influenza virus were recovered from a patient with a cold. Both viruses caused illness when inoculated into volunteers. The rhinovirus induced immunity; the para-influenza virus did not.⁶⁸ Enteric coated capsules of two types of live rhinovirus ingested by volunteers failed to cause illness and no antibody appeared.⁶⁹ The virologic, epidemiologic and preventive problems of rhinoviruses and the common cold were summarized by Andrewes.⁷⁰

Influenza

An injection of influenza vaccine caused an adverse reaction in 25% of vaccinated employees of a large company and the antibody response was poor. A second injection evoked a response in 80% to B virus and in 27% to A virus.⁷¹ Amantadine hydrochloride was said to be effective for the prevention of influenza. One per cent of treated persons as compared with 4% of control subjects

became sick.⁷² Although its value has not been established, a related drug, Symmetrel, will be available commercially soon for the prevention of influenza. According to one report amantadine given prophylactically suppressed febrile influenza A₂ infection in children.⁷³ Large dosage is apt to cause mental disturbance. Hopefully, it will be more effective than is thiosemicarbazone for smallpox. The presence of neutralizing antibody in the blood failed to prevent infection of volunteers with minimal amounts of inhaled virus.⁷⁴ Antibody against para-influenza virus is greater in strength in nasal secretion than in the blood.⁷⁵

Rapid diagnosis of influenza can be made by the use of fluorescent-antibody technique, but the results of the test are irregular and often non-specific.⁷⁶ Another 'new' virus unrelated to myxoviruses was isolated from victims of mild respiratory tract infection.⁷⁷

Adenoviruses

Inoculation of volunteers by inhalation of aerosolized adenovirus Type 4 caused illness resembling the naturally occurring disease and two had viral pneumonia. The rest were inapparently infected.⁷⁸ Orally administered adenoviral Type 4 vaccine in enteric-coated capsules caused inapparent intestinal infection and protected recruits against infection with that virus.⁷⁹ The injection of non-infectious specific antigens of adenovirus Types 1 and 2 induced antibody that persisted 4–12 months.⁸⁰ Methisazone inhibits the multiplication of adenoviruses similar to that of pox viruses.⁸¹ Experimentally, adenovirus type 7 was transformed into type 2.⁸²

Respiratory syncytial (RS) virus

RS virus caused moderately severe illness in 106 Russian children, eighty-five of whom had viral pneumonia,⁸³ confirming previous observations of the seriousness of that infection in infants and children. Ampicillin had no therapeutic effect on bronchiolitis probably caused by RS virus.⁸⁴ Vaccines against RS and para-influenza viral infections are under study.⁸⁵

Vaccination with para-influenza vaccines types 1, 2 and 3 evoked antibodies in most infants.⁸⁶ The incidence of acute respiratory tract infections in children was reduced 15% by immunization with a heptavalent vaccine (RS, para-influenza 1, 2 and 3, influenza A₂ and B viruses and *Mycoplasma pneumoniae* organisms). The absence of influenza A₂ and B in the community suggested that vaccination prevented infection with para-influenza and mycoplasma microbes. Ten weeks after injection, vaccination no longer was effective.⁸⁷ Hilleman summarized current knowledge

about vaccines, chemotherapy and host resistance in viral infections.⁸⁸

Reo virus was considered as an uncommon cause of infection, but specific antibody was demonstrated in 55% of children.⁸⁹

Mycoplasma respiratory tract infection

As predicted from epidemiologic and clinical observations 25 years ago there are two general forms of acute respiratory tract infections, one with a short incubation period with a predominance of mild disease; the other, a non-seasonal one, with a 2–3 week incubation period and a high proportion of severe disease and pneumonia, no doubt, was caused by *Mycoplasma pneumoniae*.⁹⁰ Recently, that agent caused disease in twenty-three observed families. Eighty-four per cent of the children and 41% of adults were infected. Of fifty-nine patients, nine were not sick, six had pharyngitis and forty-two had pneumonia that often was unrecognized without skiagraphy. Tetracycline seemed neither to relieve the symptoms completely nor to end the carrier state.⁹¹ Elsewhere, the infection occurred throughout the year, but especially in the summer and seldom was severe in children.⁹²

In another study, *M. pharyngis* and *M. salivarium* present in 50% of pneumonic patients were not causal. *M. pneumoniae* was recovered in 9–20% of patients and accounted for 13–50% of non-pneumococcal pneumonias. The cold agglutinin test was not discriminative in diagnosis.⁹³ Nor was it of diagnostic value among 444 children with respiratory tract infections. In 28%, the test gave a positive result without other evidence of mycoplasmal infection.⁹⁴

An antigenic formalin-killed vaccine was prepared and recommended for use because of the severity and duration of the infection.⁹⁵ Others doubted the need for vaccination because of the preponderance of mild illness.⁹²

Other viral infections

Measles

Naturally occurring measles evoked the highest antibody titre; vaccine and immune globulin less, inactivated vaccine and live vaccine the lowest.⁹⁶ Vaccination with live attenuated virus induced specific antibody in most of Eskimo and white children. Fever of 103°F (39.4°C) and a rash ensued about 1 week later in one-third of the Eskimo vaccinees.⁹⁷ Measles vaccine caused lymphadenopathy which may be mistaken for other disease.⁹⁸ In one infant, inguinal adenopathy persisted for 2 weeks.⁹⁹ Because only 85% of vaccinated children in Britain were protected against measles, routine immunization of children

was postponed.¹⁰⁰ Diagnosis of measles can be made 2 days before to 5 days after the rash appears by the use of a fluorescent-antibody procedure on the urinary sediment.¹⁰¹

Mumps, at times, may evoke an exanthem or an enanthem.¹⁰² There is evidence for¹⁰³ and against¹⁰⁴ the causal relationship of gestational mumps to endocardial fibroelastosis. Antimumps vaccine was not recommended for exposed persons,¹⁰⁵ but a newly prepared live attenuated virus was said to be highly successful.¹⁰⁶

Rubella

In Alaska, rubella was as contagious as measles. Inapparent infections were common in persons who had lived during a previous epidemic and evidence of second attacks was observed.¹⁰⁷ Elsewhere, two infants with congenital rubella were born by mothers who had not had rubella nor were exposed to it. The infants' blood contained antibody, the virus was excreted for months and several attendant persons were infected.¹⁰⁸ Arthritis frequently occurs in the hands.¹⁰⁹ Five instances of rubellar encephalitis were observed¹¹⁰ and virus was present in the brain of several infants.¹¹¹ Thrombocytopenia and purpura were noted in fifteen victims one of whom died.¹¹² This occurrence is not peculiar to rubella and may occur in most other infections.¹¹³ Rubella and measles early in pregnancy and hepatitis later were more dangerous to the foetus than varicella.¹¹⁴

Intradermally inoculated virus caused overt or inapparent rubella in seven volunteers. Others with pre-existing antibody were immune.¹¹⁵ A haemagglutinin-inhibition test determines the presence or absence of specific antibody in 3 hr.¹¹⁶

Varicellar lesions in the bladder apparently caused haematuria in two children with chickenpox.¹¹⁷ In others, lesions were seen by cystoscopy.¹¹⁸ Renal lesions and haematuria were described in a patient with infectious mononucleosis.¹¹⁹ These observations together with mention later of ECHO virus,¹⁷⁵ are among the first to show viral infection of the urinary tract. The virus of lymphocytic choriomeningitis, by its name, was considered as a neural infection, but in ten laboratory workers the infection without meningeal invasion was contracted from infected hamsters. The symptoms and signs were fever, aching, lymphadenopathy and an enanthem which lasted 3 weeks.¹²⁰ Observations mentioned in this paragraph add to the evidence that viruses are multitropic.

Vaccines

An attenuated live rubella virus vaccine was immunogenic and the induced infection did not spread to susceptible children.¹²¹ Live virus vac-

cines of any kind should not be inoculated during pregnancy lest the embryo be infected. Influenza and polio vaccines were said not to be teratogenic,¹²² but defective infants were born of two mothers who had received polio vaccine during pregnancy.¹²³ A rare instance of paralytic poliomyelitis occurred in a mother 22 days after her child received vaccine orally.¹²⁴ Administration of live polio vaccine temporarily suppressed the tuberculin reaction in children.¹²⁵ Fatal vasculitis occurred after vaccination against pertussis.¹²⁶ The first known instance of fatal encephalitis followed inoculation of yellow fever vaccine. Fifteen non-fatal cases are on record.¹²⁷

According to one report, sixteen foetuses with generalized vaccinia were delivered from mothers who had received vaccinia vaccine during pregnancy,¹²⁸ but in another study of sixty-five women no virus was in the placenta, nor were the infants harmed.¹²⁹ Fourteen children had meningococcal meningitis and two had pneumococcal meningitis 4–21 days after anti-smallpox vaccination, attributed to post-vaccinal impaired resistance.¹³⁰ Vaccinia vaccine causes more complications than any other biologic product according to Thomson who summarized the problem of 'mass' immunization for the control of infectious diseases.¹³¹

The increasing number of immunizing agents raises questions as to which ones really are effective, how many a person should receive alone or combined, which ones to use, when and how, and if any harm ensues. At present, agents are available against smallpox, poliomyelitis, measles, yellow fever, influenza, adenoviruses and rabies, typhoid, cholera, tuberculosis, pertussis, plague, pneumococcosis, tetanus and diphtheria. Under investigation are vaccines for RS, mumps, parainfluenza, rhinovirus, rubella and Japanese B viruses, mycoplasma, Q fever, streptococcosis, tularaemia, anthrax and others. The status of vaccines incorporated with adjuvants to increase their potency was reviewed by Hilleman.¹³²

The possibility that adenoviruses may be oncogenic has precluded the use of these live virus vaccines. If they do cause cancer, then properly prepared vaccines should not only prevent adenoviral respiratory tract infections safely, but also prevent the resultant cancers and their metastases after excision of the primary site.¹³³

Chemotherapy of viral infections

Thiosemicarbazone for the treatment of smallpox has not fulfilled its early promise. Given prophylactically, it reduced the incidence of infection slightly, but not the fatality rate. It was not recommended for routine use.¹³⁴ IDU (5-iododeoxyuridine) for prevention will be tested in India.¹³⁵ In a limited trial, methisazone failed

as a prophylactic agent against varicella.¹³⁶ Predictably, many reports of tests of the drug in other viral infections will appear. Electron microscopy of virus particles in vesicular fluid or crusts provides a method of diagnosis of variola and varicella within minutes.¹³⁷ Therapy with cortisone and N-ethylisatin B-thiosemicarbazone reduced the inflammatory response in the brain of mice infected with neurovaccinia virus.¹³⁸

Despite contradictory evidence, idoxiuridine when used properly was effective in the treatment of cutaneous herpes simplex. Treatment must be applied at short intervals after the first evidence of lesions and for about 4 days.¹³⁹ A patient with herpes simplex encephalitis recovered after craniotomy was performed and IUDR was injected intravenously.¹⁴⁰ Herpes virus and SV40 virus particles, present in the same nuclei of simian renal cells, suggested the possibilities of phenotypic mixing and the production of different viral particles.¹⁴¹ Antiviral substances were sought in Chinese plants. One derived from magnolias and narcissi was active against lymphocytic choriomeningitis virus.¹⁴² A review of therapeutic measures for viral diseases was published.¹⁴³

Viral encephalitis

Herpes simplex virus caused encephalitis^{144, 145} and pneumonic respiratory tract infection in which oral vesicles also were present.⁶⁴ Meningo-encephalitis occurred in twenty-five patients with herpes zoster with one death,¹⁴⁶ and in sixteen children with measles.¹⁴⁷ The occurrence of asymmetric neural signs resembling the effects of a tumor caused diagnostic difficulty.¹⁴⁸

Adenovirus type 7 probably was the cause of encephalitis in one of three infected siblings.¹⁴⁹ Several antigenic types of the California encephalitis virus appear to be unstable. They are widely distributed in the world and increasing numbers of infections in man are reported. An epidemic occurred in Indiana in 1965. Children are involved chiefly and inapparent infections are common. Ninety-six cases have been recorded.¹⁵⁰ Man seems to be accidental dead-end host.¹⁵¹ During an epidemic of St Louis virus encephalitis in Texas, virus was isolated from bats in the vicinity.¹⁵²

Although rabies in man is considered always to be fatal, it is possible that milder attacks have occurred unrecognized many months after infection. In vaccinated victims, illness caused by the vaccine may resemble rabies, but proof of diagnosis rests on isolation of the virus. Instances of recovery from rabies have been cited,¹⁵³ but are unconvincing. Study of the matter is in progress.¹⁵⁴ Hyperimmune serum and vaccine are the best available agents for prevention, but ten in-

stances of failure are known.¹⁵⁵ The matter was reviewed.^{156, 157} A monkey developed rabies in a laboratory.¹⁵⁸

Viral hepatitis

Infectious hepatitis has recurred in 7-year epidemic cycles, but the interval seems to be lengthening.¹⁵⁹ After a high incidence in 1960–61, the present rate of occurrence indicates a downward trend.¹⁶⁰

The occurrence of eight cases of hepatitis in hospital employees in a year indicated a greater risk of infection for them than for the general population. Education in basic aseptic technique is of more value in prevention than the injection of γ -globulin.¹⁶¹ Among 3529 oriental military men in Taiwan, tests of their blood disclosed evidence of anicteric hepatitis which progressed to chronicity and cirrhosis. Whether all of these patients had viral hepatitis or other disease is uncertain.¹⁶² Acute hepatitis was fatal in two of three women after parturition.¹⁶³ Hepatitis ensued in five of nine patients treated with fibrinogen.¹⁶⁴ γ -Globulin failed to prevent post-transfusion hepatitis when injected before cardiac surgery and a month later. The incubation period was less than 50 days in half of the patients.¹⁶⁵ Adenovirus Type 5 was present in blood clots from twenty-seven of thirty patients with infectious hepatitis and in only one from seventy control persons.¹⁶⁶ Questions are: does hepatitis favour the growth of the virus or was the virus causal?

A disease resembling icteric infectious hepatitis, but with a negative heterophile reaction, was caused by cytomegalovirus. Infection was transmitted to a person in contact with the patient.¹⁶⁷

Enteroviruses

Coxsackie B3 virus was added to the list of causes of hepatitis, myocarditis and pleuritis.¹⁶⁸ Virus B4 caused neural and valvular endocarditis in inoculated mice. It is probable, at times, that this and other viruses are responsible for endocarditis in man, especially in the absence of streptococcal or rheumatic infection.¹⁶⁹ Virus A16 was recovered from children with 'hand, foot and mouth' disease, at first mistaken for measles. There were high fever, meningoencephalitis, an enanthem, and extensive dermal desquamation in the places named.¹⁷⁰ The disease was observed in Wisconsin¹⁷¹ and in Denmark.¹⁷² Curiously, a similar infection of cattle, horses and swine is caused by the Indiana-type vesicular stomatitis virus. Accidental infection in laboratory workers resulted only in brief fever, aching, vomiting, diarrhoea and leukopenia.¹⁷³ During an epidemic, 15% of persons were infected with ECHO virus 4.

Half of the attacks were inapparent, minor illness predominated and a few had mild encephalitis.¹⁷⁴ ECHO-9 virus was implicated as a cause of acute glomerulonephritis in two brothers.¹⁷⁵ Current knowledge contained in 181 publications about Cocksackie and ECHO viruses was summarized.¹⁷⁶

Miscellaneous viral infections

Enteroviruses isolated from thirty-eight infants with diarrhoea and not present in healthy ones suggested that they caused infantile viral dysentery.¹⁷⁷ Rubeola, varicella, para-influenza, RS, and adenoviruses were associated with otitis media in 23% of 106 cases. No mycoplasma were isolated. The attack rate of Type 1 poliomyelitis among Marshall Island children in 1963 exceeded eighty-five per 1000. The known date of its arrival established the average incubation period as 9 days, the shortest 4 days in unimmunized natives.¹⁷⁸ Dengue occurs in diverse clinical forms as breakbone fever, haemorrhagic fever and as a mild exanthem.¹⁷⁹ The presence of inclusions in glial cells suggested a virus to be the cause of subacute sclerosing leukoencephalitis.¹⁸⁰

Disease resembling kuru among natives of New Guinea ensued in chimpanzees 18–21 months after intracerebral inoculation of brain tissue from patients as evidence of a 'slow' chronic viral infection.¹⁸¹ Adams demonstrated inclusion bodies of measles in victims of multiple sclerosis. Knowledge about slow, latent and temperate viral infections was summarized in a monograph.¹⁸² A résumé about viruses also was published.¹⁸³

Viral contaminants of animal cells in tissue culture confuse diagnostic studies. A simian renal cell culture infected with SV40, SV5 and measles viruses also was susceptible to poliovirus.¹⁸⁴

Viruses and tumours

According to Hilleman, extensive investigations on the immunology of cancer have failed to yield any procedure of significant application to man. 'The main problems of cancer still remain: Find the cause and find the cure.'¹⁸⁵ Another review shows how obscure the problem is.¹⁸⁶ No evidence of viral tumour-inducers was detected in neoplastic tissues from thirty-two cancers in man.¹⁸⁷ Cytomegalovirus was present in eleven of thirty-two patients with neoplasms, but none in seventeen healthy persons. In most cases the virus probably was inactive or caused inapparent infection.¹⁸⁸ The virus caused death in three leukaemic children.¹⁸⁹ There is no evidence that adenoviruses are oncogenic in man.¹⁹⁰

Electron microscopy of a virus obtained from a Burkitt lymphoma suggested its relationship to the herpes virus group.¹⁹¹ Herpes simplex virus, an

agent related to reovirus, and two others were isolated from eight patients.¹⁹² The variety suggests that they may have been commensals. On the other hand, a noncarcinogenic virus, like other irritants, may incite malignancy.¹⁹³ Lymphoma similar to the Burkitt type was observed in the United States.¹⁹⁴ Particles resembling murine leukaemia virus were seen in tissues from leukaemic children and their pet dogs,¹⁹⁵ but also from patients with hepatitis and from normal persons. They were said to be platelet granules.¹⁹⁶ No virus was isolated from leukaemic cells grown in tissue culture.¹⁹⁷

Because Langat and Kyasanur viruses cause leukopenia, they were inoculated into patients with leukaemia and cancer for their possible oncolytic effect, but transient therapeutic benefit occurred in only four of twenty-eight patients.¹⁹⁸ 1-Adamantanamine prevented the penetration of animal sarcoma viruses and inhibited their growth *in vitro*.¹⁹⁹

Infections in lymphomas usually occurred late in the disease. Bacterial sepsis was the commonest, infections by viruses and fungi occurred less often. The outcome of disease with or without infection was similar.²⁰⁰ In another report, fever occurred in 50% of 137 patients with Hodgkin's disease, but was caused by infection in only nine, usually in the terminal period. Antimicrobial therapy rarely is indicated.²⁰¹ At necropsy, one patient with Hodgkin's disease had herpetic esophagitis, pulmonary cytomegalovirus infection, toxoplasmosis and sarcocystic invasion.²⁰²

Bacillary infections

As reported at the May 1966 meeting of the Association of American Physicians, vaccination prevented illness only when volunteers had ingested small numbers of *S. typhosa*. Apparently, vaccination prevents 'light' infections such as would occur from polluted water. Except for known exposure to typhoid or to a carrier, for institutional outbreaks and travel in endemic areas, vaccination is not needed in the U.S.A. The value of paratyphoid A and B vaccines has not been established.²⁰³

Refractoriness to endotoxins in typhoid and in tularaemia induced in volunteers did not mitigate fever or toxæmia. Sustained endotoxaemia therefore is not responsible for the continuous illness in either disease. Other mechanisms as in non-endotoxin containing microbes probably are operative.²⁰⁴

Salmonellar disease usually is caused by ingesting contaminated food, but infection may spread undetected from person to person afterward. Among 100 senile persons, salmonellas were

isolated from forty-five. Only nine were sick, the rest were inapparently infected or were carriers. Antibody developed in only four of seven patients with enteritis and in about a third of the symptomless carriers. Serologic surveys evidently are not of much value to detect mild or inapparent infections or carriers.²⁰⁵ Antimicrobial therapy prolonged the excretion of *S. typhimurium* in infected children, as compared with untreated ones. The suppression of normal enteric flora by therapy may favour the persistence of *Salmonella*.²⁰⁶

The failure of cholecystectomy to eradicate the carrier state was ascribed to the persistence of *S. typhosa* in the liver. Prolonged therapy with ampicillin and probenidol also was unsuccessful.²⁰⁷ Prophylaxis, specific therapy of salmonellar infections and the control of carriers still fall short of perfection. The problems are discussed in two articles and an editorial in the *British Medical Journal* of 3 September 1966.

Bacillary dysentery

Thirty sporadic cases of bacillary dysentery and two deaths in adults were observed in 4 years in a hospital in Florida. Aside from diarrhoea, abdominal pain and fever, no other evidence was helpful in clinical diagnosis. Antimicrobial therapy failed to influence the course of disease.²⁰⁸

Urethritis, conjunctivitis and polyarthritis (Reiter's syndrome) ensued 7–10 days after attacks of bacillary dysentery in nine of 602 sailors with dysentery on shipboard. The symptoms were uninfluenced by antimicrobial, antihistaminic, and steroid therapy, and persisted for 3 months in some victims.²⁰⁹

Bacteria probably cause 50% of infantile diarrhoea in the United States, the rest are of viral or of unknown origin. Among forty sick infants, coxsackie, ECHO and polioviruses were isolated and specific serologic responses were detected. No virus was recovered from well babies.¹⁷⁷

Cholera

Despite warnings,²¹⁰ there is little danger of cholera spreading to regions where hygienic conditions exist. It is one of the easiest diseases to prevent and the most satisfactory to treat. An epidemic of cholera-like disease affected a Mexican village.²¹¹ If it actually were cholera, it was its first natural appearance in the Americas for many years. In the United States, two technicians were accidentally infected in a laboratory. The enteric mucosa was normal except for hyperaemia and degeneration of the capillary endothelium.²¹² Cholera was induced in a volunteer who ingested a filtrate of *V. cholerae*²¹³ suggesting that a toxin causes the symptoms. Cholera induced in guinea-

pigs also suggested that a toxin accounts for cardiac, hepatic and renal disturbance.²¹⁴ Cholera-like disease was induced in dogs fed with vibrios.²¹⁵ The proceedings of a cholera research symposium in Honolulu, January 1965, were published.^{216, 217}

El Tor and 'classic' cholera are identical clinically.²¹⁸ That a toxin probably alters enteric mucosal permeability, that vibrios cannot be seen in the uninjured mucosa, that rapid rehydration is essential, that cholera vaccine is of doubtful value and that inapparent infections and healthy carriers occur, were discussed at a conference.²¹⁹ Most of these facts, including the use of fenestrated pallets for the passage of stools, were described and illustrated in 1946.²²⁰ The need to restore water and salt in the blood was known in 1832. One suggestion at that time was to plug the rectum with beeswax to prevent the loss of fluid.²²¹

Extensive studies on the treatment of cholera were described in six papers in the March 1966 issue of the *Bulletin of the Johns Hopkins Hospital* and elsewhere.²²² No significant new facts emerged. Proper rehydration with 2 : 1 saline-lactate solution saved almost all lives. Tetracycline, like streptomycin²²⁰ and other antibiotics, eliminated vibrios from the stool during its administration, and was said to reduce the volume and duration of diarrhoea.

Tuberculosis

Among nearly 3000 medical students observed for 23 years, 904 had reacted to the tuberculin test on first examination. Of these thirty-one (3·4%) later had overt tuberculosis, three had pleurisy and one died.²²³ Tuberculous peritonitis often is difficult to diagnose because of its disparate manifestations. A history of exposure to tuberculosis, its presence elsewhere in the body and the nature of the exudate are helpful in diagnosis. Proof depends upon peritoneoscopy, biopsy or laparotomy and the demonstration of bacilli in the tubercles. The tuberculin skin test is unreliable for diagnosis.²²⁴ Ethambutol, despite its toxicity, appears to have a role in the initial treatment and the retreatment of tuberculosis unresponsive to other drugs.²²⁵

In a 14-year study of persons vaccinated with BCG vaccine, almost three-fourths of tuberculosis occurred in initial reactors to tuberculin. Among non-reactors, infection was reduced only 14% by vaccination. The net reduction of tuberculosis among 64,000 persons was about 5% which hardly justifies the procedure. Perhaps chemoprophylaxis with isoniazid or other drugs will be more successful.²²⁶

From world-wide sources, the incidence of tubercle bacilli primarily resistant to antimicrobics

varied from 2.6% to 38.9%. Drug-resistant bacilli from a treated patient may infect untreated ones or less likely may have been naturally resistant.²²⁷

It was the consensus at a panel discussion that the use of BCG vaccine should be restricted further in the United States and applied only to uninfected persons or small groups unavoidably exposed to tuberculous patients who cannot be supervised. Medical students and personnel and inmates of institutions should not be vaccinated so as not to impair the diagnostic value of the tuberculin test.²²⁸

Leprosy

Paradoxes and misconceptions of leprosy were clarified. The diseases mentioned in the Bible were not leprosy. The infection was carried from the Old World to the New in contrast to syphilis. Susceptibility of the host determines infection of this 'highly contagious' disease but most persons are resistant. Neural and dermal leprosy always occur together. Digits never 'drop off'. Chaulmoogra oil, unless given in large doses, is useless and the term Hanson's disease should be discarded.²²⁹ *M. leprae*, demonstrated in the skin of normal persons in contact with leprosy,²³⁰ indicated a carrier state or inapparent or latent infection. Vaccination of Ugandan children with BCG seemed to prevent leprosy. The incidence of infection was reduced to one-fifth of the expected rate.²³¹ Years of observation will be needed for final evaluation of the procedure. A combination of streptomycin and sulphones was more effective for treatment than either drug alone.²³²

Other bacillary infections

Viable *Brucella* inoculated in volunteers in small amounts as a vaccine caused no fever or illness and specific agglutinin appeared after 9 months. Large numbers (20,000) caused febrile illness and specific agglutinin appeared in 3 weeks. Vaccination was not recommended.²³³

In Iowa, eighteen cases of diphtheria occurred in September 1962, with one death. Four families accounted for twelve of the cases and forty-eight persons were found to be carriers. No carriers were detected in a survey 1 year later.²³⁴

Because of allergic reactions and occasional failure to prevent tetanus, the use of antitoxin of animal origin is no longer desirable. Antitoxin of human origin²³⁵ and tetanus toxoid are preferable. Peripheral neuropathy followed the injection of toxoid in one rare instance.²³⁶

Dog ticks transmitted tularaemia to twelve children in South Dakota in an area relatively free of the disease.²³⁷ An attenuated strain of *Francisella* (*Pasteurella tularensis*), administered

as an inhaled aerosol, prevented tularaemia in volunteers.²³⁸

Urinary tract infections

Urinary tract infection was twice as common in girls as in boys. Structural anomalies were present in 45% and 30% had a vesico-ureteral reflux or a bladder-neck obstruction. Most infections occurred in winter. Infection was not controlled in twenty-eight patients, many of the others had relapses usually within 3 months, often preceded by colds.²³⁹ Only 20% of chronic urinary tract infections were cured by antimicrobial therapy. Recurrences were caused by the original bacteria or by new invaders. Antimicrobial therapy should be guided by identification of the pathogens.²⁴⁰

Factors other than the presence of bacteria in the kidney may cause pyelonephritis as demonstrated in seven of eighty juvenile diabetic patients. No correlation was found between bacteriuria, bacteria in the kidney and the histologic evidence of pyelonephritis.²⁴¹

The proper hydrogen-ion concentration in the urine is important for the antibacterial activity of drugs. The penicillins require reactions in the acid range while kanamycin and streptomycin act best in alkaline urine. Disregard of the pH at times may account for the failure of treatment of urinary tract infections.²⁴² The hydrogen-ion concentration is optimal for the growth of colon bacilli in most pregnant women.²⁴³

Tetracycline given prophylactically after instrumentation of the urinary tract did not reduce the incidence of bacteriuria. Many such infections are self-limiting and need no therapy.²⁴⁴ Tetracycline effectively sterilized the urine of rats with pyelonephritis induced by *E. coli*, but infection persisted in the kidneys of 78%. The addition of streptomycin was not helpful. Ampicillin and penicillin were less effective. Evidently, renal infection may persist after the urine is cleared of bacteria.²⁴⁵

Coccal infections

In one study, the home not the school was the major locus of haemolytic streptococcal infections and the source of spread to a community.²⁴⁶ Among 8000 cultures from the nose and throat of patients less than 18 years old, group A haemolytic streptococci were present in only 6.4%, and in 15% of children with exudative tonsillitis.²⁴⁷ Renal lesions after haemolytic streptococcal infection are not as benign as previously believed. According to biopsy evidence, about one-third of patients had renal abnormalities afterward.²⁴⁸ In another study, in six of twenty-one patients, biopsy and electron microscopy 20 months later disclosed changes in the mesangium. In ten others the residual changes were less severe.²⁴⁹

Because of higher living standards, improved medical care, new drugs and streptococcal control, deaths from scarlet fever, streptococcal pharyngitis and erysipelas have dropped 93% in 25 years. Deaths from rheumatic fever and rheumatic cardiac disease were reduced 38%, but exceed those caused by tuberculosis and syphilis.²⁵⁰ Anti-streptococcal prophylaxis apparently can be discontinued with safety for adolescents who have had no recurrent rheumatic fever 3–5 years after a known attack.²⁵¹

Penicillinase-producing staphylococci and haemolytic streptococci were present in 28% of children with upper respiratory tract infections. There was no evidence that therapy against these staphylococci had any greater value than the one of penicillins against the streptococci.²⁵² Deliberate implantation and colonization of avirulent staphylococci for protection against invasion by virulent ones was unsuccessful in adults.²⁵³

Staphylococci may become antimicrobial resistant in the body by transduction from resistant strains. Such genetic transmission of resistance probably occurred in addition to selection of resistant strains even before the general use of antimicrobics.²⁵⁴

Sixty-one per cent of septicaemias among 512 patients occurred in infants and in old age. About half of the aged victims had chronic debilitating diseases. Staphylococci and Gram-negative bacilli were the chief causes. The incidence of septicaemia has increased since 1955 mostly caused by infection with Gram-negative bacilli, the mortality-rate of which remains the same, while that of staphylococcal septicaemias has diminished.²⁵⁵

The death-rate from bacterial pneumonias declined from seventy to twenty-five per 100,000 between 1940 and 1950. The rate has not changed much to date and ranged between twenty per 100,000 in 1954, the lowest, to twenty-eight per 100,000 in 1957, 1960 and 1963. About 60,000 deaths from pneumonia occur annually in the United States, mostly in infants and in old age.²⁵⁶

So far, eighteen instances of pneumonia caused by tetracycline-resistant pneumococci of Types 6, 7, 9, 11 and 14 were observed, mostly in persons older than 60 years. One patient with Type 14 infection died during treatment with tetracycline.²⁵⁷

Gram-negative bacilli caused 3.7% of 'primary' pneumonias in a hospital. In four cases, Gram-negative bacilli superinvaded pneumococcal infection. Among thirty-eight others, *Klebsiella* was associated with twelve, colon bacilli with ten, *Pseudomonas* with seven, *Bacteroides* with four, *Proteus* with three, and *H. influenzae* and *Achromobacter* with one each. Seventy-four per

cent of patients were between 40 and 70 years old. Other chronic diseases were present in thirty-six of thirty-eight. Leukocytosis occurred in most cases and seventeen (45%) were fatal. Antibiotic therapy was not very effective.²⁵⁸ Pneumococci and influenza bacilli were the chief causes of otitis media in children. Cultures made from aspirated otitic fluid were more reliable for diagnosis than those from the oro-nasopharynx.²⁵⁹ As cited previously, viruses were associated in 23% of cases.

Meningitis

As in 1964, meningococcal meningitis in 1966 caused epidemics among military recruits. Antimicrobial prophylaxis failed and the installations had to be closed to stop the outbreaks.²⁶⁰ Gamma-globulin had no prophylactic value.²⁶¹ In twenty-eight cases of meningococcal meningitis, the cocci in 40% resisted sulphadiazine. Penicillin alone was curative.²⁶² About 16% of new recruits at one Air Force Base were carriers of meningococci, chiefly of group B. Of these, 15% resisted sulphadiazine.²⁶³ Two cases of pneumococcal meningitis were induced probably by contaminated needles during myelography.²⁶⁴ A 47-year-old woman had eleven attacks of meningitis in 18 years caused by Types 8, 14, 24 and 29 pneumococci, without evidence of residual injury. Higher numbered types caused similar recurrences in thirty-seven other cited cases with a low death-rate.²⁶⁵ One wonders whether or not the pneumococci were commensals or opportunistic invaders.

Corticosteroid therapy was deemed necessary in only ten of 159 victims of tuberculous meningitis with cerebral or pulmonic oedema, or overwhelming infection. Surprisingly intrathecal chemotherapy and PPD were applied,²⁶⁶ probably as measures of desperation.

Five children had meningitis caused by *N. subflava*. Four other cases were cited²⁶⁷ but one was omitted.²⁶⁸ In two cases, *Proteus mirabilis* was the cause,²⁶⁹ and in two others *Mima polymorpha*.²⁷⁰

Combinations or successive infections with *Strep. fecalis*, staphylococci, coliforms, *Pseudomonas*, *Proteus* and influenza bacilli caused meningitis in forty-three patients with underlying cranial disease or after surgical intervention. Some were regarded as contaminant commensals. Antimicrobial therapy was successful in eight cases.²⁷¹ Three patients with eosinophilic meningitis were observed in Guam. The infection was first described in 1948, and *Angiostrongylus cantonensis*, a nematode parasite of rats and molluscs, was suspected as the cause.²⁷²

Gonococcaemia may occur without urethritis, especially in women, who often are symptomless

carriers.²⁷³ With the increased incidence of gonorrhoea in recent years, there has been an increase of gonorrhoeal conjunctivitis.²⁷⁴ The instillation of 1% solution of silver nitrate still is advocated for the prevention of gonorrhoeal ophthalmia neonatorum. Penicillin is not recommended because of its sensitizing property nor are broad-spectrum antibiotics.²⁷⁵ A single injection of 2.4 million units of procaine penicillin, or of tetracycline in penicillin-sensitive patients, gave a 'cure-rate' of 97.9% of gonorrhoeal urethritis. Respository penicillin increased the incidence of treatment failures to 5.9%; and according to other observers, the failure rate ranged from 11% to 37% after treatment with the new orally administered semisynthetic penicillins. Because microbes of the tribe *Mimeae* were not encountered in 350 patients, the authors doubted their clinical significance.²⁷⁶

A T-strain of mycoplasma isolated from 70% of patients with nongonococcal urethritis was suspected as the cause. It was present in 13% of normal persons.²⁷⁷ Bedsonia also have been implicated as a cause.

Endocarditis

Despite general advice to the contrary,^{278, 279} huge doses of antimicrobics were recommended as prophylactic agents during and after cardiac surgery.²⁸⁰ When penicillin fails to cure enterococcal endocarditis, erythromycin or bacitracin are needed.²⁸¹ Ampicillin may prove to be the drug of choice with or without streptomycin.²⁸² Staphylococcal endocarditis had increased six-fold in a hospital since 1953. The cocci usually resisted penicillin, but often were controlled with semisynthetic penicillins given for 6 weeks.²⁸³ The fifth case of endocarditis caused by *Mimea* was described.²⁸⁴ Endocarditis caused by the experimental inoculation of coxsackie B4 virus suggests that some instances of endocarditis in man may be caused by viruses.¹⁶⁹ The subject of endocarditis in the antimicrobial era was reviewed in the 28 January, 3, 10 and 17 February issues of the *New England Journal of Medicine*.

Mycoses

Histoplasmosis

Erythema multiforme and erythema nodosum occurred in thirty victims during the 1962 epidemic of histoplasmosis in Iowa. Pulmonic lesions preceded dermal erythema in ten. Dermal lesions in some instances were thought to represent the primary site of infection.²⁸⁵ A second epidemic arose in 1964 after disturbing the soil of the same starling-roost area and 280 cases were reported. Wind-borne fungus chiefly infected children in

down-wind schools, and was present on the roofs of adjacent buildings.²⁸⁶ Histoplasmosis may occur in early infancy.²⁸⁷ *H. capsulatum* caused chronic meningitis and symptomless endocarditis. The histoplasmin test gave a negative result.²⁸⁸ Localized dermal infection followed an accidental puncture of the skin in a laboratory worker.²⁸⁹ Many victims with early pulmonary histoplasmosis recover spontaneously. Surgical excision or therapy with amphotericin is needed only for severe infections.²⁹⁰ A dual infection with *H. capsulatum* and *C. immitis* was reported. Amphotericin was successful in therapy.²⁹¹

Histoplasma usually are present on the surface of soil, but some were 25 in. below making eradication practically impossible.²⁹² Bats harboured *H. capsulatum*.²⁹³ The Amazon valley like the Mississippi valley may be a major endemic site of histoplasmosis. Dermal tests with histoplasmin gave positive results in 43% of natives.²⁹⁴

Mycotic infections are increasing in incidence in persons whose resistance is impaired or are receiving antimicrobics. Intravenously inserted catheters favour the invasion of *Candida*.²⁹⁵ and peritoneal dialysis induced peritoneal candidiasis. Meningitis in a leukaemic patient disappeared during therapy with amphotericin. Twenty-six other cases were cited in five of which amphotericin was given.²⁹⁶ Contraceptive medication favours the development of vaginal candidiasis and balanoposthitis²⁹⁷ that heal when medication is stopped.²⁹⁸ Congenital candidiasis probably followed the aspiration of infected fluid from the maternal vagina.²⁹⁹ Symmers reviewed forty cases of deep mycotic infections in Britain including exotic ones of histoplasmosis, coccidioidomycosis and others.³⁰⁰

A sporotrichin skin test gave a positive reaction in a person who had had sporotrichosis 65 years ago.³⁰¹ Inhalation of the spores of *Cryptostroma corticale* caused pneumonia (maple-bark not maple-syrup disease) in five persons.³⁰²

Malaria

A resident of Pennsylvania who had never visited an endemic area, nor received injections, had *P. malariae* malaria. Infection may have been transmitted from a carrier by a mosquito (*A. quadrimaculatis*) which is present in eastern United States.³⁰³ *P. ovale* malaria became overt in a patient who had left West Africa more than a year before. The disease usually is mild and often is mistaken for a respiratory tract-infection or fever of unknown origin.³⁰⁴ *P. vivax* obtained from a patient caused parasitaemia in inoculated monkeys whose resistance was impaired by splenectomy and an immunosuppressant drug. The infection then was transmitted from monkeys to

volunteers.³⁰⁵ Diamino diphenylsulphone (DDS) used for leprosy was effective in the treatment of falciparum malaria.³⁰⁶ A newly recognized plasmodial parasite (*Michina*) destroyed many oysters along the Middle Atlantic coast.³⁰⁷

Miscellaneous

Gsell noted the decline in the incidence and mortality rates of pneumococcal, streptococcal, meningococcal, brucellar and tuberculous infections as a result of antimicrobial therapy, and of poliomyelitis and smallpox from vaccination. In contrast, no changes ensued in the incidence of many viral diseases, pertussis and shigellosis. Excepting typhoid, salmonellosis has increased as have other Gram-negative bacillary infections. The reported increase of viral hepatitis, leptospirosis, infectious mononucleosis and Q fever may owe to better diagnoses. Because of the changing incidence of infections, young physicians are apt to be unaware of some formerly dangerous ones which are prevalent in primitive regions and rarely seen elsewhere.³⁰⁸ It is becoming more and more important to ask patients 'unde venis?' For examples, haemorrhagic fever contracted in Korea became overt and fatal in a patient in New York City.³⁰⁹ Bubonic plague contracted in New Mexico became overt in a fatal case in Boston.³¹⁰ Another case occurred in a returnee from Vietnam. Cutaneous leishmaniasis became overt in travellers from endemic regions.^{311, 312} Peculiar histologic dermal changes aid in diagnosis when the microbes cannot be found.³¹³

Diarrhoeal disease and respiratory tract infections most often of viral origin and malaria are the chief causes of illness among foreign troops in Vietnam. Dengue, scrub typhus, leptospirosis also are prevalent and about 20% of fevers are of unknown origin.³¹⁴ Thirty cases of melioidosis occurred. Falciparum malaria resistant to synthetic drugs is of especial importance. A prophylactic agent DDS (diaminodiphenylsulphone) is under trial. As after the Korean conflict, there is concern about the importation of malaria into the United States and elsewhere. In 1965, 156 cases were reported.

Among ninety-six British abattoir workers, antibodies indicating previous infections were present in about half, including those of *Coxiella* (28%), *Brucella* (12%), leptospiras (6%) and louping ill (8%).³¹⁵ In Ohio, evidence was detected of trichinellosis, psittacosis, Q fever and brucellosis in that order.³¹⁶

In one area of Ohio, 41% of cows were infected with *C. burnetti*. The microbe was present in fifty-two of ninety samples of milk. Antibody was present in 21% of people, but only two overt cases

were reported.³¹⁷ Although infection usually is inapparent or mild, in a 5-year period fifty persons acquired Q fever in a laboratory and half of them had pneumonia. All had been vaccinated previously.³¹⁸

Bedsonia

Ornithosis-psittacosis in Scotland caused twenty-nine recognized cases and others probably occurred. Contact with birds was proved in only six. Person-to-person infection apparently occurred in two instances.³¹⁹ Thirty patients in Germany had psittacosis, four with meningoencephalitis. Parrots were the source of infection in twenty-eight.³²⁰ Acute febrile pulmonic disease in persons exposed to birds is not always ornithosis, but may be the result of an allergic reaction to avian dust.³²¹ Bedsonias were cultivated from the synovia, urethra and conjunctiva of five of eight victims of Reiter's disease. Complement fixation was demonstrated in five.³²² Mycoplasma also has been suspected as a cause of rheumatoid arthritis.³²³ Both microbes may have been commensal.

Infection with *Toxoplasma* in adults often occurs during the use of immunosuppressive drugs and causes lymphadenopathy or miliary or localized disease.³²⁴ In a survey of families, 35% of serums of adults had antibody for toxoplasma, but only 5% of children. Mild febrile episodes in four persons caused antibody to appear, and lymphadenopathy occurred in only one. Evidently, in families, toxoplasmosis may be inapparent and seldom is contagious.³²⁵ In searching for toxoplasmosis, the complement fixation test is not always of diagnostic value and a titre of less than 1:512 of the dye test has no clinical significance.³²⁶

Chimpanzees infected with *Schistosoma mansoni* shed eggs constantly in faeces 6 weeks later. Eggs were in the lungs, pancreas, kidneys, small intestine, bladder and spleen. Fever and bloody diarrhoea were followed by hepatomegaly and ascites, and fibrosis ensued similar to that in man.³²⁷ Ambilhar was effective in reducing the output of eggs in adults.³²⁸

Bathers in ponds polluted by the excreta of livestock and rats may acquire leptospirosis³²⁹ as first described in 1940.³³⁰ Ten instances are known wherein dead *Dirofilaria immitis* were present in nodular pulmonic lesions.³³¹ Eosinophilic lung or tropical eosinophilia in Singapore is an entity different from others in the tropics and is caused by microfilariae.³³²

According to studies reported at the May 1966 meeting of the Association of American Physicians, unusual microbes resembling protoplasts were visualized in the lesions of Whipple's disease.

On culture, these forms changed into streptococci. Whether they are causal or incidental must be determined.

Remnants of a bacillus, *Eobacterium isolatum*, the oldest known plant life, were found in 3-billion-year-old rocks in Africa.³³³

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