ANNUAL REVIEW

Infectious Diseases: Annual review of significant publications

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Introduction

Yearly reviews since 1935 recorded significant contributions to knowledge about infectious diseases. On the occasion of this, my thirty-fifth consecutive annual review, it is of interest to pause and recall some of the advances made during that time.

Momentous events included the introduction of practical antimicrobial drugs by Domagk, by Fleming and by Waksman; Avery's discovery of DNA and RNA pertinent to microbic genetics; recognition of autoimmunity and of various globulin and complement components as related to infection; the development of electron microscopy; and several wars that emphasized exotic diseases. Regarding antimicrobics, proper therapy reduced the death-rate of bacterial pneumonias, coccal sepsis, endocarditis, tuberculosis, syphilis, rickettsioses, typhoid and plague. The incidence of rheumatic fever and mastoiditis lessened. Available antimicrobial drugs reached the limit of effectiveness. Staphylococci, Gram-negative bacilli and fungi assumed importance as drug-resistant pathogens. Therapeutic use and misuse of antimicrobics, immunosuppressive drugs and corticosteroids brought about diseases caused by these agents and by resulting opportunistic invaders.

Influenza virus was the first of many respiroviruses subsequently discovered. Viral pneumonias were distinguished from those of bacterial origin. Viruses also proved to be causes of mild dysentery. The advent of Ender's cultural technique aided virology. Vaccines against poliomyelitis, yellow fever, measles, mumps, rubella and influenza became available. Pneumotropic, enterotropic, neurotropic, and polytropic viruses were discovered. Cytomegalovirus, herpes simplex, rubella, and toxoplasmosis as well, proved to be congenital infections. The relation of viruses to cancer and the significance of virus-like particles in tissues during neoplastic and systemic diseases entailed much research without conclusive results. Attempts began to find antiviral drugs and to determine the role of interferon in infections.

Insecticides controlled vector-borne malaria, typhus, leishmaniasis, sandfly fever and several neural viroses. Prompt rehydration made cholera a benign

disease. Bedsonias, mycoplasmas, *Listeria*, *R. burneti* and *Pn. carinii* came to attention as pathogens. Inapparent and previously ignored mild attacks of disease when included in spectrums of severity, raised the previously reported statistical incidence and lowered the recorded death-rates of poliomyelitis, typhoid, shigellosis, yellow fever, melioidosis, cholera and plague. Histoplasmosis and coccidioidomycosis, once regarded as fatal, emerged as widespread, usually mild diseases. Epidemiologic measures, vaccines and antimicrobial drugs when applied alone or in combination, held promise to eradicate some infections, but not in the foreseeable future.

During the past year, antimicrobial therapy, opportunistic, nosocomial and iatrogenic infections received continued attention. The importance of animals and birds as reservoirs of microbes was reaffirmed. Vaccines for measles, rubella, influenza, adenoviral and other infections were further tested with variable results. Cholera reappeared in epidemics. A causal relation of herpes-like virus to infectious mononucleosis and lymphomas was proposed. Much interest and many publications concerned the Australia antigen and hepatitis. Despite the importance of infectious diseases, those of other origin dominated interest. Among eighty-six papers on the 1970 programme of the Association of American Physicians, four dealt primarily with infections.

Antimicrobial therapy

Penicillin or ampicillin and streptomycin cured thirty of thirty-six patients with enterococcal endocarditis. Adverse reactions affected fifteen, one with fatal enteritis.¹ Vancomycin and streptomycin were recommended for treating enterococcal endocarditis in patients intolerant to penicillin.² Cloxacillin therapy failed to influence the course of septic lesions.³ Staphylococci increasingly resisted methicillin.⁴ Among twenty-one tested agents, ampicillin, penicillin and vancomycin in that order were most active against Group D Streptococci.⁵ Gentamicin successfully controlled serious infections caused by *E. coli* and *Enterobacter*. Those caused by *Proteus* and *Pseudomonas* were less responsive.⁶ Gentamicin

was 100 times more active *in vitro* at pH 8.5 than at pH 5 against most strains of Gram-negative bacilli. Concurrent administration of an alkalinizing agent allowed smaller effective amounts of gentamicin and erythromycin.⁷

The value of cephalothin, cephaloridine, cephaloglycin and cephalixin was assessed.⁸ Forty-two papers about cephalosporins appeared in a supplement (Oct. 1970) of the *Postgraduate Medical Journal*. Cephalixin controlled staphylococcal infections of soft tissues.⁹ It was useful for treating urinary tract infections in moderately uremic patients.¹⁰

Carbenicillin, 18 g daily, controlled pseudomonal bronchial infections.¹¹ The drug caused improvement in seven of ten children, but four died. Bacilli persisted in sputum.¹² It was active *in vitro* against many Gram-negative bacilli¹³ and was useful for urinary tract infections with *Pseudomonas* and *Proteus*. Bacillary resistance developed rapidly.¹⁴ According to two reports, carbenicillin has not fulfilled its promise. Of fifty-five pseudomonal infections only sixteen were cured. Superinfections often ensued.^{15, 16} All of thirty-eight strains of *Bacteroides* were sensitive to chloramphenicol representing one of the few indications for its use.¹⁷

In a 10-year period no evidence of increasing antimicrobial-resistance appeared among isolates of *E. coli* or *Klebsiella*. Resistance actually declined.¹⁸ The report is at variance with others wherein resistance of the bacilli in question was far greater.

During therapy of mycoplasmal pneumonia, microbial resistance increased greatly to erythromycin and to five other antimicrobial drugs as well.¹⁹ Erythromycins are the first choice only for mycoplasmal infections.²⁰

The value of rifampicin for treating tuberculosis was established. It may exceed isoniazid and streptomycin in efficacy because of its rapid action, low toxicity and oral administration.²¹ Rifampicin was of especial value when the bacilli resisted other drugs.²² The drug may be of value for leprosy.²³ It also has antiviral action.²⁴ It reduced the percentage of meningococcal carriers by 80% when given orally.²⁵ Lincomycin controlled actinomycoses in four patients allergic to penicillin.²⁶ Clindamycin, a drug of second choice for coccal infections may replace lincomycin as an oral agent.²⁷ Herrell reviewed the historical development of antimicrobics after the first one, pyocyanase, was isolated in 1899.²⁸

Ramycin restricted growth of Gram-positive bacteria.²⁹ New antifungal agents are denofungin, scopafungin, ticlatone, zorbamycin, cephapirin, nifungin and clotrimazole.

Misuse

A neutropenic child had previously received

penicillin and a sulfonamide for a cold and again for gingivitis; erythromycin for small furuncles; tetracycline for infectious mononucleosis, and penicillin for nonstreptococcal sore throat. None of this therapy was indicated.³⁰ There is no justification for the use of tetracycline or any other antimicrobial in the prevention or treatment of minor viral respiratory tract disease.³¹

In seven hospitals, 30.6% (range 24–75%) of patients received antimicrobial therapy, oftenest on the pediatric and surgical services. Probably 62% of these were treated prophylactically. Only 38% of treated patients had recorded evidence of infection.³² Evidently the wastage of antimicrobial drugs continues unabated. In my own 450-bed hospital the cost of antimicrobics to patients in the past year was \$290,000, most of it unnecessary. Physicians, patients and third-party payers evidently make little or no effort to reduce the misuse.

Unwanted effects

The number of bacteremic patients in Finland's hospital doubled between 1935 and 1953, and almost doubled again by 1965. Gram-negative bacillary sepsis increased threefold. That from *Pseudomonas* appeared after 1943 and from *Klebsiella-enterobacter* after 1957, dependent upon the increased use and ensuing resistance to antimicrobial drugs. *Mima*, *Herellea* and *Serratia* appeared as pathogens. Deaths from sepsis increased each year: in 1965 twice as many as in 1953. The mortality rate in 1965 equalled that of 1941 before antimicrobics were available. To reverse the trend, unnecessary and improper use of antimicrobial agents, particularly for prophylaxis will have to be modified or stopped.³³ In a surgical ward, cessation of all antimicrobial therapy reduced the incidence of *Klebsiella* infections.³⁴

Antimicrobial therapy in early childhood may interfere with the development of immunity against *H. influenzae* and account for the increasing frequency of Type B infections in adults.³⁵ Renal failure, deafness and paralysis accompanied irrigation of body cavities with antimicrobial drugs for prophylaxis or therapy.³⁶ Therapy is hazardous in patients with myasthenia gravis.³⁷

Penicillin given intravenously caused convulsions.³⁸ Anaphylactoid reactions followed orally given ampicillin.³⁹ Exanthems occurred during infectious mononucleosis.⁴⁰ Ampicillin and carbenicillin caused local injury after intramuscular injection.⁴¹ Carbenicillin, like penicillin, in large dosage during renal failure is neurotoxic.⁴² Encephalopathy appeared from chloramphenicol.⁴³ Sodium colistimethate caused adverse renal reactions in 20% of 288 patients, neurotoxicity in 7% and respiratory difficulty in 2%. Harmful effects contributed to the death of 4% of patients.⁴⁴ Oral administration of

neomycin resulted in six instances of ototoxicity during hepatic encephalopathy. Paromomycin may be similarly dangerous.⁴⁵ Ototoxicity affected five patients receiving gentamicin during renal failure.⁴⁶ Kanamycin-resistant *Klebsiella* caused bacteremia in six infants and spread to others in a nursery.⁴⁷ Six of seventy-five patients treated with cephaloridine developed a direct reaction to the Coomb's test but without haemolysis.⁴⁸ Cephaloridine in large dosage is nephrotoxic, especially for previously injured kidneys.⁴⁹ Rifampin caused jaundice in four of fifty tuberculous patients⁵⁰ and thrombocytopenia in another patient.⁵¹ Hepatitis was a rare occurrence during isoniazid therapy.⁵²

Methicillin-resistant staphylococci infected six patients in a hospital. Two died. Transmission apparently was hand-borne.⁵³ Elimination of antimicrobial-sensitive faecal flora by antimicrobial drugs induced urinary tract infections with resistant bacteria in infants.⁵⁴

When all precautions have been observed before therapy, physicians are not held negligent should adverse reactions ensue.⁵⁵

Viral respiratory tract infections

Influenza

Polyvalent influenza A₂ vaccine gave a high degree of protection against infection in 1968–69. The antibody response equalled that after natural infection.⁵⁶ According to other experience, adjuvant influenza vaccine afforded moderate protection during outbreaks, but not among preschool age children, to outbreaks of either A or B infection.⁵⁷ Recent vaccination or multiple prior vaccinations of military personnel failed to prevent A₂ influenza. Twelve per cent or more of men were infected.⁵⁸ The incidence of influenza B during an epidemic was the same in vaccinated and unvaccinated victims.⁵⁹ Pandemic influenza, so far, has resisted control.⁶⁰ Aerosol vaccine increased antibody in pharyngeal secretions of volunteers six-fold and persisted a year.⁶¹ Meningoencephalitis of unknown cause followed 2 weeks after vaccinating an adult.⁶²

In a controlled study, 200–300 mg of amantadine given for 10 days prevented influenza A₂ in eighteen inoculated subjects. Four of eighteen control persons were infected but had a greater antibody response.⁶³ Russian physicians found amantadine to be about 80% effective in preventing severe A₂ influenza when given before symptoms appear. Influenza B was not influenced.⁶⁴ Therapeutically, the drug was said to cause more rapid improvement of influenza A₂ patients than of control subjects without affecting virus shedding or increase of antibody titre.⁶⁵

Severe myositis of the legs affected twenty-six children during influenza.⁶⁶ Acute myoglobinuria accompanied Type A influenza in a patient. Other

respiroviruses rarely cause similar troubles.⁶⁷ During an epidemic of A Hong Kong virus infection, among 127 patients, ten had mild pneumonia and two died. Ten had diffuse pneumonia caused by the virus itself, of whom six died. Cough, sore throat and fever were commoner than myalgia, headache and malaise.⁶⁸

Among 399 patients, chiefly children during a 4-year period from whom parainfluenza viruses were isolated, pharyngitis and colds predominated. The rest had croup, bronchitis, and pneumonia. Laboratory diagnoses were ready within 5 or 10 days.⁶⁹ Parainfluenza 3 virus caused mumps-like parotitis in two children.⁷⁰ Parainfluenza 2 vaccine administered as an aerosol gave a better neutralizing antibody response than after subcutaneous injection.⁷¹

Adenoviruses

Adenoviruses Types 1–7 isolated from infants and children with respiratory tract infections also were present in two thirds of healthy children, many of whom probably were inapparently infected.⁷² New Types 32 and 33 were isolated from infants.⁷³ Live and inactivated adenovirus 4 vaccine given orally reduced respiratory tract infections among recruits by 50%.⁷⁴ Vaccination protected about 75% of other army recruits.⁷⁵ In another study, adenoviral vaccine eliminated homologous infections, but these were replaced by infections with Types 7 and 24.⁷⁶ Polyvalent vaccine is necessary.⁷⁶ Faulty care caused a hospital epidemic of forty-four cases of adenoviral keratoconjunctivitis.⁷⁷ Surprisingly, typical pertussis may be caused by adenoviruses, not always by *Bordetella*. Types 1, 2, 3, or 5 were present in eleven of thirteen infants with whooping cough. The circumstance may explain the occasional failure of pertussis vaccine.⁷⁸ Rich and McCordock in 1932 had noted inclusion bodies in the lungs. It may be recalled that a parainfluenza virus once was regarded as 'croup associated'.

Other viruses

Antigenic variants of several rhinoviruses were isolated. The prototype of immune serum neutralized them weakly or not at all.⁷⁹ The circumstance resembles the variability of influenza viruses and will have a bearing on the ultimate value of vaccine. Eighty-nine serotypes are known.⁸⁰ Rhinoviremia occurred in two infants who died suddenly.⁸¹ Injected poly I : C complex has promise for the prevention of some viral infections especially with the rhinoviruses.⁸²

Tyrrel described the technique which discovered the coronaviruses. Viral particles resemble the solar corona, hence the name. In inoculated volunteers, they caused colds differing from rhinovirus infection by a longer incubation period, shorter duration,

more catarrh, less sore throat and cough.⁸³ According to antibody responses, epidemics of coronavirus infection affected adults oftener than children.⁸⁴ In an outbreak in 1967, about 34% of a population were affected. The neutralization test detects both recent and past infections. Complement-fixing bodies were evanescent.⁸⁵

Respiratory syncytial virus may cause death from mucosal necrosis and pulmonic damage or by allergic effect after reexposure to the virus.⁸⁶ Infection in the newborn was mild. Severe infection in later life may be ascribed to specific sensitization. Fluorescent antibody technique enabled early diagnosis.⁸⁷

Coxsackie B virus caused upper respiratory tract disease in 227 of 311 patients chiefly children from whom the virus was isolated. The rest had fever and headache only, or pleurodynia, meningoencephalitis, abdominalgia or pericarditis.⁸⁸ Aerosolized coxsackie virus A₂₁ infected each of twenty-one volunteers as shown by virus isolation and antibody response. Respiratory tract disease occurred in most and involved the lower portion in four.⁸⁹

An extensive review covered progress in the control of viral and mycoplasmal respiratory tract infections. Much has been learned, but these infections persist. Differences in pathogenicity and of local or systemic immunity impedes progress in developing vaccines.⁹⁰

Viral hepatitis

Several articles summarize knowledge about the relationship of the Australia (AU) antigen and antibody to hepatitis.^{91, 92, 93} Imperfect differentiation of infectious (IH, type A, MS-1, short incubation) hepatitis from serum (type B, SH, MS-2) hepatitis at first confused the issue. Furthermore, AU antigen present during leukaemia, Hodgkin's disease, mongolism, polyvasculitis, leprosy and in healthy persons raised doubt as to its causal relation. Hepatitis probably was, or had been, present to account for the antigen, or the supposed virus caused different diseases. Four of eleven patients with polyarteritis and hepatic involvement had AU antigenemia probably as an immune reaction.⁹⁴ Some uncertainty resolved when the antigen and virus-like particles were demonstrated only in cases of SH,^{95, 96, 96a} not during epidemics of IH.⁹⁷ The particles also were present in patients with biliary cirrhosis.⁹⁸ Antiserum clumped the 42 μ m sized particles⁹⁹ which may be the causal agent.¹⁰⁰ Serum hepatitis induced by injecting plasma containing the particles and SH antigen supported their etiologic relationship.^{101, 102}

Plasma from hepatitis victims caused cytopathic effects in tissue culture cells. Plasma from the same person prior to illness did not. Marmosets injected with IH serum developed serologic evidence of infection and cytopathic changes in the liver.¹⁰³ The

results tend to support the work of McLean, Richtsel and others who incriminated a viral agent in 1956.¹⁰⁴

AU and SH antigen are the same. The significance of 'smooth muscle' antibody during chronic hepatitis^{105, 106} and of a 'new' antigen present during three epidemics of IH¹⁰⁷ is undetermined. The far greater prevalence of SH antigen in residents of the tropics than among blood-donors in New York City, suggested an arthropod transmission of the infection.¹⁰⁸ In a Danish hospital among 10,000 patients, thirty-five had the SH antigen, of these six had acute hepatitis, seven had chronic hepatitis or cirrhosis and twenty-two had no demonstrable hepatic disease.¹⁰⁹

Blood transfusion annually accounts for about 30,000 cases of SH and more than 1500 deaths in the U.S.A. No doubt, many inapparent or undiagnosed mild attacks occur. According to Medical News in the *Journal of the American Medical Association* of 23 November, cessation of one and two unit transfusions would prevent 65% of SH.

The absence of demonstrable AU antigen in donors' blood does not guarantee freedom from the virus.¹¹⁰ Hepatitis developed in recipients of antigen-negative blood.¹⁰² Other means are needed to identify hazardous blood-donors. A precipitin test detected AU antigen in 0.1–0.5% of normal persons.¹¹¹ Donor erythrocytes washed with a special technique reduced the incidence of hepatitis.¹¹² Rapid screening tests are available.^{113, 114}

Re-examination of soldiers who had had hepatitis 20 years before gave no evidence of risk of developing hepatic cirrhosis.¹¹⁵

Rubella

During the 1966 epidemic, 20,000 defective children were born eventually entailing a cost of \$2 billions for care. The only significant undesired effect during the first year after vaccination among 13 million persons was transient arthralgia.¹¹⁶ Of three vaccines tested, two caused neither rubella nor arthralgia but the third caused both.¹¹⁷ Therapeutic abortion was performed 8 weeks after rubella vaccination during the third week of unsuspected pregnancy caused an intrauterine infection.¹¹⁸ The incidence of rubella was reduced among Japanese schoolboys vaccinated subcutaneously during an epidemic as compared with control subjects. Intranasal vaccination seemed to be effective.¹¹⁹

Vaccination occasionally fails. Inapparent rubella affected 50% of children 5 months after vaccination.¹²⁰ Eighty per cent of vaccinated men and 3.4% of naturally immune men were reinfected during an epidemic as shown by serologic tests. Each of twenty-six susceptible men was infected.¹²¹ The degree of immunity conferred is uncertain and vaccination may confuse the issue.¹²² It is doubtful if rubella can

be eradicated by vaccination. Immune globulin failed as a preventive measure.¹²³

As in the case of polio vaccine, vaccine-strain rubella from vaccines may infect others.¹²⁴ In another study, however, transmission did not occur. Antibody level in vaccinees was lower than that after natural infection. The duration of induced immunity is unknown.¹²⁵ Failure of vaccination at times may be due to deteriorated vaccine. Official recommendations for vaccination were outlined.¹²⁶ The advantages, disadvantages and unknown factors regarding rubella vaccines were presented in three papers in the September issue of the *American Journal of Epidemiology*.

Smallpox

In a 9-year period, sixty-eight deaths from vaccinia necrosum, encephalitis, eczema vaccinatum and mucocutaneous fever were attributed to smallpox vaccination in the U.S.A. Twenty-four were infants. Some persons acquired vaccinia from vaccinees.¹²⁷ Direct inquiry of physicians disclosed complications to be ten to seventy times greater than the rate computed by national surveillance. Eighty-four per cent occurred after primary vaccination. The rates of potentially fatal encephalitis and vaccinia necrosum were 12 and 1.5/million respectively.¹²⁸ In 326 persons without serious sequels, ocular vaccinia followed vaccination in 70%, and by contact with vaccinees 19%.¹³⁰ Nine instances with five deaths from vaccinia necrosum followed vaccination for the futile treatment of chronic herpes hominis viral infection.¹³⁰ When only 50% of a population had been vaccinated, an outbreak of smallpox affected 2.6%.¹³¹ Smallpox may be airborne.¹³² Serologic evidence suggested the natural transmission of smallpox from man to monkeys. These may be a reservoir of infection.¹³³

Varicella in a child was accompanied by genual arthritis.¹³⁴ Meningoencephalitis occurred in eight patients with herpes zoster. Most patients recovered. Corticosteroid therapy was not helpful.¹³⁵ Chickenpox and zoster were interchanged among patients and personnel in a hospital. Zoster occasionally is exogenous in origin especially when host-resistance is impaired.¹³⁶ Other evidence suggests that previous exposure, latency and reactivation rather than exogenous reinfection from patients accounts for zoster.¹³⁷

Antimeasles vaccination failed to affect the course of an epidemic among Chicago school children.¹³⁸ Koplik spots share giant cells and virus particles with dermal lesions.¹³⁹ During a *mumps* epidemic, 126 victims were observed. Twenty-five per cent of family contacts were inapparently infected. Secondary household infections ranged from 14% to 46%.¹⁴⁰ *Hand, foot, and mouth disease* (stomatitis,

pedal and manual exanthems) caused by coxsackievirus A16 affected children in Baltimore.¹⁴¹

The demonstration of specific antibody in patients with *trachoma* may lead to the development of a vaccine.¹⁴² It is doubtful, as suggested, that vaccine applied locally will be effective. Infection is in the tissue not in the exudate.

Encephalitis

Oral application of rabies virus killed mice. Gastric secretion failed to inactivate the virus.¹⁴³ Evidently rabies virus can penetrate the enteric and the pulmonary mucosa. This accounts for rabies previously reported in spelunkers. A newspaper recorded the probable first known recovery from rabies: A boy bitten by a rabid bat was promptly vaccinated, developed typical symptoms, either from the infection or from the vaccine, and recovered after three weeks. By electron microscopy the Negri bodies of rabies were composed of viral particles as intracytoplasmic bodies.¹⁴⁴ Methods for the control of rabies were outlined.¹⁴⁵

Brain tissue from subacute sclerosing panencephalitis yielded measles viruses. They were the same antigenically as 'wild' viruses, but differed in ability to neutralize antibody to wild viruses and in their growth.¹⁴⁶ Perhaps long residence in the brain changed the nature of the pathogen. Besides measles-like virus, an unclassified virus was in brain tissue of two patients.¹⁴⁷ Encephalitis produced in hamsters by inoculating material from brains of patients with subacute sclerosing panencephalitis provides a convenient method for study.¹⁴⁸ Patients with multiple sclerosis have slightly higher titres of measles antibody than normal persons.¹⁴⁹

A series of articles about kuru, regarded as viral encephalopathy, appeared in the January, 1970, issue of the *American Journal of Tropical Medicine and Hygiene*. The first indigenous case of Venezuelan encephalitis was observed in Florida. Specific antibody was demonstrated in five of 353 residents in the vicinity.¹⁵⁰ The infection probably is endemic.

Migratory birds appeared to transport arboviruses southward.¹⁵¹ One wonders whether the reverse occurs when they return? Birds probably have carried microbes to and fro for ages, but population growth has increased human sources and recipients of viruses. How did Venezuelan encephalitis virus get to Florida, and California virus to Minnesota? Similar questions once pertained to the spread of plague eastward in the U.S.A. Research and discovery spread eastward to the residence limit of rodent hosts.

That arboviruses may remain latent in the human brain for years was indicated by the recovery of Langat virus from brains of mice for 261 days after intraperitoneal inoculation.¹⁵² The transmission of

mink encephalopathy to monkeys further supports a view that viral encephalopathies may be common to man and animals.¹⁵³

Virus-like particles were in cerebral tissue of two patients with Creutzfeld-Jakob disease.¹⁵⁴ Since 'slow' viral infections have been associated with chronic encephalitis, other diseases may have similar origin. Antibody to measles and parainfluenza 1 viruses appeared during systemic lupus erythematosus and Reiter's disease.¹⁵⁵ Their significance is undetermined.

During an outbreak in Seattle of Echovirus 30 disease, sixty-four persons were infected. Their families contained 291 members among whom the serologic infection rate was 80%. It was 24% in the total population. Apparently, thousands of cases occurred of which more than half were asymptomatic. Few were diagnosed as meningoencephalitis.¹⁵⁶

Investigations by electron microscopy demonstrated endothelial inclusions resembling myxovirus in patients with systemic lupus erythematosus and rheumatoid arthritis. Whether they are causal or evidence of injured tissue is unknown.¹⁵⁷

Viral meningoencephalitis

During an epidemic of meningitis in Florida, one of fifteen known victims died. Echo 9 virus caused eight infections, meningococci five and in several both microbes were pathogenic.¹⁵⁸ As in pneumonia, viral infections probably predisposed patients to coccocal invasion. In an outbreak of Echovirus 6 infection, eleven children had meningoencephalitis, seven had pharyngitis and five had myalgia. As unusual features, one had pericarditis and one had nephritis.¹⁵⁹ Echovirus 30, detected in the spinal fluid by culture in human diploid cells, induced minimal or no pleocytosis.¹⁶⁰ Gsell presented current clinical and therapeutic problems about meningitis and encephalitis.¹⁶¹

Other viroses

Herpes hominis

Disseminated herpes affected five infants, one fatally.¹⁶² Bleeding and intravascular clotting were fatal in another instance.¹⁶³ A newborn infant contracted infection from the mother who had been infected by the husband's penile herpes.¹⁶⁴ Genital herpes antibody often was present in cervical squamous neoplasia as if it might have been the cause.¹⁶⁵ Herpetic paronychia affected medical personnel exposed to patients' oral lesions.¹⁶⁶ The virus may have caused hepatitis in one patient¹⁶⁷ and acute prostatitis in another.¹⁶⁸ It occasionally becomes pathogenic in burned patients.¹⁶⁹ Among six patients with encephalitis treated with intravenous idoxuridine, two died. The others recovered but had

either stomatitis, bacterial infection, marrow depression or alopecia.¹⁷⁰

Herpes-like (EB) virus and cytomegalovirus

Isolation of these viruses or the presence of antibodies during lymphomas, nasopharyngeal carcinoma, infectious mononucleosis and sarcoidosis¹⁷¹ is of unknown significance. Increased titre to EB virus appeared in 25% of patients with Hodgkin's disease, which is less than during Burkitt's lymphoma.¹⁷² The etiologic relation of the viruses to the diseases is in question.¹⁷³ In one instance, infectious mononucleosis developed during acute leukaemia.¹⁷⁴ Both viruses often are commensal. The matter was summarized elsewhere.¹⁷⁵

Thirty-seven of forty German patients with Burkitt's lymphoma carried EB virus,¹⁷⁶ but four American patients did not.¹⁷⁷ Malaria was said to be the only single identifiable factor common to, or more or less limited to, regions where Burkitt's lymphoma is prevalent.¹⁷⁸ Yet this lymphoma occurs in malaria-free Germany and elsewhere. Is EB virus causal or an opportunistic invader? The problem was discussed editorially.¹⁷⁹ In an American, Burkitt's tumor appeared 16 months after an attack of mononucleosis.¹⁸⁰

EB or cytomegalovirus seemed to cause fifty-four cases of infectious mononucleosis-like disease minus the heterophile agglutinin.¹⁸¹ Cultivated marrow cells from patients induced malignant tumours when injected into hamsters.¹⁸² Neither virus was associated with infectious lymphocytosis.¹⁸³ EB viral antibody was present in 83% of control subjects.¹⁸⁴ Antibody increased in college students and persisted for years. Twenty-eight of ninety-seven had had mononucleosis and fifteen others either had been inapparently infected¹⁸⁵ or had had other disease.¹⁸⁶ In a family of twenty-one, seven index patients had increased titres. Seven others acquired antibody of whom five had atypical lymphocytes and a positive heterophile reaction.¹⁸⁷ About 87% of recruits of low economic status had antibody for EB virus. The incidence of infectious mononucleosis among them was 18/1000 and for Vietnam veterans 24/1000. Seroconversion exceeded hospitalization ten-fold.

EB viral infections in childhood may be dormant for years, manifested by persistent antibody and occasional mild nasopharyngeal discomfort. None of the tested children had mononucleosis.¹⁸⁸ All Aleutian children more than 2 years old had EBV antibody.¹⁷⁷ Antibody for EB virus appeared after cardiac surgery and transfusion of blood in eighteen of 229 patients. Antibody against cytomegalovirus developed in eighty.¹⁹⁰

The Henles reviewed the sequential development of knowledge and the primary contributions they made to the subject. Accordingly, EBV most likely

causes the major form of infectious mononucleosis. Its relationship to lymphoma is less firmly established, but has become more probable.¹⁹¹

Cytomegalovirus. Congenital infection of twenty-six infants with cytomegalovirus was overt in only one. Neurologic difficulties appeared in three within 8 months.¹⁹² In another study the virus was absent in healthy neonates. It was present in 60% of those between 5 and 9 months old but excretion ceased within a year. Virus also was found in 10% of women during pregnancy and in 28% at term.¹⁹³

Viral dysentery

'Winter vomiting disease' affected 300 college students and people in the community. As usual, 'food poisoning' was suspected but disproved. No virus was isolated.¹⁹⁴ Seventeen monkeys inoculated with reovirus developed leucopenia and slight fever. Thirteen had diarrhoea lasting 6-15 days.¹⁹⁵ Ileocolitis during measles in a child apparently was viral in origin.¹⁹⁶ The use of human foetal intestinal cell cultures may facilitate the recovery of viruses from that tract.¹⁹⁷

Exotic viroses

Five papers about Lassa fever, a 'new' disease in Nigeria, appeared in the July 1970 issue of the *American Journal of Tropical Medicine and Hygiene*. Person-to-person transfer occurs. Prominent features are viremia, pharyngitis, myositis, myocarditis, leucopenia and thrombocytopenia. Mild and inapparent infections occur. Virus persists in the throat and urine for weeks. The mode of transmission is unknown. The virus particles resemble those of lymphocytic choriomeningitis, Machupo and Tacaribe viruses. The *Yale Journal of Biology and Medicine* of April 1970, contained five articles about dengue haemorrhagic fever. Asian viral haemorrhagic fevers were the subject of a review in the November 1970 *Journal of Infectious Diseases*. They are related to infections in Africa and South America.

Virus and cancer

Antibody to genital herpes virus appeared in 95% of patients with cervical carcinoma and in 55% of control subjects. Virus may initiate the cancer but a causal association is uncertain. In normal women, antibody increases with advancing age and poor economic status.¹⁹⁸ Similar results but with percentages of 83% and 35% respectively were reported by others.¹⁹⁹ Some members of the herpes and cytomegalo groups of viruses are oncogenic.²⁰⁰ In other studies, antibody to *herpesvirus* type 2 was present in 83% of women with cervical cancer, in 30% with carcinoma *in situ*, but only in 9% to 22% of control subjects. Acquisition of antibody seemed to precede

neoplasia.²⁰¹ Is the virus causal or merely able to grow in injured tissue? The subject was discussed by Stoker.²⁰²

A sarcoma-specific antigen appeared in cultivated sarcoma cells of patients and occasionally of normal genetic relatives. C-type particles like those of animal sarcomas were present in human sarcoma cells.²⁰³

Dermal deposits of malignant melanoma disappeared in six of ten patients after local smallpox vaccination.²⁰⁴ A virus from a monkey's mammary cancer grew in cell-culture. Animals inoculated with the cells will be observed for a year. Similar viral particles were found in human cancers where they may have localized.²⁰⁵ Human embryogenic cells were susceptible to infection with feline leukaemia and sarcoma viruses. The latter transformed the cells to malignant ones.²⁰⁶ The development of an anticancer vaccine is an unlikely prospect. The C-type particle of virus suspected as a cause of cancer is present in normal tissue.²⁰⁷

Miscellaneous viral studies

Electron microscopy disclosed virus-like intracellular particles in the kidneys of twenty-nine of thirty-nine patients with systemic lupus erythematosus. Similar particles were in the glomerular endothelium in patients with discoid lupus. Particles were absent in two patients receiving hydralazine.²⁰⁸ Tissue from patients with regional enteritis inoculated into mice seemed to contain a transmissible agent. Granulomas developed after 6-8 months.²⁰⁹

Interferon. A tilorone compound, probably an interferon, given orally to mice prevented infection against nine viruses.²¹⁰ Inadequate production of interferon may favour dissemination of herpes zoster. Because patients with underlying neoplastic disease formed little or no interferon in chickenpox vesicles, zoster ensued.²¹¹ Besides an 'interference' factor, the reason why a host infected with one microbe can resist infection with another is unknown. Mice infected with *Listeria* were protected against inoculated pneumococci. Enhanced macrophage action probably occurred.²¹² Endotoxins given to animals altered resistance to parasitic, mycotic, bacterial and viral infections. The effect is due to interference of granulocytic diapedesis and exudation, or of phagocytosis by the reticuloendothelial system.²¹³ Stimulation of interferon production by poly 1 : C may provide a means to prevent or treat viral diseases. The July 1970 *Archives of Internal Medicine* contained a symposium about interferon. The information was summarized in the November 1970 *Southern Medical Journal*, page 1199 and in *Science* of 4 December, page 1068. Persistent salmonellosis, probably because of defective phagocytosis as a familial trait, occurred in a woman whose children died from granulomatous disease.²¹⁴

Procedures were described for identifying many viruses by combinations of ten pools of ten antisera each.²¹⁵ The fluorescent antibody technique for rapid diagnosis of viral and bacterial infections also was described.²¹⁶

Mycoplasmas

T-strain mycoplasmas live in the diseased urogenital tract of most patients, especially women.²¹⁷ The microbes also were present in the cervix and urine of 84% of pregnant women,²¹⁸ and in 92% of those with venereal disease. They may be pathogenic during pregnancy,²¹⁹ but have no relation to pre-cancerous changes.²²⁰ They were associated with 60–90% of cases of nongonococcal urethritis, but present in 25% of normal persons. Tetracycline or erythromycin controlled infection.²²¹

Mycoplasma fermentans often is present in joints afflicted by rheumatoid arthritis. The microbic membrane inhibited leucocytic migration in twenty-nine of forty-three patients, but not in osteoarthritis or in normal persons. The inflammatory process may be a hypersensitive response.²²² Intensive antimicrobial attempts, no doubt, are in the offing. Question arises—are they causal or opportunistic invaders? *Myco. hominis* caused dermal abscesses in the newborn.²²³

Bacillary infections

Shigellosis

Twenty-five food-borne outbreaks of shigellosis occurred in the U.S.A. in a 5-year period. Sonne and Flexner bacilli accounted for 50% of the outbreaks.²²⁴ Carriers were the sources. After decades of absence, epidemics of Shiga dysentery in 1969 affected more than 100,000 victims and caused 8000 deaths in Central America. More than 50% of cases were asymptomatic. Tourists carried infection elsewhere. Sulphonamide drugs, tetracycline and chloramphenicol had no therapeutic effect. Ampicillin may be the drug of choice. Reports of the outbreak appeared in the September 1970 issue of the *Journal of Infectious Diseases*. Among naval personnel in Vietnam, ampicillin shortened the course and the carrier state. Kanamycin was ineffective.²²⁵ According to other opinion, no benefit can be expected from the treatment of acute salmonellar or shigellar dysenteries with antimicrobics. Their use often prolonged the carrier state.²²⁶

Thirty-eight soldiers had diarrhoea within 14 days of arrival in Aden. Salmonellae were present in two stools and a new serotype of *E. coli* in fourteen.²²⁷ A causal relationship was not established. Acute diarrhoea was considered a 'toxin' disease²²⁸ which is especially pertinent to cholera.

Typhoid

In three reports in the *British Medical Journal*, 8

August 1970, trimethoprim-sulphamethoxazole was as effective as chloramphenicol for treatment and for typhoid carriers. No serious side-effects occurred. In another study, chloramphenicol given orally appeared in the blood sooner than after intramuscular injection.²²⁹ Typhoid was induced in volunteers according to reports in the 24 September and 1 October issues of the *New England Journal of Medicine*. Titres of O, H, and Vi antibodies bore no relation to susceptibility to infection or to its clinical severity. Illness occurred regardless of high antibody titres. Endotoxemia played no role in the pathogenesis of sustained disease. Parenterally and orally administered vaccine gave protection only against small numbers of ingested bacilli. The Widal reaction may be unspecific and appears during other salmonellar infections.²³⁰

In other studies, after ingesting live, attenuated *S. typhosa* as a vaccine, five of thirty volunteers were subsequently infected as compared with thirteen of twenty-six control subjects.²³¹

As occurs when toilets are flushed, colon bacilli were emitted as aerosols during sewage processing.²³²

Cholera

Vibrios harboured in the gall-bladder diminish or disappear during passage through the bowel. They reappear in faeces during induced catharsis or by suppressing the normal flora with polymixin.²³³ Three of eighty-one cholera patients remained vibrio carriers for 50 to 331 days.²³³ The circumstance probably accounts for interepidemic reservoirs.^{233a}

The severity of cholera induced in thirty-five volunteers by ingested cultures ranged from inapparent infection to severe diarrhoea. Smaller numbers of vibrios were pathogenic when sodium bicarbonate was administered. Achlorhydria probably is conducive to disease²³⁴ as surmised for decades.²³⁵ Unless vomiting interferes, water and electrolytes given orally obviate much intravenous injection and equipment.²³⁶ A supplement of the May 1970 issue of the *Journal of Infectious Diseases* contains new information about cholera. Attention to epidemiology, vaccines, cholera toxin and anti-toxin predominated. A book on the cholera problem was published.²³⁷

Small outbreaks in various parts of southern Asia, western and northern Africa and eastern Europe caused much apprehension elsewhere. Mass vaccination was recommended despite better methods of prevention. Single victims appeared in England and Japan, 107 in Israel and forty-five in Syria.²³⁸

Diphtheria still is prevalent in Iran²³⁹ and elsewhere. Exposure to infection by travellers and spread by rapid transit is ever-present. During 19 months, eighty-eight cases and three deaths occurred in

Austin, Texas.²⁴⁰ Small outbreaks were observed in Chicago, Miami, and Phoenix since 1967.²⁴¹

Plague. Mild attacks predominated in an outbreak in Vietnam. Bacilli persisted in buboes and throat during antimicrobial therapy. Carbuncles resembling anthrax pustules occurred. Antibody developed in about half of exposed but inapparently infected persons.²⁴² A fatal case contracted from a rabbit occurred in November in Oregon. A book describes bubonic plague as it affected Britain.²⁴³ *Yersinia pseudotuberculosis* caused two instances of mesenteric adenitis and ileitis. Both patients recovered.²⁴⁴

Tuberculosis

In observations on BCG vaccination, vaccinees surprisingly had a slightly higher rate of tuberculosis than control subjects.²⁴⁵ (How will proponents regard that report?) Prophylaxis with isoniazid provided a substantial degree of protection.²⁴⁶ Polemic about the value of BCG vaccination persists according to three letters to the Editor of the *Annals of Internal Medicine* of August, pp. 339–340. Primary resistance of *M. tuberculosis* to isoniazid is minimal in North America and Europe. Elsewhere in Africa and Asia from 21 to 70% of bacilli were said to be resistant.²⁴⁷

Two students contracted dermal tuberculosis while performing necropsies on tuberculous patients. Surgical excision of the lesions and chemotherapy were curative.²⁴⁸ Noncaseating granulomas were present in eight of thirty-two patients with pulmonary tuberculosis.²⁴⁹ A convenient dosage outline of eleven antituberculosis drugs and methods of therapy appeared in *Clinical Notes on Respiratory Diseases*, Vol. 9, No. 2.

Knowledge of atypical mycobacteria was reviewed by two authors. According to one,²⁵⁰ latent infections appeared to outnumber overt tuberculosis in the United States. In other reports atypical bacilli cause 2–5% of all acid-fast bacillary infections. Misdiagnosis and delayed therapy are deprecated.

Handling tropical fish and dolphins in aquariums resulted in persistent dermal infection with *Mycobacterium marinum* in four persons.^{251, 252} A patient of mine who abraded his thumb on a rock in the Chesapeake bay has had a dry 2 cm ulcer for more than a year. Isoniazid reduced the lesion which again resumed after cessation of therapy. Excision and a skin-graft are contemplated.

Coccal infections

Streptococci

During a month, the source of thirteen post-operative haemolytic streptococcal wound infections was traced to an anaesthetist who carried the cocci in an anal verge.²⁵³ Dermal infections do not result in rheumatic fever.^{254, 255} Acute nephritis followed impetigo in four family members.²⁵⁶ Legally enforced

detection and treatment of streptococcal pharyngitis begun in 1954 in Wyoming apparently lowered the isolation rate of haemolytic streptococci to 1.8%. New cases of rheumatic fever were rare.²⁵⁷ Milk was the source of infection of Group C haemolytic streptococci which were nephritogenic in one-third of eighty-five patients with sore throat.²⁵⁸

Carditis

After the introduction of antimicrobial therapy, viridans streptococci, once the commonest cause, have been replaced partly by staphylococci, enterococci, Gram-negative bacilli and fungi. These microbes often are nosocomial in origin and drug-resistant.²⁵⁹ Congenital cardiac disease and alpha-hemolytic streptococcal invasion accounted for repeated attacks of endocarditis. Antimicrobial therapy succeeded in controlling relapses.²⁶⁰ Group L streptococci of animal origin,²⁶¹ *Serratia*²⁶² and anaerobes²⁶³ caused endocarditis. *Serratia* was said to form white colonies, but red variant ones probably would appear after growth on agar.^{263a} *Staphylococcus*, *Aspergillus*, or *Candida* alone or mixed were invasive after valvectomy. Antimicrobial therapy failed.²⁶⁴ After valve replacement during acute endocarditis, six of seventeen cases ended fatally. The rest had no recurrent or persistent infection.²⁶⁵

Echovirus 6 and 19, and *Coxsackie* type B viruses are prominent causes of acute carditis and pleurodynia.²⁶⁶ *Echovirus* 4 probably caused myocarditis during a respiratory track infection.²⁶⁷

Tonsillectomy

After years of quiescence, controversy about tonsillectomy revived. In rheumatic children, the size of tonsils did not influence the incidence of recurrences when patients received antistreptococcal prophylaxis. In others, the size of tonsils was associated with increases in the rate of streptococcal infection and rheumatic recurrence. The collected data did not justify fully the reason for tonsillectomy but it was recommended prophylactically for unprotected children who have major cardiac injury.²⁶⁸ Extensive studies by Kaiser and others 30 years ago,²⁶⁹ failed to justify the operation to prevent rheumatic fever. Tonsillectomy with few exceptions is questionable.²⁷⁰

Meningitis

Treatment of Group C meningococcosis was disappointing despite prompt penicillin injection. Among eighteen patients, systemic involvement developed in twelve. Disseminated intravascular clotting caused death in shock of five.²⁷¹ Perhaps a 'new' virulent strain was extant. Of sixteen adults with skull fractures, eight developed meningitis within 2

weeks and four after more than a year, mostly with pneumococci. Six had recurrent attacks but only one died.²⁷² In one case, *E. coli* was the cause.²⁷³ Two patients had meningococcal arthritis.²⁷⁴

According to two editorials in the April 1970 *Journal of Infectious Diseases*, neither sulphonamide drugs nor penicillin controlled meningococcosis. Experiments with antimeningococcal vaccines (immunogens) show promise. Immunization with a Group C polysaccharide preparation seemed to reduce the incidence of meningococcosis in Army recruits. Infections with group B cocci appeared in several immunized men.²⁷⁵ Studies with pneumococcal and *H. influenzae* antigens are underway. While serologic and other evidence indicated immunization, the real test will come after practical application.

Neonatal meningitis especially from Gram-negative bacilli occurred in twenty-five of 54,000 live births. Complications during pregnancy or delivery and of underweight infants were factors accounting for death in fifteen.²⁷⁶ Phlebitis, drug fever and unrelated infections prolonged fever in 9% of children with bacterial meningitis.²⁷⁷

Pneumonia

A committee of the American Thoracic Society formulated classifications of acute pulmonic infections.²⁷⁸ Essentially the same grouping appears in a forthcoming compend on pneumonia.²⁷⁹ Type 70 pneumococci resisted erythromycin but not tetracycline. Other high-numbered types resist tetracycline.²⁸⁰ Obviously, the need increases for serotype and sensitivity determinations to control therapy.²⁸¹ Pneumococcemia caused death of four children with hemoglobinopathy.²⁸² Intravascular clotting and peripheral gangrene also occurred.²⁸³ *Meningococcus* in the sputum of thirty pneumonic patients raised question as to its significance as a cause of pneumonia.²⁸⁴

Pneumonia followed tracheostomy in seventeen of 139 patients, especially aged ones, usually within a week. Eleven died.²⁸⁵ Experiments support the clinical impression that prolonged oxygen therapy increases the susceptibility of the lung to infection.²⁸⁶

Pneumocystis carinii was the commonest cause of diffuse interstitial pneumonia in patients receiving immunosuppressive therapy²⁸⁷ and in children with cancer. Needle aspiration facilitated diagnosis.²⁸⁸ An outbreak of nineteen cases and forty inapparent infections were recorded. *Cryptococcus*, *Aspergillus* and *Toxoplasma* were other invaders. The onset of pneumonia was fulminant and often fatal. Treatment with pentamidine isothionate was recommended.²⁸⁹ During *Myc. pneumoniae* pneumonia, the microbe became resistant to erythromycin and to other antimicrobial drugs. The patient recovered anyway.²⁹⁰

Gonorrhoea and syphilis

Venereal diseases are pandemic and out of control. Gonorrhoea ranks first and syphilis fourth among reportable diseases in the U.S.A.²⁹¹ Several factors are blamed: decline of moral values, permissiveness, contraceptive practice, over-reliance on prophylaxis and therapy, re-exposure and lack of effective immunity.²⁹² According to national statistics, about one-half million cases of gonorrhoea and 18,000 of syphilis were reported in 1969. Probably more than four times as many failed registration.²⁹³ According to another view, 80% of venereal diseases are unreported.²⁹⁴

The risk of contracting gonorrhoea after exposure was 22% among Navy personnel on shore leave.²⁹⁵ After orogenital contact, a man had gonococcal pharyngitis followed by septicemia and arthritis. Erythromycin was curative.²⁹⁶ Gonococcal meningitis and shock were fatal in an infant.²⁹⁷ Instances of gonococcal perihepatitis²⁹⁸ and haemorrhagic bullae²⁹⁹ occurred. Several patients had papules, pustules and arthritis.³⁰⁰ Diagnostic and therapeutic procedures for the management of gonorrhoea were outlined.³⁰¹ Gonococci and meningococci survive for days in a special medium for diagnostic purpose.³⁰²

The increased incidence of syphilis heralds the resurgence of foetal infections. In one instance, massive penicillin therapy failed to influence a fatal course. Viable treponemes persisted in the tissue.³⁰³ Between 1958 and 1968 reported cases of syphilis increased 202%; of congenital syphilis 168%.³⁰⁴

Mycoses

Histoplasmosis

Progressive disseminated disease ensued in twenty-five of 530 patients with histoplasmosis. The mortality after treatment with amphotericin was 7%, without treatment 100%.³⁰⁵ Amphotericin therapy failed in an English patient with disseminated disease probably acquired in Burma.³⁰⁶ Besides the usual features, peritonitis,³⁰⁷ hepatitis, endocarditis, meningitis,³⁰⁸ and exfoliative dermatitis³⁰⁹ occurred. Histoplasmosis declined by 86% among Michigan school children as a result of covering dusty areas and applying other measures.³¹⁰ Blackbird and starling roosts are sources of infection.³¹¹

Darling who discovered histoplasmosis in 1906, probably was the first to describe *Toxoplasma* 2 years later.³¹² Darling also noted the morphologic resemblance of *Histoplasma* to *Leishmania donovani* for which he was searching.

Coccidioidomycosis

During an outing in Texas, nine of ten persons contracted coccidioidomycosis. The lungs were

involved in seven and exanthems appeared in six.³¹³ Eight children contracted coccidioidomycosis from sandy soil in San Diego. Seven had pulmonic infiltration. Illness lasted 1–3 weeks.³¹⁴ Pregnancy may activate benign coccidioidomycosis into fatal systemic dissemination. The foetus also may be involved.³¹⁵ Many of 109 patients with chronic coccidioidomycosis had been suspected of having tuberculosis. Roentgenographic changes were unspecific. Amphotericin B is the drug of choice.³¹⁶ Difficulties and delays in diagnosis involved nine victims of coccidioidal meningitis. The dermal test gave negative results in all. Diagnosis was made by the complement-fixation test and spinal fluid pleocytosis.³¹⁷

Disseminated sporotrichosis is an increasingly important occurrence in debilitated patients. Four cases were described and twenty-seven others referred to. Amphotericin B is the therapeutic agent of choice.³¹⁸ An air-conditioning system contaminated with an actinomycete induced hypersensitivity and granulomatous interstitial pneumonia in office workers.³¹⁹ Five of twenty-two surgical patients nourished intravenously developed *Candida albicans* (monilia) septicemia. Two died.³²⁰ Epithelial tissue unable to combat superficial mycotic infections because of immunologic deficiency and its correction was discussed.³²¹

The value of skin testing with fungal antigens was questioned. The high rate of false negative reactions, the thousands of healthy persons who react and the interference with serologic procedures are well known. Tests with blastomycin and histoplasmin are not needed when overt disease is suspected. Coccidioidin should only be used after careful evaluation. Simultaneous application of several antigens was condemned.³²²

Opportunistic invaders

The length of this section reflects the growing hazard of opportunistic and nosocomial infections. A review summarized the problem.³²³ Anaerobic bacteria were present in 482 of 1223 specimens of lesions; in pure culture in 21%. *Bacteroides* was the commonest.³²⁴ *Bacteroides* septicemia developed during incomplete abortion in 50% of 111 women. All survived regardless of antimicrobial therapy.³²⁵ Bacteremia in thirty-five patients (0.2% of 25,000 blood-cultures) caused death from shock in twelve. Only one victim less than 40 years old died. Jaundice, hepatic abscess and pyelophlebitis were commoner than in other Gram-negative bacillary infections.³²⁶ In another study, thirty-four patients were bacteremic chiefly after enteric surgery.³²⁷ Six per cent of patients with gastrointestinal, hepatic or urinary tract disease had bacteremia with more than one microbe. Endocarditis developed in three.³²⁸

In a hospital, Type 24 was the most frequent

endemic strain of *Klebsiella*. It was often associated with urinary catheterization. Type 26 was endemic in the nursery. Nearly all strains were sensitive to gentamicin.³²⁹ Pseudomonal infections involved 26% of eighty-seven leukaemic patients. While in a hospital 54% became carriers.³³⁰ Injection of a contaminated muscle relaxant caused nonfatal Gram-negative bacillary infection and shock in five surgical patients in one day.³³¹ Another nosocomial outbreak of *Serratia* infection from contaminated inhalation apparatus was described. 374 patients were involved in a 10-month period.³³² *Serratia* was discussed in two papers in the *Journal of the American Medical Association* of 21 December. Bizio applied the name *Serratia* in 1823.

B. bronchoseptica, *Ps. multophilus*, *H. vagincola*, *M. polymorpha*, heretofore disregarded as saprophytes, occasionally are incidental invaders particularly in hospital patients.³³³ Infections of the feet, lungs, kidneys, gallbladder, and skin in that order affected 10% of 640 diabetic patients.³³⁴

Staphylococcus aureus sepsis complicated six cases of arteriovenous fistula maintained by hemodialysis. *Ps. aeruginosa* caused one. There was no relation between local infection and sepsis.³³⁵ *Staphylococcus albus* bacteremia and renal infection complicated ventriculo-atrial shunts in three patients. Improvement followed the removal of the shunts. Fluorescent micrography showed immunoglobulin in glomeruli suggesting an immune reaction as the cause.³³⁶ No reports of invasion of *Micrococcus tetragenus*, a common saprophyte, were encountered. The coccus is easily mistaken for staphylococci.

Antimicrobial therapy has allowed many instances of acute subphrenic abscess to become chronic.³³⁷ The danger of serious infections, haemorrhage and intravascular clotting after splenectomy in children was re-emphasized.³³⁸

Herpes hominis, rubella and cytomegaloviruses which occasionally infect the foetus are teratogenic. Other invaders are the viruses of rubeola, equine encephalitis, vaccinia, variola, polio, hepatitis and Cocksackie disease. These are invasive oftener than believed especially in disadvantaged persons. About 5% of pregnancies are complicated by viral infections, chiefly colds, *herpes simplex* and viral dysentery.³³⁹

Routine blood cultures from four men who had no contact with animals, but had an underlying chronic condition, disclosed *Vibrio fetus* septicemia during a 4-year period in Boston.³⁴⁰ Probably fewer than 1% of *Vibrio fetus* infections are recognized. So far about seventy-four case reports have been published. The infection is widespread and affects infants, pregnant women and particularly aged and decrepit men. Eight cases were observed in a 30-month period in New York City. Tetracycline therapy was beneficial but relapses followed.³⁴¹

Candida infected a tricuspid valve after an aged man was treated with antimicrobial drugs for pulmonary disease.³⁴² Severe diabetes predisposes to fatal rhinocerebral phycomycosis.³⁴³ *Torulopsis glabrata* as an opportunistic invader infected thirty-seven patients in a 16-month period.³⁴⁴

'Septic shock' is a common host-response to Gram-negative and Gram-positive bacillary and coccidial infections³⁴⁵ and probably to viral infections.

Relation of complement to infection

Repeated infections involved a patient whose measurable immunity factors were normal except for deficiency of C3 serum complement component. The addition of C3 to his serum did not restore haemolytic activity and its lack may not be entirely accountable for susceptibility to infection.³⁴⁶ In another patient susceptible to infections, deficiency of C5 as a heritable trait impaired phagocytic activity. Addition of C5 restored phagocytic ability.³⁴⁷ The matter is of interest in regard to the relation of serum complement components to hypothetical opsonins and their role in controlling infections.³⁴⁸ The matter was discussed editorially.³⁴⁹ Specific nonhereditary deficiencies of various γ -globulins accounted for recurrent pyogenic infections. Replacement therapy was preventive.³⁵⁰

Infections acquired from mammals, birds, and fish

Chapman cited histoplasmosis, coccidioidomycosis, cryptococcosis, toxoplasmosis, rickettsioses, cat-scratch disease, avian and atypical tuberculosis, relapsing fever, rabies and plague as zoonoses.³⁵¹ Salmonellosis, anthrax, glanders, orf, yellow fever, tularemia and others could be added to the list. Increasing travel, out-door living and camping favour greater contact with sources of infection. For example, thirty-one cases of plague were reported from the western U.S.A. between 1965 and 1969. A fatal case was contracted from a wild rabbit in Oregon in 1970.

Two reports dealt with 316 *Pasteurella multocida* infections. Bites or scratches from animals caused 180 cases and 136 victims had no known animal contact. The respiratory tract, abdominal organs, extremities, central nervous system and other areas were affected in that order.³⁵² Dermal infection with *Myco. marinum* acquired from fish was mentioned elsewhere.³⁵¹

Sixteen necropsy studies of melioidosis disclosed a variety of widely scattered lesions containing the bacilli. Granulomatous lesions confined to a single organ characterized chronic disease. Like glanders, melioidosis affects cattle, pigs and sheep in Asia, Australia and the Dutch Antilles.³⁵³

Hospital food, especially meat and poultry contained large numbers of *E. coli* able to invade

patients. Antimicrobial prophylaxis for animals and birds may cause the emergence of resistant bacilli which in turn may cause resistant infections in man.³⁵⁴ A book describes food-borne viral, bacterial and vibriol infections.³⁵⁵ Mammalian ecology has importance in the epidemiology of zoonoses of which 150 are known.^{355a}

Rickettsia canada a newly discovered member of the typhus group caused severe febrile disease in four patients. Clinically it resembled Rocky Mountain spotted fever.³⁵⁶ Rocky Mountain spotted fever was acquired by inhalation in a vaccinated laboratory technician.³⁵⁷ Cat fleas were vectors of murine typhus in Texas.³⁵⁸ The July 1970 issue of the *Archives of Environmental Health* contains three papers about Q fever in Milwaukee. The incidence has increased among cattle since 1957. Volunteers who drank naturally infected milk showed no evidence of infection. Since 1955, evidence of Q fever was present in 2428 persons in the city.

Carrithers summarized the historical development of knowledge concerning cat-scratch disease.³⁵⁹ As might have been expected, relatives of two exotic viruses exist in the U.S.A. *Cache Valley* virus, a member of the Bunyamwera group, was present in mosquitoes in Virginia and antibody was found in domestic animals and man.³⁶⁰ Rats in Florida harboured *Tamiami* virus which is related to *Tacaribe* viruses.³⁶¹ Man may be a source of fowl plague for fowl.³⁶²

Cutaneous leishmaniasis is hyperendemic near Jericho. During a month, 50% of newly arrived men were infected. A wild rodent is the source and phlebotomus the vector.³⁶³ Dermal myiasis caused by a rabbit bot fly occurred in Connecticut.³⁶⁴ *Taenia multiceps*, a dog tapeworm, probably transmitted by a rabbit, caused a fatal intracranial cyst in a child.³⁶⁵ Migration of a proglottid of *Taenia* into the uterus caused bleeding.³⁶⁶

The piroplasma *Babesia* causes world-wide, tick-borne, haemolytic disease of many wild and domestic animals. Four splenectomized patients were reported from Yugoslavia, California and Ireland. It is easily mistaken for malaria. Other instances probably have not been recognized.³⁶⁷

Newly recognized *Toxocara* harboured by dogs and cats caused ocular, hepatic, pulmonic, myocardial and other lesions in man. Two per cent of Britons were said to be infected.³⁶⁸ Serologically, toxocara and toxoplasma are unrelated.³⁶⁹ Toxoplasmic encephalitis occurred in three adults.³⁷⁰

An outbreak of leptospirosis involved about 4% of the population of an Israeli farming community. Twenty-nine victims were studied but probably many more were mildly or inapparently infected.³⁷¹ During epizootics of feline pneumonia caused by one of the *Bedsonia*, infection transmitted to man caused

corneal ulcers.³⁷² Infection with *Fasciola hepatica* (liver fluke), probably contracted from watercress in sheep and cattle raising districts, by forty-four English patients responded to therapy with emetine and chloroquine.³⁷³ Enteric coccidiosis present in six patients may be a cause of malabsorption diarrhoea and steatorrhoea. Therapy was ineffective.³⁷⁴

Gnathostomiasis, indigenous to Southeast Asia, occurred in two Mexicans. Larvas inhabited the abdominal wall in one, the eye in the other.³⁷⁵

Miscellaneous items

Urinary tract infection

Kunin summarized information gained in a 10-year study of bacteriuria in girls. Bacteriuria occurs in more than 5% and often is symptomless. The risk of infection is enhanced by marriage and pregnancy. Serologic typing of *E. coli* aids in distinguishing between relapses and recurrent reinfection. Ampicillin was no more effective therapeutically than nitrofurantoin and sulfonamide drugs. Bacteriuria requires treatment to reduce morbidity. Vesicoureteral reflux occurs in about 20% of girls, decreases with age and often resolves spontaneously. Surgical correction seldom is necessary.³⁷⁶ Closed sterile drainage of the urinary bladder by a new apparatus obviated cystitis in twenty-eight of fifty-one patients. Ascending infection occurred in others through the lumen of the tube.³⁷⁷

Immunologic features, serious consequences and the therapy of malaria were discussed at a conference.³⁷⁸ Fifteen years after eradicating malaria on an island, 1% of population still had antibody.³⁷⁹ A purified fraction of *Pl. berghei* used as an immunogen prevented parasitemia, anemia and death of mice inoculated with the same strain.³⁸⁰ Returnees from Vietnam accounted for 3800 new cases of malaria in the U.S.A. in 1969.

Four persons contracted fatal amoebic meningoencephalitis in public swimming places in Virginia. Antimicrobial therapy failed.³⁸¹ The first observed fatal case occurred in Britain.³⁸² The latex agglutination test for diagnosis of rheumatoid arthritis, gave positive results during invasive amoebiasis.³⁸³ Metronidazole promises to be effective in treating amoebic dysentery.³⁸⁴ Of sixty-five hepatic abscesses, fifty-eight were pyogenic in origin; four were amoebic; two were mycotic and one was ecchinococcal.³⁸⁵

Ten bathers in a Puerto Rican river contracted schistosomiasis. One was symptomless, six had mild fever and diarrhoea, and seven had hepato- or splenomegaly and were severely sick. All had eosinophilia. All recovered without chemotherapy.³⁸⁶ The event is reminiscent of leptospirosis involving seven bathers in a Pennsylvania stream I described in 1941. Filtration of portal blood removes the flukes from victims of schistosomiasis.³⁸⁷

Among 178 Samoan immigrants, 14% had microfilaremia after 8 years' residence in the U.S.A. The danger of spread is unlikely.³⁸⁸

The matter of autogenous vaccines was reviewed. They may be dubious desensitizers or act by stimulating specific antibodies anamnesticly.³⁸⁹ Multivalent vaccine containing two strains of staphylococci, six types of *Pseudomonas* and staphylococcal toxoid failed to affect the death-rate of thirty-nine burned patients.³⁹⁰ The general cost of immunizing infants was estimated at \$42 per child.³⁹¹

Persons who handle the proteolytic enzymes of *B. subtilis* occasionally suffer severe asthmatic attacks. In forty-six hamsters, aerosol inhalation of the enzymes caused pulmonic haemorrhages and death in eight.³⁹² Allergy to intestinal parasites was proposed as a cause of asthma.³⁹³

Because of sanitary and housing deficiency, the health status of Navaho Amerinds has not advanced for 30 years. Tuberculosis is seven times the national rate. Trachoma, gonorrhoea, syphilis, dysentery, measles and chickenpox are three to seven times as common.³⁹⁴

The United States Government stopped work on agents for biologic warfare. Besides aggressive psychologic influence and affecting local groups, the chance of inflicting significant epidemics is meagre.

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