ANNUAL REVIEW

Infectious diseases: Annual review of significant publications

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Introduction

Interest in viral infections and immune responses thereto dominates. Advances in knowledge of hepatitis, the herpes group and of 'slow' viral diseases continued. The relation of viruses and virus-like particles to cancers remains unclear. Vaccines are useful against several infections, and efforts continue to improve others. The question arises whether or not a number of viral, bacterial or other diseases will ever be eradicated. Venereal infections have assumed alarming proportions. No outstanding improvements accrued in antimicrobial prophylaxis or treatment. New agents appeared without evidence of their superiority over older ones. Nosocomial and iatrogenic infections continued to be problems. Interest in exotic diseases increased.

Viral infections

Respiratory tract infections

According to a compilation, physicians prescribed antimicrobial drugs for 60% of common colds.¹ Almost all were wasted if, as a rule, bacterial superinfection occurs in only 1% of cases. Pauling still defends his opinion about the value of vitamin C for colds² and some studies partly support it.³ As if it were a new observation, it was implied that viral infections may involve the small pulmonary airways.⁴ It is well known that in the spectrum of severity of any viral entity, the lungs are affected in 0-10% or more of victims.

Among marine recruits between 1967 and 1971, *Adenovirus 7*, *Mycoplasma* and *Coxsackievirus A21* caused most illness. 51% of 492 victims had pneumonia. Haemolytic streptococci also were present in fifty-one who had pharyngitis.⁵ Five marine trainees had parainfluenzal viral pneumonia requiring 19-41 days of hospital care.⁶ About two-thirds of all serious respiratory tract disease among 18,000 infants occurred in December and in June-July.⁷

Influenza. Ten Australians had severe type A2 virus pneumonia and circulatory failure. Eight died.⁸ Nine other patients died, including two who had received immunosuppressive therapy.⁹ The virus

may have caused¹⁰ (or incited) a case of Goodpasture's syndrome. Cyclooctylamine applied topically to the nasal membrane as a prophylactic appeared to be as effective as amantadine for meliorating A2 influenza.¹¹ Neuraminidase also afforded resistance to infection.¹²

In mouse tissue-culture the virus destroyed the epithelial layer within 11 days, but not the underlying tissue. Clusters of virus particles adhered to and clumped the cilia.¹³ Research at the National Institutes of Health was summarized.¹⁴

An imbroglio at the National Institutes of Health concerned the faulty testing and value of influenza vaccine. At a hearing, the Chief of Service stated: 'I have never been impressed with ... the efficacy of influenza vaccine.'¹⁵ If the distributed defective vaccine had been applied, how can one account for favourable results reported from its use? Other vaccines also were questionable. A newly prepared recombinant influenza virus vaccine holds more promise.¹⁶ Intranasal application gave better results than subcutaneous injection,¹⁷ but an adjuvant added to the latter gave an equally good titre and broadened the antibody response to variants of the virus.¹⁸ A new antigenic variant of the current A2 strain appeared in outbreaks in the Far East. In Peking, acupuncture of 1006 patients abolished fever within 5-16 hr sooner than aspirin.¹⁹ It may also serve as a prophylactic, an advantage, if true. As a result of stringent regulations, commercial vaccines against staphylococci, *Micrococcus catarrhalis*, streptococci and *Haemophilus influenzae* were withdrawn from the market.²⁰ Their value had never been established.

Adenoviruses. Despite oral immunization of 900 recruits against viruses 4 and 7, virus 4 later caused about one-third of 149 hospital admissions, seventeen with pneumonia. In most instances, several different viruses were present. Excepting influenza A and *Adenovirus 7*, vaccination against other infections was unsatisfactory.²¹ Three trainees died from virus type 7 pneumonia. Each had transient lymphopenia, multisystem involvement and intravascular clotting.²² Virus 7 caused twenty-nine cases of pneumonia in

children. Encephalitis, hepatomegaly, cardiac failure and bleeding occurred. Three died and four had permanent pulmonary damage.²³ Until further knowledge accrues, it is uncertain if adenoviruses alone can cause whooping cough. Possible dual infection with *Bacillus pertussis* affected seven of fourteen cases.²⁴ Was the virus commensal?

Rhinoviruses. Experimental infection with rhinoviruses resulted in a degree of immunity with correlation between nasal and serum antibody.²⁵ Inactivated virus 13 evoked high titres of neutralizing serum antibody in all volunteers and nasal antibody in about 50%. Vaccination, however, failed to prevent experimental infection.²⁶ Poly 1 : C, an interferon-inducer, administered intranasally before infecting volunteers with rhinovirus 13 or A2 influenza virus resulted in a small reduction of symptoms. Virus shedding persisted.²⁷

Coronaviruses caused winter epidemics in 4–8% of adults with colds.²⁸ Infection, determined serologically, involved from 15 to 35% of students during three cold seasons.²⁹

Coxsackievirus A21 infections usually involve the nasopharynx and *adenovirus* B4 the lower respiratory tract.³⁰ *Coxsackievirus* B3 and B4 caused moderately severe respiratory tract disease during 10 weeks among children in an institution. Various tissues were involved.³¹ Hand-foot-and-mouth disease affected fifty children in North Carolina, caused chiefly by virus A16. It occurs unrecognized oftener than usually believed.³² Similar disease 'associated' with virus A9 involved seven adults, all with other underlying diseases. Virus types A5 and 10 also have been implicated.³³ The question of commensalism arises. Virus B2 and B4 infections of mothers were associated with various congenital defects in their offspring.³⁴

In Britain, more mycoplasmal infections occurred in 1971 than in the previous 4 years.³⁵ Meningo-encephalitis occasionally accompanied mycoplasmal pneumonia and three children had acute cerebellar ataxia.³⁶ Other neural involvement was reviewed.³⁷ An antigenic component is responsible for the cold-agglutinin during mycoplasmosis.³⁸

Viral hepatitis

In new terminology, infectious (IH, MS-1) infection is hepatitis A and serum hepatitis (SH, MS-2) is hepatitis B. HB Ab (Australian antibody) is B antibody: HB Ag is B antigen.

Hepatitis B. The proportion of drug-addicted patients with hepatitis rose from about 4% before 1966 to 30% in 1971.^{39,40} Hepatitis B acquired either parenterally or orally affected eleven hospital patients during 3 months. Hospital personnel at risk, if infected, are potential sources of infection and may present legal problems. An outbreak

involved five family members by contact.⁴¹ HB Ag apparently crossed the placenta via cord-blood from mothers who had hepatitis before or during pregnancy. Three infants had antigenemia and inapparent infection.⁴² Other studies showed such transmission to be rare.⁴³ Antigen in saliva,⁴⁴ and faeces⁴⁵ may be a factor in spreading infection. Hepatitis B among Ghanaians who had never received injections suggested an air-borne or arthropod-borne source,⁴⁷ or infection by contact. Mosquitoes carried HB Ag and probably account for the high incidence of hepatitis B in the tropics,⁴⁸ in Japan,⁴⁹ and to a lesser extent elsewhere.

Transfusions of blood containing HB Ag gave rise to disease in 52% of recipients of whom 23% had an immune response. HB Ag-negative blood caused anicteric hepatitis in 16% and mild icterus in 2%. Commercial donor blood contains the antigen thirteen times more often than volunteers' blood.⁵⁰ In a co-operative study, the risk of acquiring symptomatic hepatitis by transfusion among 5000 patients was 2.8% with death in 0.1%. Current tests for HB Ag fail to detect all donor blood able to transmit infection. Exclusion of commercial blood and HB Ag-positive donors resulted in a great decrease of hepatitis.⁵¹ Serum globulin containing HB Ab failed to give protection.⁵² According to another study, gamma globulin did afford protection for 6 months. A sensitive radioimmune assay method detected HB Ag in 1% of donors.⁵³ Patients with Down's syndrome may serve as reservoirs of infection. Some with persistent antigenaemia had mild hepatic disturbance and others had no evidence of hepatic disease.⁵⁴

Antigenaemia and antigenic forms persisted in a patient with leukaemia and polyarthritis without evidence of hepatitis. Antibody appeared in hepatic cell nuclei.⁵⁵ Chronic antigenaemia or antibody occurred in six patients with polyarthritis. In two, the antigen was in blood vessel walls.⁵⁶ In two patients, arthritis preceded hepatitis diagnosed by the presence of HB Ag and increased serum enzymes. Biopsy was not mentioned.⁵⁷ Urticaria preceded hepatitis in three patients.⁵⁸ Because HB Ag was present in only 5% of ninety-seven cases of primary biliary cirrhosis, it may have been coincidental from prior infection.⁵⁹ The persistence of HB Ag in chronic hepatitis had no prognostic significance.⁶⁰

Three groups of investigators succeeded in transmitting B virus to animal primates causing inapparent infections detectable by the development of antigenaemia and later of HB Ab. Intracellular and Dane particles appeared. The radio-immunoprecipitation test revealed HB Ab in 14% of blood donors, most of whom had not had blood transfusions or known hepatitis. An agent related to HB Ag transmitted serially to rhesus monkeys gave

an antibody response similar to that in man without any evidence of hepatic disease.⁶¹ A rapid diagnostic screening test combines speed and sensitivity.⁶²

HB Ag may not be the causal virus. Three other agents are suspected, especially the Huang particle which becomes a Dane particle and resembles the picorna viruses.⁶³ Authorities are not yet convinced that the particles are the virus. Two types of HB Ag are AB and AC. Carriers of either type in separate places suggested that two different agents are causal. Persons contracting hepatitis in a hospital had the type prevalent at the time.⁶⁴ Other investigators applied the terms HBV-D and HBV-Y to the same subtypes. A preponderance of Y subtype occurred in drug-addicts.⁶⁵ Similar findings were reported from Germany.⁶⁶

The April 1972 issue of the *American Journal of Diseases of Children* and the May issue of the *British Medical Bulletin* are devoted to hepatitis and its problems.

Hepatitis A (viral; IH; infectious; MS-1). During an epidemic of hepatitis A, persistent carriers of HB Ag contracted the infection, indicating the aetiological difference of the two diseases.⁶⁷ In addition, a transitory A-associated antigen (HA Ag) different from HB Ag appeared during the first 2 weeks of hepatitis A.⁶⁸ Similar report came from Italy.⁶⁹

Reminiscent of the 1933 outbreak of amoebiasis in Chicago, polluted drinking water caused icteric disease in thirty-two persons, twenty-two were anicteric and the rest had inapparent infection. Hepatitis was said to be the only known water-borne viral infection,⁷⁰ but poliomyelitis and others also may be.

Official recommendations cover the indications for using immune serum globulin to prevent hepatitis A. It has no value against B infection.⁷¹

Echovirus 14 isolated from the liver seemed to be the cause of fatal hepatic necrosis in a newborn, probably acquired *in utero*.⁷² The virus was seen by electron microscopy. Many patients receiving long-term dialysis develop hepatitis of nonviral origin as detected by lymphocytic infiltration, scattered areas of focal necrosis and increased plasma transaminase.⁷³

Viral dysentery

An elusive filtrable agent causes viral dysentery as a seasonal epidemic disease.⁷⁴ Studies failed to reveal the cause in 5000 victims among 36,000 Americans in the Philippines.⁷⁵ A local outbreak affecting 600 school children led to a needless search for the source in the water supply, food-handlers and restaurants.⁷⁶ The prophylactic or therapeutic use of Enterovioform is without value.⁷⁷

Viral dysentery resembles mild cholera. Both are non-inflammatory, of short duration, afebrile, without

leukocytic mucosal invasion and much fluid is lost. As a diagnostic aid, the stools in both diseases contain no leukocytes in contrast to other enteric infections.⁷⁸ Enterotoxin is causal in cholera and probably in viral dysentery. As mentioned later in the discussion of cholera, some strains of *Escherichia coli* and *Shigella* cause similar disease.

At a conference,⁷⁹ the ingrained name gastroenteritis persisted, but *itis* (inflammation) is absent. The fitting name is viral dysentery (bowel trouble of viral origin). Sceptics question its viral cause in the absence of proof, yet the agents of hepatitis, syphilis and leprosy can be seen, but not grown *in vitro*.

In experiments like mine in 1945, volunteers ingesting filtrates from patients' stools sickened within 48 hr. A filtrable, ether- and heat-stable, non-cultivable agent was detected and homologous immunity developed.⁷⁹ Clarke *et al.* reported similar observations. The agents resembled the picorna viruses.⁸⁰ It may be the pathogen discovered 28 years after filtrable agent was implicated⁸¹ and after ECHO, coxsackie and reovirus were suspected as causes. A transmissible filtrable agent caused massive enteric fluid loss in piglets.⁸²

Herpes hominis. Evidence of type 2 infection appeared in 70% of prostitutes more than 20 years old and in 7% of younger ones, dependent on the length of their experience.⁸³ The virus seldom existed in the genital tract of other women, but was recovered from that area in eighteen of 190 symptomless men who serve as transmitters of infection.⁸⁴ In patients with erythema multiforme, virus in dermal lesions also caused cervicitis, salpingitis and peritonitis.⁸⁵ Two of five patients with encephalitis died and one had permanent dementia. Two treated with corticosteroids survived, but with sequels.⁸⁶ Cytarabine therapy improved other patients.^{87, 88} The trigeminal ganglion contained the virus in two instances without clinical evidence of neural involvement.⁸⁹ That area and the genital tract may serve as sources of recurrent herpetosis. Recurrence of disease may follow failure of macrophage function and lymphocytic toxicity, even with intact antibody formation.⁹⁰

A herpes-like agent replicated in the nuclei of an estuarine fungus suggesting its pathogenicity.⁹¹ Some oysters contain a potentially pathogenic (for them) herpes-type virus.⁹²

EB virus. Evidence of herpesvirus-group infection appeared in sixty patients with leukaemia, in twenty-two with nasopharyngeal cancer and in eighty-two healthy subjects. All cancer patients had EBV antibody and seventeen had antibody to varicella virus.⁹³ There is highly suggestive evidence of a causal relationship of EBV to infectious mononucleosis and lymphomas. The virus, however, may be a latent one and evidence of its presence does not prove its

pathogenicity.⁹⁴ It is extremely common and harmless in millions of people.⁹⁵ Studies on leukaemic children failed to support the relation of EB virus to the disease. Two treated children got infectious mononucleosis.⁹⁶ Infectious mononucleosis appeared in a leukaemic patient 30 days after transfusion of pre-illness plasma from a donor who similarly became ill in 17 days. EB virus and heterophile antibody appeared in both.⁹⁷ Normal lymphocytes when transformed by exposure to pharyngeal exudate from a patient, contained particles resembling EBV. Oral secretions of patients contained a leukocyte transforming agent, which is the EB virus or an agent associated with it.⁹⁸ The observations favour the probable oral source of the infection⁹⁹ if the virus is the cause.

Infectious mononucleosis involved the neural system in seven of 144 patients.¹⁰⁰ Bilateral pneumonia occurred in one patient,¹⁰¹ haemolytic anaemia and probable myocarditis in another.¹⁰² The disease was said to be less likely to recur than other childhood viral infections.¹⁰³ But inapparent attacks may pass undetected. In 1 year, infectious mononucleosis caused 2811 attacks, a rate of about 1/100 students, an incidence three times more than in the general population. There was no seasonal pattern, and only a few victims had had contact with patients.¹⁰⁴ In applying a vaccine, said to induce protection, the EB virus titre increased in some persons. The titre in patients and in normal persons was the same.¹⁰⁵ Problems and uncertainties of the infection were discussed at a symposium.¹⁰⁶

Meningoencephalitis

ECHO virus type 3 caused eighty cases in infants and children in Virginia in the summer of 1970¹⁰⁷ (the adjectives 'non-bacterial' or 'viral' are preferable to 'aseptic'). Among twenty-nine other children, twenty-four had meningitis and in addition three had pericarditis and myocarditis.¹⁰⁸ Virus type 4 infected hundreds of persons in Alaska during 2 months. Many had meningitis and 62% were asymptomatic. The attack rate in different places varied from 10 to 27%. Prior outbreaks of type 30 infection conferred no immunity.¹⁰⁹ Seventy instances of fatal mumps meningoencephalitis are on record, but proved as such in only a few.¹¹⁰ During 10 years, fifty children in Ohio had 'California' encephalitis.¹¹¹

Attempts are in progress to destroy mosquito vectors and to vaccinate horses against the northward spread of Venezuelan encephalitis. As predicted, the virus invaded cattle in Texas in June. Eighty-eight non-fatal cases occurred in people.^{112,113}

Polyoma-like viruses related to SV40 virus were present in the brain of two patients with progressive leukoencephalopathy.¹¹⁴ In others, virions different from polyoma virus, but related to SV40 were seen

by electron microscopy.¹¹⁵ Perhaps several viruses are causal. Brain cells from a patient with Creutzfeldt-Jakob disease transformed when grown *in vitro*. Viral-like particles appeared similar to those of oncogenic RNA viruses, but their significance was uncertain.¹¹⁶

Chronic panencephalitis was induced by inoculating hamsters with a virus obtained from a patient. Measles antigen appeared with nuclear inclusions in cerebral tissue. Antibody to measles virus often increased.¹¹⁷ Epidemic evidence showing the concentration of patients with subacute panencephalitis (SSPE) in south-eastern U.S.A., and the higher ratio of male victims than elsewhere, confuses the relation of measles virus as the cause.¹¹⁸ Two measles-like viruses isolated from patients differed from the classic strains. In contrast, the SSPE virus failed to penetrate cells in tissue culture and the titre was lower.¹¹⁹ Knowledge of the slow virus encephalopathies was reviewed.¹²⁰

Epidemic neuromyasthenia and its variant forms often are misdiagnosed. During 2 months, 220 Texans had it, eighteen with encephalitis. Mild dysentery, myalgia, conjunctivitis and lethargy were characteristic features.¹²¹

Rabies. Virus expelled nasally by bats may account for the air-borne spread of rabies.¹²² A probable airborne epizootic killed sixty-four animals in a laboratory colony.¹²³ Three newly recognized varieties are Lagos bat viruses and one isolated from Nigerian shrews.¹²⁴ Poly I:C injected as an interferon-inducer before virus inoculation gave protection.¹²⁵ Rabies was prevented when the feet of mice were amputated within 18 days of inoculating the foot pads with virus, suggesting that the virus remained temporarily *in situ*. Antiserum alone failed to prevent disease.¹²⁶ Viral particles in two patients appeared in the axoplasm of some myelinated nerves and in the trigeminal ganglion.¹²⁷

Destruction of vampire bats that cause a loss of \$250 million from rabies in the cattle industry in Mexico may be possible by the ingestion of anticoagulant drugs by bats.¹²⁸ For unknown reason, in contrast to dogs and cats accounting for 70% of human rabies in 1951, wild animals now account for 78%. Bats, raccoons and especially skunks emerged as prominent reservoirs of infection.¹²⁹ Nine persons have died from skunk bites in the USA since 1946. Vaccination alone was said to be little better than no treatment, unless equine antirabies serum also is applied.¹³⁰ Rodents rarely are carriers and, except in unusual circumstances, bitten persons need no therapy.¹³¹ Report of recovery from rabies mentioned in last years' review appeared in detail with citation of nine other non-fatal cases.¹³² Proceedings of a conference on rabies appeared.¹³³

Measles vaccination was estimated to be 96%

effective. An epidemic occurred in an insufficiently protected population, but not in an adjoining immunized community.¹³⁴ An attack-rate of 8.5% involved children vaccinated after the age of 1 year. Vaccine failure contributed to dissemination of infection. If eradication of measles fails, there is also little promise in controlling rubella.¹³⁵ Official directions for immunization were published.¹³⁶

The Guillain-Barré syndrome and encephalitis followed vaccination in two patients.¹³⁷ Measles virus was isolated from the brain during measles.¹³⁸ The increased amount of measles antibody in systemic lupus erythematosus, suspected as evidence of chronic infection, was correlated with increased gamma globulin.¹³⁹ During an epidemic, severe measles in atypical form with pulmonary consolidation affected five patients who had received killed measles virus vaccine. Probably a cell-mediated, delayed-type hypersensitivity or humoral mechanism may be involved.¹⁴⁰

Rubella. By age 20, 80–90% of persons have antibody to rubella. Two-thirds of attacks occurred between ages 5 and 14. Immunity rates were higher in urban schools than in others.¹⁴¹ None of sixty-seven susceptible teachers contracted rubella from vaccinated students.¹⁴² However, persons regarded as 'vaccine failures' shed live virus from the pharynx and may spread infection.¹⁴³ Myeloradiculitis in thirty-six children¹⁴⁴ and recurrent genual pain in eleven¹⁴⁵ followed rubella vaccination after 6 weeks and 6 months respectively. Evidence suggests some connection between rubella and juvenile rheumatoid arthritis. Rubella antibodies were four to six times higher in arthritic children than in normal ones.¹⁴⁶ This may be accounted for by increased globulin as in measles.¹³⁹

Serologic evidence of *cytomegalovirus* appeared in seventeen of forty-eight children with hepatic disease as compared with fifteen of 410 control children.¹⁴⁷ Electron microscopy, although less sensitive than tissue culture, provided rapid diagnosis in others.¹⁴⁸ Characteristic inclusion bodies, often with chronic inflammatory cells appeared in the enteric mucosa.¹⁴⁹ Because lead injected in rats induces characteristic intranuclear inclusions in renal epithelial cells within 6 days,¹⁵⁰ such bodies do not always reflect viral infections.

According to two articles in the February, 1972, *Annals of Internal Medicine*, varicella-zoster complicated 11–25% of lymphomatous disease, probably because of low host-resistance. In another report three adults had zoster, not from reactivation of the latent virus, but probably by contact with a patient.¹⁵¹ Poly I:C applied topically was said to prevent local progression of zoster lesions.¹⁵² Serologic test differentiates Hunt's syndrome (zoster) from Bell's palsy.¹⁵³ Pulmonary infarction or embolism occurred

in four adults with varicella,¹⁵⁴ as it may in other infections. Glomerulonephritis and nephrosis occurred in another.¹⁵⁵

Camelpox occurs in Iranian camels. This poxvirus is related to that of variola, but human infection was not encountered.^{156a} Monkeypox, closely related to but immunologically different from variola and vaccinia, affected a number of Africans. Man-to-man transmission has not been observed.^{156b} The question arises if monkeys or camels are perennial sources of smallpox-like disease.

As reported in three papers in the February, 1972, *American Journal of Epidemiology*, smallpox in Pakistan had a high attack-rate in the unvaccinated. Routine vaccination of school children in endemic regions had more importance than revaccination. Vaccination of any sort is neither required nor recommended for travel abroad,¹⁵⁷ unless epidemics occur such as smallpox in Yugoslavia, 1972. Vaccination does not control epidemic typhoid or cholera. For unknown reasons, immunization with oral poliovirus was less successful for children in the tropics than elsewhere. Five paralytic cases followed the third dose within 2 years.¹⁵⁸ Testing 32,000 respiratory tract and faecal samples yielded 2800 poliovirus isolates, presumably of vaccine origin, especially 14 from infants.¹⁵⁹ The June issue of the *American Journal of Clinical Pathology* contains fourteen papers about recent advances in the laboratory diagnosis of viruses and its clinical application. Prompt diagnosis would obviate much unnecessary antimicrobial therapy, admission to hospitals, and expense when hospital treatment is not needed.¹⁶⁰

Filamentous cytoplasmic bodies like those of paramyxoviruses appeared in renal and dermal endothelial cells of patients with 'collagen' diseases, rheumatoid arthritis, Sjögren's syndrome or polymyositis. They were absent in drug-incited lupus erythematosus and other diseases.¹⁶¹ Myxoviruses isolated from the brain in multiple sclerosis may or may not have been pathogens.^{162,163} The same doubt concerns picornavirus-like structures in acute dermatomyositis.¹⁶⁴ The presence of various 'virus-like' bodies in disparate diseases raised questions of their relevance. Picornaviruses caused epidemic conjunctivitis in Singapore and Japan.¹⁶⁵ Particles, called viroids (infectious or pathogenic RNA), 80 times smaller than the smallest virus may be plant pathogens.^{166,167} Investigation, no doubt, will be extended to diseases of man. A polyhedral virus derived from *Entamoeba histolytica* may have clinical significance.¹⁶⁸

Virazole, with a complex generic name, applied topically or intraperitoneally inhibited viral invasion in inoculated animals.¹⁶⁹ Amantadine controlled some warts.¹⁷⁰ Family studies suggest that the host's

genes may play a role in determining susceptibility or resistance to viral invasion.¹⁷¹

Interferons and their inducers were reviewed in the *New England Journal of Medicine*, 6, 13 and 20 July.

Viruses and cancer

Further studies supported a relation between human and murine mammary cancer. Most human tumours contain RNA, and hybridization suggests a causal relation of a virus.¹⁷² Virus-like particles in four of nine breast cancers and in two cases of cystic mastitis resembled those of mouse tumours.¹⁷³ Inoculated simian virus 40, a papova virus, induced leukaemia, lymphoma and bone tumours in infant hamsters.¹⁷⁴ Eighteen of twenty-five human sarcomas contained RNA sequences like those found in a viral agent that causes murine sarcoma. These were absent in normal human tissue.¹⁷⁵ Dimethylsulphide and 5-iododeoxyuridine increased the production of C-type virus in cell cultures from human sarcomas.¹⁷⁶ The inhibition of chemical carcinogenesis by viral vaccines in mice suggests that type C RNA viruses serve as determinants.¹⁷⁷ The complex molecular genetics involving the provirus, the oncogene and the provirus were discussed in detail.¹⁷⁸

Much evidence fails to support a direct viral cause of cancers. No serologic evidence of oncogenicity of papova virus SV40 appeared in cancer patients.¹⁷⁹ Myxovirus-like particles in a brain tumour may have indicated their invasion of injured tissue.¹⁸⁰ '60 years of work with oncornaviruses has not incriminated them in any human disease . . . however, these viruses could be virtually impossible to detect' as stated in a review.¹⁸¹ At present \$48 million is being spent on grants for cancer virology.¹⁸²

Optimistically, an anticancer vaccine may eventuate in a few decades.¹⁸³ For which kind of cancer? Because oncogenic viruses may be a cause, immunotherapy after chemo- or radiation-therapy was considered.¹⁸⁴ The problems involved were extensively reviewed.^{185,186}

Several recent authors describe groups of cases of Hodgkin's disease among persons in contact resembling the pattern of an infectious disease.^{187a} Evidence of contagion is not convincing.^{187b}

Bacillary infections

Clostridium perfringens accounted for 60% of food-borne disease in 1970, exceeding the importance of other pathogens.¹⁸⁸ Antimicrobial prophylaxis and therapy are not indicated for food-poisoning caused by any enteric bacilli or staphylococci.

The largest known common source epidemic of *Sonne* shigellosis in Hawaii arose from contaminated poi. Only a few of 600 patients had tenesmus or melena.¹⁸⁹ In another region, 95% of strains resisted

ampicillin, and fewer resisted other drugs.¹⁹⁰ Resistant coliforms, many with the R factor, existed in almost all tested fresh-water samples in Alabama and in 50% of sea-water tests.¹⁹¹ Multiple drug-resistance mediated by the transmissible R factor depends on the wide use of antimicrobics.¹⁹⁰ The genetic factors involved were reviewed.¹⁹²

Perhaps an episome (R factor) accounted for the increased virulence of chloramphenicol-resistant *Salmonella typhi* in the 1972 epidemic of typhoid in Mexico.^{193,194} Several American tourists acquired the infection. Hepatitis, nephritis and thrombocytopenia are features of typhoid,¹⁹⁵ not 'complications' as reported. I described typhoid pyelonephritis in 1938.¹⁹⁶ Ampicillin added to chloramphenicol excelled either drug alone for typhoid.¹⁹⁷

Paratyphoid B-infected cattle were the source of infection, via the water supply, in ninety persons in Britain.¹⁹⁸ Also in Britain, 681 cases of brucellosis were reported in 1971, but only ten in abattoir workers.¹⁹⁹ By contrast in the U.S.A., where 6321 cases occurred in 1947, as many as 68% of such employees were involved in some places.²⁰⁰ Effective control of infected cattle reduced the number to 231 by 1969.²⁰¹ *Brucella canis* from a pet dog with asymptomatic bacillaemia caused sepsis in a patient with cardiovalvular disease. Recovery followed ampicillin-streptomycin therapy.²⁰² The dermal test for brucellosis was unreliable for diagnosis. It often increased the serum antibody titre. Antibody was present in 25% of dermal non-reactors.²⁰³ Two small outbreaks of pertussis involved a pediatric unit during 3 months. Several adults were ill, two seriously. Serologic evidence of inapparent disease and detection of carriers indicated the unsuspected high incidence of infection.²⁰⁴ As occurs elsewhere, Gram-negative bacilli predominated in infected combat injuries in Vietnam hospitals. Bacillaemia appeared in forty-six patients, *Staphylococcus aureus* in only one.²⁰⁵

Although hyperbaric oxygen therapy for gas gangrene reduced the need for serotherapy and extensive debridement, it is of uncertain value and risky. Dutch physicians reported recovery in most of 130 patients.²⁰⁶ *Edwinia* bacilli derived from various sites in thirty-one patients were mixed with other bacteria in twenty-eight. In these, they may not have been pathogenic even when in the blood.²⁰⁷ *Pasteurella multocida*-infected wounds inflicted by cats, dogs and an opossum occurred in eleven patients.^{208a} Two patients in the U.S.A. diagnosed as having tularaemia and four as suppurative lymphadenitis actually had plague.^{208b} *Haemophilus influenzae* type B epiglottitis affected English children. Obstruction, at times, required prompt tracheostomy.²⁰⁹ Immunization with a capsular antigen of *H. influenzae* evoked antibody persistent for 6 months.²¹⁰

Cutaneous *diphtheria* probably accounted for an epidemic of nasopharyngeal infection in Trinidad children. Many infected but asymptomatic children developed high titres of antitoxin.²¹¹ Commercial immune serum globulin when tested contained insufficient antitoxin for therapy.²¹² Only six of 100 known victims of anthrax meningitis survived. A seventh occurred in Shiraz.²¹³ Prostatic fluid injures Gram-negative bacilli, excepting *Pseudomonas* and *Proteus*. Study is in progress to detect similar action of female periurethral gland secretion.²¹⁴

Tuberculosis

Six-month courses of therapy with regimens containing rifampin or pyrazimide were effective. Relapses with drug-sensitive bacilli occasionally followed within 9 months.²¹⁵ By electron microscopy, isoniazid, rifampin, kanamycin, ethambutol or cycloserine each affected the ultrastructure of bacilli differently. Three drugs combined had the greatest action.²¹⁶ Among 2300 employees receiving isoniazid prophylaxis, evidence of hepatic disease appeared within 9 months in nineteen. Thirteen had icterus and two died. Viral hepatitis was an unlikely cause.²¹⁷

A patient with undetected tuberculous pneumonia spread infection to 35% of hospital personnel, two having active disease, twenty-one being asymptomatic. Transfer of the patient to an efficiently ventilated ward reduced the number of converters to 11%.²¹⁸ Peritonitis in thirty-two Iranians most likely resulted from dissemination, chiefly from the lung. Culture and guinea-pig inoculation were less reliable for diagnosis than laparotomy. Specific therapy 'cured' seventeen for 4 years.²¹⁹ Monarticular arthritis, often without pulmonary lesions, occurred in twenty-five patients. Narcotic addiction, local trauma, intra-articular steroid injection and systemic involvement were predisposing factors. All reacted to the tuberculin test.²²⁰ In 1958, tuberculosis caused most deaths from infectious disease in China despite a diminution from a rate of 230/100,000 in 1949 to 46/100,000. BCG vaccination was said to be successful.²²¹

Eighteen persons contracted *Mycobacterium marinum* dermal infections from Chesapeake Bay water²²² and thirty-one along the Gulf of Mexico coast.²²³ Lesions usually persisted for 2 years and spontaneous recovery occasionally occurred. Otherwise, excision or fulguration was needed.

Coccal infections

Gonorrhoea

In comparable periods, Philadelphia statistics registered 10,672 cases of gonorrhoea in 1971 and 14,021 in 1972. Nationally, the incidence increased 15%. An estimated 7000 Vietnam returnees yearly

had asymptomatic infection with antimicrobial-resistant gonococci.²²⁴ About 12% of 1900 girls in a closed population were infected and in 4% of these penicillin therapy failed.²²⁵ After treatment of 908 women, cocci persisted in the cervix and rectum. Examination of cervical smears alone would have left 30% of treatment failures undetected.²²⁶ Rectal and pharyngeal involvement commonly affects homosexual men.²²⁷ Primary stomatitis occurred.²²⁸

Nine days of penicillin therapy cured three meningitic patients.²²⁹ Penicillin, the drug of choice, incited anaphylactoid reactions in 1 to 4/100,000 patients.²³⁰ For so common a disease, tetracycline therapy was proposed instead.²³¹ Others demur in letters to the Editor and suggest spectinomycin or ampicillin (*Journal of the American Medical Association*, **220**, 419, 420). Official recommendations and treatment schedules appeared in two places.^{232, 233a}

Gonococci are attached to and deeply embedded in urethral epithelial and secreting cells.^{233b} Experimental infection was established in a variety of laboratory animals besides chimpanzees.²³⁴ Vaccines against gonorrhoea and syphilis are under study.²³⁵ Penicillin therapy has modified²³⁶ and obscured the diagnosis of neurosyphilis. Classic clinical evidence disappeared and serologic tests failed to aid in diagnosis in 39% of cases. Excepting paralytic psychosis, 20 megaunits during 3 weeks were curative.²³⁷

Haemolytic streptococci

Although tonsillectomy appeared to reduce the carrier state, the incidence of throat infections remained unchanged. The antistreptolysin titre was higher when tonsils were present suggesting their function in antibody production.²³⁸ Immunoglobulin A in saliva inhibited the adherence of cocci to the mucosa as a primary defence action.²³⁹ Mechanisms of cell and tissue injury induced experimentally by haemolytic streptococci and their bearing on sequels were subjects of a review.²⁴⁰ Glomerulonephritis in one instance followed streptococcal pneumonia.²⁴¹ The Dick test, seldom applied now, induced a positive reaction in 52% of children. Surprisingly, 64% of children who had had scarlet fever reacted, in contrast with 10% 50 years ago.²⁴²

Despite intramuscular injection of penicillin as the best mode of prophylaxis in rheumatic patients, infection occasionally occurred. Oral administration deceptively eliminated streptococci in throat cultures from 34% of sixty-one sick patients and from 49% of ninety-five of those with inapparent attacks.²⁴³ Streptococci were present in 35% of children with nondescript sore throat. Only in half of these with actual streptococcal invasion and adenitis did specific antibody appear. The rest were carriers.²⁴⁴ Without special instruction to parents, oral penicillin therapy

for children often is lax.²⁴⁶ The matter of routine indiscriminate penicillin therapy for pharyngitis received critical editorial comment.²⁴⁶

In three patients, penicillin-resistant anaerobic coccal infection simulated gas gangrene.²⁴⁷

Endocarditis

Penicillin alone or with streptomycin given parenterally or orally for 2 weeks cured forty-nine patients with *Streptococcus viridans* infection.²⁴⁸ Experimentally in rabbits, vancomycin was an effective alternative to penicillin to prevent *Str. viridans* endocarditis if given 6 hr before inoculation.²⁴⁹ Infection of calcific valves usually resists cure by antimicrobial therapy or resection, as noted in several instances at necropsy.²⁵⁰ Eleven of twenty-two patients with infected prosthetic devices died. Sustained bacteraemia with Gram-positive and Gram-negative bacilli ensued. Of thirteen patients without infection, seven recovered.²⁵¹ The mortality rate from staphylococcal endocarditis was 42% in twenty-six patients less than 50 years old and in 84% of thirty-eight older ones. The disease may be afebrile and murmurless.²⁵² The first instance of mucormycotic involvement of the pulmonary valve was described.²⁵³

Staphylococci. Deliberate colonization with avirulent *S. aureus* 502A blocked infection with virulent strains in 644 infants. The colonizers caused minor infections in 6% and one died from septicaemia.²⁵⁴ To account for occasional therapeutic failures, antimicrobial-sensitive cocci ingested by neutrophil cells are protected against the action of penicillin and streptomycin.²⁵⁵ The failure of penicillin to enter phagocytes accounted for the survival of engulfed sensitive cocci.²⁵⁶ Plasma factors determine the role of neutrophils in defence against infections.²⁵⁷ When engulfed, staphylococci, tubercle bacilli, *Toxoplasma* and *Cytomegalovirus* are not always killed.

A synchronous epidemic of meningococcosis and influenza A2 among adult inmates of an institution suggested that the virus predisposed to coccal infection.²⁵⁸ Meningococci caused five cases of pericarditis.²⁵⁹ Groups A and C meningococcal polysaccharides injected subcutaneously evoked antibodies lasting 10–15 months in children.²⁶⁰

Pneumonias

Of 167 pneumonias, *Pneumococcus* caused 62%.²⁶¹ Yet, as stated, if most victims had other underlying disease, and unless cocci were in the blood or of the low-numbered types, they may, in some instances, have been commensal. Gram-negative bacilli caused 20% and staphylococci 10% of cases. The overall death-rate was 24%. It was 79% for bacillary, 41%

for staphylococcal and 19% for pneumococcal pneumonias. Viruses probably were causal in only four instances, indicating that such patients seldom need hospital care. *Mycoplasma* was absent.²⁶¹ Apparently, minor viral infections seldom incite bacterial pneumonias in patients with impaired resistance. Among twenty-one patients receiving immunosuppressive therapy, otherwise unrecognized pneumonia was discovered by needle aspiration. Diphtheroids, *Aspergillus*, *Nocardia*, *E. coli*, *Staphylococcus* and *Pneumocystis carinii* were present alone or in combinations.²⁶² Pneumococcal infection in ten children with sickle cell anaemia resulted in two deaths despite appropriate therapy.²⁶³ Peritonitis also occurs as a complication of nephrosis.

Pneumonias in nine patients in Vietnam during malaria, scrub typhus, leptospirosis and typhoid were regarded as specific 'tropical' lesions. Other unrecognized invaders may have been causal.²⁶⁴ None of the entities mentioned are limited to the tropics.

Electron microscopy disclosed inclusion bodies of obscure origin suggesting their causal relation to idiopathic interstitial pneumonia.²⁶⁵

Kühn's monograph contains a comprehensive review of historic, modern and personal work on experimental pneumonias.²⁶⁶

Mycoses

Disseminated histoplasmosis in twenty-six patients involved the liver, lungs, kidneys and oral mucosa, less often the meninges, heart, adrenal glands, gastrointestinal tract and skin. Serologic and dermal tests were less reliable for diagnosis than culturing the fungus from lesions²⁶⁷ or discovery of the spherules.²⁶⁸ Amphotericin was helpful therapeutically in most cases, but relapses occurred in half of them. Seven died from the active disease and eight from other causes.²⁶⁷ *In vitro*, amphotericin and rifampin alone were fungistatic, when combined they were fungicidal for the yeast phase.²⁶⁹ Pulmonary histoplasmosis were excised from fifty-eight patients without provoking recurrence of disease.²⁷⁰

Coccidioidomycosis was contracted by sixty-one of 103 students exposed to dust in California. Pulmonary invasion and a rash occurred in thirty. Antimicrobial therapy was not necessary.²⁷¹ Disseminated disease involved eleven of thirteen patients infected in Texas or Arizona. Disease progressed despite amphotericin therapy in six.²⁶⁸

Forty-one Brazilians with paracoccidioidomycosis (South American blastomycosis) had chronic pulmonary or disseminated disease resembling histoplasmosis.²⁷² Fulminating blastomycotic pneumonia killed an adult.²⁷³

5-fluorocytosine given orally may replace amphotericin for treating severe infections with *Candida*, *Cryptococcus*, and *Torulopsis*. Adverse effects and

drug-resistance may follow.^{274, 275} Correction of hypothyroidism aided in the cure of chronic mucocutaneous candidiasis.²⁷⁶ Similar benefit accrued in an immunodeficient child after the 'transfer factor' was added to amphotericin therapy.²⁷⁷ Without special attention and proper culture media, the antifungal activity of agents cannot be determined. Sabouraud's medium is especially antagonistic.²⁷⁸

Antimicrobial drugs

New products continue to appear, among them Spectinomycin, Minocycline, Clindamycin, Tobramycin, Sisomicin, Amoxycillin, Flucloxacillin, Candicin, and in China, Quindamycin. Whether or not they excel others remains to be seen. Ampicillin is the best drug for initial treatment of bacterial meningitis, but either tetracycline or chloramphenicol may be used.²⁷⁹ Preferably, a specific diagnosis should first be made. A maculopapular rash in patients receiving ampicillin probably was non-allergic in nature.²⁸⁰ Ampicillin in solution deteriorates rapidly when stored at room temperature.²⁸¹ Cephalixin was superior to phenoxymethyl penicillin for treating childhood streptococcal pharyngitis.²⁸² Rifampin killed staphylococci engulfed by phagocytes and prevented subcutaneous abscess formation in mice.²⁸³ It rid *Salmonella* from the intestinal tract of all but four of eighteen children²⁸⁴ and inhibited the replication of *Cytomegalovirus*, but not of *H. hominis* virus.²⁸⁵ Carbenicillin *in vitro* was active against *Pseudomonas*, *Mima*, *Herellea* and most enteric bacilli excepting *Klebsiella* and *Proteus*.²⁸⁶ Minocycline, an expensive tetracycline, controlled syphilis, lymphogranuloma venereum, granuloma inguinale and chancroid.²⁸⁷ Spectinomycin was better than penicillin for the treatment of gonorrhoea. Bacterial resistance has not occurred yet. It had no effect on *Treponema pallidum*.²⁸⁸ *Bacteroides* of forty strains were most sensitive to clindamycin, less so to rifampin, erythromycin, lincomycin and chloramphenicol. All resisted aminoglycosides, polymyxins and semisynthetic penicillins.²⁸⁹ For severe bacteroidal infection, chloramphenicol is preferred.²⁹⁰ Lincomycin and clindamycin may replace chloramphenicol.²⁹¹ Clindamycin controlled pulmonary actinomycosis.²⁹² A rise in the level of blood urea nitrogen followed the administration of tetracycline in patients receiving diuretic drugs.²⁹³ In large dosage, griseofulvin was teratogenic in rats.²⁹⁴

'Presumed infection' in febrile leukaemic patients treated with combined methicillin, carbenicillin, cephalothin, gentamicin and clindamycin²⁹⁵ represents indiscriminate prescription and generally is deprecated. Fever without infection is common in leukaemia. Similar indiscriminate prophylaxis is often routinely applied during mucoviscidosis. Information about the interactions, incompatibilities and antagon-

isms among antimicrobial and other drugs was summarized.²⁹⁶ Asbestos filters used to purify antimicrobics and other drugs shed oncogenic fibres into preparations for parenteral injection and add another hazard to logical and indiscriminate therapy.²⁹⁷ Changing patterns of bacterial resistance to antimicrobics were extensively reviewed.^{298, 299} Reversal of the trend toward drug-resistance could result from limiting the use of antimicrobics and immunosuppressives, by improving surgical techniques, the discontinuance of general and routine prophylactic regimens in hospitals, and increasing host-resistance to infections.

Antimicrobial prophylaxis. Oral prophylaxis against streptococcal infection and rheumatic fever with clindamycin gave protection comparable to that of penicillin and without significant side-effects.³⁰⁰ Among Alaskan children, ampicillin reduced the incidence of otitis media.³⁰¹

Prophylactic antimicrobial administration is not useful in 'clean' surgery, except in persons with valvular cardiac disease, severe trauma and burns. Evidence fails to support prophylaxis before non-extensive intestinal surgery. Polymyxins, gentamicin or carbenicillin should never be used to prevent pseudomonal infection in burns.³⁰² 'Prophylactic antibiotics . . . for patients undergoing heart surgery, are of questionable value and may cause serious side-effects.' In one instance, tachycardia, haemolysis and fever ceased after discontinuance of cephalothin.³⁰³ Cephalothin during cardiac surgery appeared to increase the resistance of infecting bacteria.³⁰⁴ Prophylaxis afforded little benefit during pyelonephritis³⁰⁵ and was ineffective in ophthalmologic practice except to diminish the number of bacteria on eyelids.³⁰⁶

Iatrogenic and nosocomial infections

Predictably, several more ubiquitous, previously harmless, Gram-negative bacilli caused disease during impaired host-resistance. *Aeromonas hydrophila* infected eight of twenty-seven patients and one died.³⁰⁷ *Pseudomonas thomasi* infected forty patients in a London hospital.³⁰⁸ *Peptococcus* (anaerobic staphylococci) and *Peptostreptococcus* appeared alone or mixed with other microbes in the blood and elsewhere.³⁰⁹ *Klebsiella*, chiefly of types 2, 3, and 32, were recovered from 80% of hospital patients with urinary and respiratory tract disease and from others as nosocomial colonizers or invaders. Gentamicin controlled most of these.³¹⁰

In an intensive care unit, Gram-negative bacilli colonized ninety-five of 213 patients. In these, respiratory tract infection developed in twenty-two.³¹¹ All forty-eight victims of acute leukaemia acquired multiple potential pathogens while on microbic drugs. All efforts should be directed to

prevent such recurrences, especially against *Pseudomonas*, but how? One approach is promising. Discontinuance of carbenicillin and restricted use of other antimicrobics for 2 years eliminated R-factor-containing resistant *Pseudomonas* from a burns-unit and its environment. *Proteus mirabilis* and *Esch. coli* were greatly reduced.³¹³ During 3 months, type 3 *Klebsiella* infected ten of ninety-four infants, five with pneumonia, two with aortic thrombi, and one each had meningitis, enterocolitis and abscesses.³¹⁴ Scalp-vein catheters became infected in 24% of children and needles in 8%, depending largely on the duration of use.³¹⁵ Elsewhere, nosocomial infections chiefly with staphylococci complicated 12% of 279 orthopaedic cases. All but one of 140 wound infections followed 'clean' operations. Advanced age and indwelling catheters were predisposing factors.³¹⁶ A small outbreak of salmonellosis followed the ingestion of thyroid tablets probably contaminated from animal sources.³¹⁷ Pustular acne, probably resulting from nutritional defects, affected three men after weeks of intravenous hyperalimentation. Trouble ceased when therapy stopped.³¹⁸ Dermatologists warn of a danger of inciting secondary infections by the continuous use of antimicrobial therapy, especially for acne, 'athlete's foot', pemphigus and diaper rash.³¹⁹ Lymphoma followed renal transplantation in three patients, probably as a result of suppressed immunity and the presence of the foreign organ.³²⁰ Four renal transplant recipients infected with *Aspergillus* recovered after amphotericin therapy. Biopsy is warranted if infection is suspected.³²¹ Infection may be mistaken for colonization. Resistance impaired by radiotherapy of sarcoma may have accounted for the presence of *Adenovirus* 32 in the brain during encephalitis.³²² Gsell summarized the nosocomial problem in a German article³²³ and Burnet & White in their book.³²⁴

As an example of iatrogenic 'nondisease', penicillinase contaminated with *Mima* in culture media led to fifty-six false reports of bacteraemia. Several patients received unneeded therapy.³²⁵ In concluding a discussion of management of chronic bronchitis 'such measures (dilators and drainage) may come closer to dealing with the primary problem in most exacerbations of bronchitis than any of the recommended antibiotic regimens.'³²⁶

Exotic diseases

Reeves deplored complacency about the desired world-wide eradication of the 'Big Six', namely typhus, cholera, plague, smallpox, yellow fever and relapsing fever (malaria, dengue, schistosomiasis and others could be added to the six). Domestic and wild animal hosts are difficult or impossible to control and serve as perennial sources.³²⁷ An example is the recent incursion of Venezuelan encephalitis in Texas

cattle. Silvatic yellow fever caused ten deaths in Venezuela, the first reported since 1956. Rapid transit favours importation of various exotic infections into non-endemic regions. Foreign visitors contracted myiasis from Tumbu flies in Africa,³²⁸ melioidosis, filariasis³²⁹ and malaria in S.E. Asia and typhoid in Mexico. Articles on tropical diseases comprised the *British Medical Bulletin*, 28, no. 1. The September *American Journal of Tropical Medicine* supplement contained thirty articles of a malaria symposium.

Viral hepatitis and encephalitis, dengue, leptospirosis, plague and cholera exist in Vietnam. More than 150 cases of melioidosis occurred among American personnel, some of them developing this after leaving the region. Severe diabetes permitted recrudescence 2 years after recovery from the primary infection. More examples of recrudescence, no doubt, will be encountered among the 3 million transient persons exposed in S.E. Asia.³³⁰ About 4000 Vietnam returnees brought malaria home. Those cared for in one area served to spread infection via mosquitoes to local residents.³³¹ Drug-addicts and transfusion recipients also account for the increased incidence of malaria. Of 261 cases of malaria in Britain, none was indigenous.³³² Tetracycline and quinine cured nearly all of thirty patients with chloroquine-resistant falciparum malaria.³³³ Returnees may be infected with drug-resistant tubercle bacilli. Among forty cases of plague in Vietnam all but one recovered after streptomycin therapy. Intravascular clotting was a prominent feature.³³⁴ Among twenty-four other cases, thirteen were bubonic, seven septicaemic, two meningitic, and one pneumonic. Bacilli demonstrated in the blood or in pus from buboes enabled prompt diagnosis. Kanamycin therapy cured the thirteen with buboes alone.³³⁵

Cholera

Adenylcyclase appears to be the mediator for the excessive secretion of enteric fluid.³³⁶ Its relation to prostaglandins received editorial comment.³³⁷ Another editorial summarized the matter and raised further questions.^{338a} The toxin was adsorbed and bound to the microvilli of mice without evidence of deeper penetration, aside from the development of systemic antitoxin.^{338b} Carpenter reviewed knowledge about the enterotoxins of cholera and *Shigella* that cause fluid-loss.³³⁹ Crystalline toxins of cholera, diphtheria and tetanus are proteins.³⁴⁰ A dermal test with cholera toxin may serve to indicate immunity or susceptibility.³⁴¹ In vaccinated monkeys, cholera toxoid injected subcutaneously reverted to cholera toxin causing severe local reactions preventable by immunization with antitoxin.³⁴² Protection of vibrioinoculated mice by the oral administration of

non-toxic antigen suggests the possible success of the procedure in man.³⁴³ An agent related to *Vibrio fetus* caused acute dysentery in two patients.³⁴⁴

So far as possible, Huang collected current knowledge about leprosy, trachoma, Japanese B encephalitis, schistosomiasis, malaria, filariasis, clonorchiasis, paragonimiasis and ancylostomiasis, as they affected an estimated 280 million Chinese in 1959. Trachoma was the most prevalent disabling infection involving about 300 million natives.³⁴⁵

More than a million Chinese have leprosy³⁴⁵ and 25,000 native victims are registered in South Vietnam.³⁴⁶ *Mycobacterium leprae* may be detected in blood smears in the lepromatous form. Bacillaemia disappears within 4 months of therapy and serves as an indicator of response to therapy.³⁴⁷ Rifampin excelled dapsona in its bactericidal effect on *M. leprae* in patients.³⁴⁸ One in every 125 natives in the Amazon basin was said to have leprosy.³⁴⁹ Onchocerciasis affects an estimated 30 million victims in Africa and in South America where it is spreading.³⁵⁰

Zoonoses transmissible to man in Alaska include rabies, brucellosis, tularaemia, hydatidosis, diphyllbothriasis and trichinosis.³⁵¹ In two places, fifty-three persons contracted trichinosis from bear meat.^{352, 353} Periodic administration of metronidazole to an Amerind population resulted in a seven-fold reduction of amoebiasis.³⁵⁴ The drug was recommended for treating amoebic hepatic abscess,³⁵⁵ yet abscess in one instance followed therapy.³⁵⁶ Because the risk of amoebiasis in travellers is only 2%, chemoprophylaxis was not recommended, nor was it for *Trypanosoma gambiense* infection.³⁵⁷ Pericarditis occurred in 2% of cases of amoebiasis with one fatality.³⁵⁸ The modern treatment of common parasitic infections was outlined.³⁵⁹

Miscellaneous

Rocky Mountain spotted fever, better named tick-borne typhus, is commoner in southeastern U.S.A. than elsewhere. Because of delayed diagnosis, up to 11 days elapsed before specific treatment began in forty-two patients in Tennessee. Twenty-six were lethargic or comatose. Seven died with evidence of intravascular clotting and five³⁶⁰ as expected with endothelial lesions.

Anaerobic bacteroides, streptococci, fusobacteria and *Actinomyces* caused twenty-five hepatic abscesses in an 11-year period, representing 45% of such lesions. They are apt to be regarded as sterile unless cultured properly.³⁶¹

Haemobartonella present in erythrocytes of eight the patients with systemic lupus erythematosus raised question of their possible aetiological relationship.³⁶² Epidemiologic study indicated cats as important sources of toxoplasmosis.³⁶³ Pregnant women especially should avoid contact with cats.³⁶⁴ The

efficacy of drug therapy is not established. 13–42% of samples of paper money carried staphylococci and Gram-negative bacilli.³⁶⁵ Comment about the 'febrile agglutinins' test, called the term a semantic monstrosity, its deletion was recommended.³⁶⁶

Immunity defects. If splenectomized rats and patients react similarly, a resulting defect in phagocytosis accounts for the occurrence of pneumococcal sepsis.³⁶⁷ Several patients³⁶⁸ and some with Hodgkin's disease,^{369, 370} after splenectomy, died from pneumococcal or *H. influenzae* infection. Unusual virus-like particles were observed in spleens excised for thrombocytopenia and haemolytic anaemia, but not in normal ones.³⁷¹ Knowledge of the bearing of anaemia on infections was reviewed.³⁷² Deficiency of C3 complement component was the only demonstrable abnormal immunity factor common to life-long multiple infections in two patients.³⁷³

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