ANNUAL REVIEW

Infectious diseases: fortieth and final annual review of significant publications

HOBART A. REIMANN
M.D.

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

ACCORDING to recent comment, the importance of infections and the interest in them have reached a nadir.¹ But, by reviewing these Reviews published annually since 1935, infectious diseases actually have increased in importance, if not in interest. For example, the death rate from infections is about the same now as it was in 1935, but depends upon different causal microbes. Some diseases have almost disappeared only to be replaced by others. Great advances in the knowledge of viral infections, microbic biology and immunology; the multiplicity of vaccines and antimicrobial drugs, their proper use and limited value; the unceasing resurgence of epidemics; the rising incidence of iatrogenic and nosocomial infections; and the recognition of exotic diseases imported from persistent endemic areas are largely beyond the grasp of generalist physicians and surgeons. They require specialized knowledge and undiminished interest.

Viral infections

Respiratory tract infections

During 6 years about 25% of a population with acute respiratory tract infections sought medical attention. The annual incidence of disease was six attacks in infants diminishing with age to about 1.3 in adults. Infections were especially common in women aged 19-29 years who had contact with young children.² Among 145 military recruits, influenza virus affected 72%; mycoplasma 30%, adenoviruses 17%, and parainfluenza virus 16%. All had EB virus antibody.³ Rhinovirus and influenza virus infections provoked asthmatic episodes in asthmatic children. Bacterial infections were of lesser hazard.⁴

Coronavirus infection among military recruits was low in incidence in 1970, 1972 but high (52%) in 1971. Some instances of simultaneous infection with adenovirus or *Mycoplasma* were noted. Pneumonia occurred in four. Coronaviruses caused more pneumonia in infants than did adenoviruses, influenza, parainfluenza and rhinoviruses, exceeded only by respiratory syncytial virus.⁶ Intranasal

instillation of an interferon inducer for prophylaxis in thirty-nine persons experimentally exposed to rhinovirus type 21 decreased the infectivity of the virus, reduced the symptoms, and decreased shedding of the virus.⁷ Evidence suggesting that vitamin C prevents or reduces the severity and duration of colds is unconvincing.⁸ It was ineffective in all three aspects in volunteers infected with a rhinovirus.⁹ Two-thirds of 100 million prescriptions for antimicrobics by English and Welsh practitioners were unnecessary for respiratory tract infections of the 'red-throat' category.¹⁰ According to controlled studies on eighty-nine Australian children, antimicrobial therapy for minor infections was useless. Small dosage cannot cure staphylococcal infection, has only a slight chance of eliminating the cocci, and carries the risk of sensitizing the patient and possible anaphylaxis.¹¹

Influenza

Between 1958 and 1968, one strain of virus A caused epidemics at 3-year intervals. After that, A2 caused 'severe seasons' annually. In 1972-1973 strain A-England-72 caused another peak of incidence. B virus caused mild illness in 1973-1974. At present, 'Port Chalmers' virus threatens. For the current year, high risk persons except those hypersensitive to egg protein should receive bivalent vaccine because it contains antigens of an A and a B strain. Amantadine (Symmetrel) given in two 200 mg capsules may prevent infection with A2 virus, but not with B virus. If antigenic change reduces the value of the bivalent vaccine, amantadine may serve its purpose against A2 strain.¹² Because vaccines may provoke the appearance of variant viruses, Stuart-Harris is sceptical that vaccines will ever serve to prevent epidemic influenza.¹³ A controlled study in England in 1972-1973, failed to show any effect of vaccination.¹⁴

School-grade children escaped epidemic rubella that affected ninety-six college students. Immunity levels in both groups exceeded 80%. As a result of

vaccination in childhood, the epidemic aspect has changed. Older persons now are involved and need immunization.¹⁵ The failure-rates of vaccination among children were 13% for rubella and 7% for measles indicating the need for continual measurement of antibody,¹⁶ if demonstrable antibody alone confers protection. A cataract ensued in only one of ten infants of mothers vaccinated shortly before or during pregnancy. Defects may appear later in others¹⁷.

An epidemic of more than 600 cases of measles occurred in New Jersey and Philadelphia among unvaccinated children.¹⁸ In Chicago, among low income groups, the incidence of measles had not been influenced by the availability of vaccine. Vaccination is essential for infants 6–9 months old, and reimmunization later.¹⁹

Since 1969 a newly recognized infection—acute haemorrhagic conjunctivitis—caused by Enterovirus type 70 occurred in epidemic form in Africa and South-east Asia. It is easily mistaken for epidemic keratoconjunctivitis, herpetic infection, trachoma and others. Its spread elsewhere in the world is almost certain to follow.²⁰ In the U.S.A., adenoviral type 8 keratoconjunctivitis involved 114 persons in a 4-month period.²¹

Bathing in polluted water caused Coxsackie virus infection in one group of children,²² and Echoviruses in another group elsewhere, adenovirus 7 conjunctivitis.²³ Echoviruses, especially type 4, were associated with febrile illness in fourteen of twenty-three infants.²⁴ In 1971, about 150 English hospital personnel had epidemic neuromyasthenia (benign myalgic encephalitis) characterized by fatigue, malaise, headache, neck and back pain and depression. The cause is unknown.²⁵

In a study of patients with multiple sclerosis, measles antibodies, at times, seemed to be produced in the central nervous system by activated latent viral infections.²⁶ Knowledge that wild rodents are carriers and sources of Lassa fever enables the application of control methods.²⁷ Clinical tests failed to justify the use of aspirin or other symptomatic therapy in undiagnosed febrile viral illnesses. The effect of a placebo may be equally effective on subjective impressions of patients.²⁸

An extensive investigation is under way to determine the value of adenine arabinoside for the treatment of viral infections. Its effect on cytomegalovirus is promising.²⁹ Cytosine arabinoside had no therapeutic effect in eighteen smallpox victims.³⁰ Topically applied idoxuridine with dimethyl sulphoxide (DMSO) lessened pain and shortened the duration of varicella-zoster in eighteen patients.³¹ Zoster-immune globulin apparently protected normal and immunosuppressed children from varicella, if given within 3 days after exposure.³²

Hepatitis

HB Ag may be transmitted during dental operations,³³ by clams,³⁴ by mosquitoes,³⁵ and possibly by saliva.³⁶ B hepatitis acquired by means other than parenteral injections was described in several papers in the 4 March and 11 November 1974 issues of the *Journal of the American Medical Association*.

HB Ag was harboured by 16·8% of patients and 2·4% of medical personnel in haemodialysis centres. HB Ab appeared in 34% of the former and 31% of the latter. In patients, the reactions were dependent on the duration of treatment, HB Ag or HB Ab was present in 61% of family contacts.³⁷ Observations on personnel of a 'liver unit' staff disclosed twelve of fourteen (86%) to have immunity to B hepatitis antigen and five had HB Ab. By contrast, only 30% of control subjects had evidence of immunity. Frequent oral exposure to HB Ag may result in an immune response in the gastrointestinal mucosa without viraemia or illness and probably offers protection against infection.³⁸ Despite the exposure of fetuses to mothers who are symptomless chronic carriers of HB_s Ag, infants seldom become infected before or at birth.³⁹ From 25 to 42% of patients during an epidemic had either arthropathy or dermal rashes; during an epidemic of hepatitis A none did.⁴⁰ Evidence suggests that human immune-complex glomerulonephritis may result from chronic hepatitis B infection.⁴¹

HB Ag, subtype Y, appeared mostly after 'needle-stick' hepatitis, often in those in close contact with addicts. Subtype D occurred chiefly in those with chronic hepatitis.⁴² No generalization about the clinical relevance of the subtypes is yet possible.⁴³ Agents other than HB virus caused post-transfusion hepatitis. In thirty-six of fifty-one cases, no evidence of that antigen was detected, nor was cytomegalovirus the cause. Probably an HC virus exists.⁴⁴

Marrow transplantation and platelet transfusions caused hepatitis A among donors and recipients.⁴⁵ Because of the number of positive reactions to different diagnostic tests, none or only one of the microbes supplying its antigen may be causal.⁴⁶

Herpes viruses

As a result either of better diagnosis or actual increased incidence, genital *Herpes* was found to be seven times more common than primary syphilis. Types 1 and 2 viruses were equally involved. The incubation period lasted 3 to 14 days. Asymptomatic persons spread infection.⁴⁷ That the regional sensory nerves were invaded was confirmed by studies on mice, wherein infection became latent in the local sensory ganglia. Reactivation followed various forms of trauma.⁴⁸ The occurrence of *H. hominis* infection in ten patients in whom Burkitt's lymphoma developed shortly afterward, suggested a possible

causal relationship.⁴⁹ Epstein-Barr virus (EBV) latent in tissue may be activated by immunosuppressive therapy. It appeared in the pharyngeal secretion of 52% of treated patients but in only 18% of others.⁵⁰ Although respiroviruses cause most cases of acute non-streptococcal tonsillitis, EBV may also do so without having the features of infectious mononucleosis.⁵¹ Cytomegalovirus, like EB virus, caused an infectious mononucleosis-like disease.⁵² The virus was present in the semen of a convalescent patient. It temporarily suppressed spermatozoal motility, persisted for months and was recovered from the uterine cervix of a sexual contact. Venereal transmission apparently occurred.⁵³ A vaccine applied to adolescent girls may reduce the incidence of fetal involvement.⁵⁴

Encephalitis

House (English) sparrows seemed to be the principal avian hosts of St Louis encephalitis during three urban epidemics in Texas.⁵⁵ Sporadic Powassan virus encephalitis occurred in three children. Tick-bite was evident in one. Specific antibody was detected in only one of 1000 persons in the vicinity.⁵⁶ Virus-like particles in ependymal cells during mumps meningitis suggested that they may be a cause of hydrocephalus.⁵⁷ Brain tissue from a patient with Creutzfeldt-Jakob disease gave similar disease in inoculated monkeys 20 months later.⁵⁸

The complement fixation test for measles antibody in spinal fluid is the best one for diagnosing subacute panencephalitis. If results are repeatedly negative, the diagnosis is unlikely.⁵⁹ Question again was raised as to the association of measles virus with multiple sclerosis.⁶⁰ The virus of lymphocytic choriomeningitis from a colony of infected hamsters in a laboratory spread to hospital personnel. It caused serious disease in several but curiously without evident meningitis.⁶¹

Papovavirus particles appeared in the urine of ten renal transplant patients. They differed from those derived from patients with leukoencephalopathy. Antibody against the virus was present in 81% of samples of blood from 400 persons.⁶² If EB virus is a harmless opportunistic invader, not as a cause of African lymphoma, and renders malignant cells more vulnerable to cytotoxic drugs, perhaps deliberate inoculation of the virus might increase the effectiveness of drug therapy for other lymphomas.⁶³ Among 113 patients with uterine cervical *Herpes* virus infection, forty-three had atypical cells or invasive cancer. In twenty-eight of the latter, neoplastic changes appeared before the virus was recovered. Atypical cells seemed to be susceptible to viral infection.⁶⁴ In both of these studies, the viruses may not have been the cause.

Question of opportunistic invasion arises when

several different viruses are isolated from the same diseased location by as many investigators. EBV, cytomegalovirus, and Australia antibodies were present in untreated Hodgkin's disease patients.⁶⁵ One may be the cause, or none or all may be implicated.

Viral dysentery

Reovirus particles present in the faeces of young children with diarrhoea resembled those found during the flux of newborn calves. The agent called 'rotavirus' differed from orbiviruses and reoviruses found in adults.⁶⁶ Particles probably of orbivirus were seen in the duodenal mucosa of six of nine other children with viral dysentery. They disappeared after recovery.⁶⁷ The term gastroenteritis persists despite no evident inflammation.

Two outbreaks of similar diarrhoeal disease occurred, one in Hawaii, the other in Maryland, caused by antigenically different viruses.⁶⁸ In orally inoculated volunteers, small enteric mucosal lesions appeared.⁶⁹ It is possible that the lesions resulted from the mechanical irritation of diarrhoea. Osler in 1892 discussing 'catarrhal enteritis' remarked on the rarity of mucosal injury.

Many aspects of the immune response to viral infections relating to either the progress of or recovery from the diseases can be explained on the basis of a dsRNA. It plays a much more important role than has been believed.⁷⁰

Viruses and cancer

The possible role of viruses as causes of certain cancers was discussed in the 15 and 22 March issues of *Science*. According to some investigators, an approach by the isolation of oncogenic human viruses 'may be futile' and that 'it is unlikely that an infectious virus causes cancer in humans'. 'Chemicals may be the single most important causes'.⁷¹ On the other hand, Stuart-Harris feels that 'at least some human cancers are almost certainly caused by viruses'.⁷²

Coccal infections

Streptococcus spp. Erythromycin, penicillin and clindamycin were equally effective for treating streptococcal pharyngitis in children.⁷³ Patients with suspected haemolytic streptococcal sore throat who were treated promptly with penicillin before the diagnosis was established, recovered a day sooner than untreated ones.⁷⁴ It is doubtful if the time gained was justified because non-streptococcal infections may have been included. Furthermore, if the infection were streptococcal, immunity may not have a chance to develop fully. In treated children, the amounts of antistreptolysin and streptozyme were lower than the accepted normal titres.⁷⁵ Among

students in a classroom, three had acute glomerulonephritis after an outbreak of scarlet fever caused by cocci of type 2, not known to be nephritogenic.⁷⁶ The reason for the alarming increased incidence of Group B streptococcal meningitis, pneumonia and septicaemia in newborn infants is unknown.⁷⁷ It may be a 'new' event or a cyclic resurgence of old ones. Ordinary laboratory tests may fail to differentiate *Streptococcus mutans* from *Enterococcus* during endocarditis. Antimicrobial therapy differs for each. The latter has greater drug-resistance.⁷⁸

Except in hospitals, *Staphylococcus* in the past was sensitive to penicillin. Now, 84% of 'community' strains in one study were resistant as compared to 95% in hospitals.⁷⁹

A vaccine (or, rather, an immunogen) is under study for the prevention of meningococcosis.⁸⁰ It consists of polysaccharides of types A and C but not B cocci. As in the case of pneumococcal polysaccharide immunogens, because of the unpredictable occurrence of any of three types of meningococcal infection, immunization would be of chief value for controlling epidemics. Group Y cocci caused twelve infections in an Army hospital.⁸¹ In view of the recurrence of meningococcosis in five patients, and in one case, reinfection by the same B strain within 2 months,⁸² the effectiveness of artificial immunization remains to be proved.

Pneumococcal pneumonia

The incidence of pneumococcal lobar pneumonia was said to be unchanged.⁸³ That may be so in some municipal hospitals, but at large it probably has been decreased inadvertently by the widespread use of antimicrobial therapy for colds. Between 1967 and 1970 types 8, 4, 5, 12, 3, 1, 7 and 9 caused bacteraemic pneumococcal pneumonia in 262 patients.⁸⁴ Years ago, type 1 was the commonest. Massive daily doses of 20 million units of penicillin gave no better therapeutic results than 1 million units.⁸⁵ When penicillin was scarce 30 years ago, 50,000 u/day were curative and probably still would be in most non-bacteraemic cases.

Polysaccharide 'vaccines' against pneumococci of types 1 to 9, 12, 14, 18, 19 and 23 are under investigation. Because the mortality-rate of bacteraemic pneumococcal pneumonia ranges between 20% and 30%, immunization of older persons and of those with debilitating conditions is needed.⁸⁶ However, the many pneumococcal types involved, the changing incidence of types from year to year, the dilution of many specific antigens in a polyvalent vaccine, and the relative rarity of lobar pneumonia in a population raise questions of practicability.

Other pneumonias

Despite 40 years of antimicrobial therapy, pneu-

monias still remain the fifth ranking cause of death in the U.S.A. But the causal microbes have changed and the proportion of susceptible older patients has increased. Among 148 patients in a hospital, untyped pneumococci were causal in 53%, *Staph. aureus* in 7%, *Klebsiella* in 6%, *Escherichia coli*, *Bacteroides* and *Haemophilus influenzae* each in 2%, and *Enterobacter* in 1.5%. Influenza A virus caused 5% and *Mycoplasma* 4%, and no cause was determined in 17%. The death-rate from Gram-negative bacillary infections was 47% and from all others about 14%.⁸⁷ In another hospital, coliform bacilli were the cause in 258 pneumonia patients who had had prior antimicrobial therapy, but in only four of 344 previously untreated ones.⁸⁸

Although its presence often is obscured by the underlying disease, pneumonia was observed in fifty-two of sixty-eight leukaemic patients. As causes, Gram-negative bacilli (54%), fungi (25%) and Gram-positive cocci (19%) were isolated in half the cases. The death-rate of 65% was abetted by prior antimicrobial therapy.⁸⁹ In a 3-year period, *Pneumocystis carinii* pneumonia developed chiefly during underlying disease in patients whose resistance was further depressed by immunosuppressive therapy. Pentamidine was said to be therapeutically effective but often with adverse reactions.⁹⁰ Bacteria invaded six of forty-four viral pneumonias, in four during antimicrobial therapy. Minocycline given prophylactically failed to prevent invasion.⁹¹

Mycoplasma caused fatal sepsis, pericarditis, diaphragmatic myonecrosis and patchy pneumonia in a patient.⁹² Contrary to earlier belief, in one study *M. pneumoniae* infections were more common in young children than in adults. The lower respiratory tract often was involved. Inapparent infections occur.⁹³

Gonorrhoea. A further increase of 13% in the incidence of gonorrhoea between 1971 and 1972 as expected brought about an increase of ophthalmia neonatorum. Silver nitrate prophylaxis must also include discovery and treatment of pregnant women for better control.⁹⁴ Gonococcal pharyngitis after orogenital contact was overt clinically in only 20% of cases. Among 1346 infected persons, the cocci were present in the pharynx in 110. Therapy was effective in about 40% of cases, and the rest continue to serve as potential sources of infection.⁹⁵ Among thirty-one pregnant women, the throat was the sole culture site in eleven. Sixty-eight per cent of 2600 military personnel were inapparently infected. Such persons as reservoirs of infection enhance the current pandemic. For diagnosis, cultural procedure is superior to smears of exudate and the fluorescent antibody test.⁹⁷

Non-gonococcal and gonococcal urethritis were present in equal number among 500 male patients.

The latter was commoner in Negroes. The symptoms were similar. Penicillin was used against gonococci and tetracycline for others except trichomonal, herpetic and candidal infections.⁹⁸

Bacillary infections

Eikenella corrodens,⁹⁹ *Nocardia*,¹⁰⁰ *Chromobacterium violaceum*,¹⁰¹ *Yersinia* and anaerobes heretofore regarded as unimportant commensals now are opportunistic invaders especially when immunity is impaired. Yersiniosis so far has been reported on mostly in Scandinavia where it is considered to be endemic. Rheumatic fever often was suspected. The symptoms of sixty patients observed in a Finnish hospital were chiefly fever, arthritis, abdominalgia and diarrhoea.¹⁰²

Bacillary dysenteries. Questions arise whether or not to treat shigellosis with antimicrobics. Most victims recover spontaneously. Severe disease requires therapy with drugs to which the bacilli are sensitive. Bacterial resistance develops rapidly. An afflicted family member treated with an antimicrobial may be a source of infection for other members with a strain that has become resistant.¹⁰³ Antimicrobial therapy failed to rid carriers of *Salmonella*. Cholecystectomy fails when the bacilli also reside elsewhere in the body.¹⁰⁴

Y. enterocolitica caused dysentery in sixteen of twenty-one persons in neighbourhood families. Two died. The infection may be systemic, but the usual features are those of appendicitis, mesenteric lymphadenitis or ileitis.¹⁰⁵ *Salmonella virchow* caused septicaemic or typhoid-like illness in seven of twenty-one persons in England. One died. Chloramphenicol was said to have cured the others.¹⁰⁶ Thirteen outbreaks of dysentery caused by *Vibrio parahaemolyticus* had occurred in the U.S.A. by 1972. Sea food was the source.¹⁰⁷ The expense entailed by food-borne epidemics far exceeds that of established preventive measures. Some algae release a diarrhoea-producing toxin in fresh water.¹⁰⁸

Toxicogenic *E. coli* may be one cause of traveller's diarrhoea. The bacilli were present during illness in four of twenty-eight persons who visited developing countries.¹⁰⁹ Two outbreaks of acute diarrhoeal disease occurred in a school, one caused by *Shigella sonnei*, the other during the second term seemed to be 'winter vomiting disease'. Poor hygiene in the premises was suspected as the cause.¹¹⁰ *Giardia* sp. from water in a contaminated cistern caused diarrhoea in ten persons in Kentucky.¹¹¹

The value of cholera vaccine remains uncertain. Its use gives a false sense of security. Far better are methods of hygiene and sanitation.¹¹²

Until recently, and partly because of improper cultural technique, anaerobic bacterial infections failed to attract attention. Because of improved

methods the recorded incidence of *Bacteroides* infection in wounds rose from 13% to 81% in three years.¹¹³ In a hospital, *Bacteroides* sepsis accounted for 9% of all positive blood cultures with a death rate of 43%. Most victims had had other underlying disease, trauma or a surgical operation. Chloramphenicol was used for initial therapy. Twelve of fifteen patients treated with clindamycin recovered.¹¹⁴ Anaerobes were present in twenty-three of eighty-three infected paranasal sinuses.¹¹⁵ Among 143 patients, anaerobes were the chief cause of aspiration and necrotizing pneumonia, pulmonary abscess and some empyemas. Anaerobes were present in fifty, and present alone in twenty-five. *Bacteroides*, fusobacteria and microaerophilic Gram-positive cocci were the commonest. Anaerobes responded best to therapy.¹¹⁶ Penicillin remains the drug of choice. Surgical drainage often is imperative for empyema. Many patients had other debilitating conditions. Aetiological diagnosis may be erroneous unless cultures are made from exudate free of oropharyngeal flora. Direct Gram stain usually shows the anaerobes.¹¹⁷ Anaerobic bacteria were present among others in most of sixty-four patients with intra-abdominal infections and were present alone in twenty-four.¹¹⁸ It is questionable at times if they are saprophytic or pathogenic.

In addition to the unexpected prevalence of diphtheria in south-western U.S.A., it has spread among indigent persons in Seattle where 30% of victims had dermal lesions. Three died.¹¹⁹ The incidence of diphtheria declined greatly in 50 years, but the death-rate remains the same—10%, usually in non-immunized persons and those infected with toxicogenic bacilli.¹²⁰

Thirty outbreaks of botulism between 1970 and 1973 involved ninety-one persons of whom twenty-one died. Only three came from commercially prepared food; home canned foods were the main source. The therapeutic value of antimicrobics and botulinal antitoxins is uncertain.¹²¹ The bacilli were present in wounds of nine patients.¹²²

In twelve cases of typhoid and paratyphoid, hepatitis appeared as an integral part not as a complication in 27%. One-third were icteric.¹²³ By renal biopsy, glomerulitis was present in three typhoid patients, probably as an immune complex,¹²⁴ not as simple proteinuria present during most febrile diseases. Osler described typhoid nephritis on page 26 in the first edition (1892) of *The Principles and Practice of Medicine*.

Mycobacterioses. The death-rate from tuberculosis in the U.S.A. fell from 5.1 to 2.2 per 100,000 in 10 years. The average stay in hospital in 1953 was 10 months; in 1963, 7 months, and currently it is about 3 months.¹²⁵ Even that may be too long. Untreated victims usually spread infection before diagnosis is

made. Treated ones in whom bacilli disappeared need not be isolated in hospitals. They can be managed as outpatients since recovery from illness is prompt and patients then are not infectious for others. Gowns and isolation procedures are no longer in vogue.¹²⁶ BCG vaccination has not changed the pattern of the ordinary postprimary tuberculosis as compared with the non-vaccinated persons.¹²⁷ Arguments for and against the use of isoniazid for preventing or treating tuberculosis were aired in the January 1974 issue of the *Annals of Internal Medicine*, p 113, 114.

Tuberculosis or other infections may begin in patients treated with dialysis for long periods. Five cases occurred among 136 others. The dermal tuberculin test was unreliable for their detection.¹²⁸

In a 12-year study, isoniazid prophylaxis lessened the incidence of 'bacillary' infections, but not that of cavitory cases. Long continued prophylaxis with its side effects raised doubt of its value in regions of low prevalence of tuberculosis¹²⁹ except in persons more than 35 years old. The drug induced tumours in animals. Indeed, its discontinuance was recommended¹³⁰ because tuberculosis now is easily controlled with therapy.

Thirty-five patients treated with antimicrobics for *Mycobacterium kansasii* infections were observed for 2 years. No relapse ensued in thirty-one. Surgical excision was done in four and six died from other causes.¹³¹ *Myco. abscessus* infected two renal homo-graft recipients and resisted therapy.¹³²

Leprosy. Differences in the epidemiological spread of leprosy and tuberculosis are not so great as believed. Both induce household infections. Persons with inapparent leprosy may be overlooked.¹³³ According to a letter in the *Journal of the American Medical Association* of 9 December, page 1388, two U.S. soldiers contracted leprosy in Vietnam. It may first appear 10 years after exposure and be misdiagnosed. In describing experience at the leper colony in Hawaii, Moser summarized advances in knowledge. Cellular and plasmal factors, lymphocytes and a transfer factor play a role in immunity and influence the different manifestations of tuberculoid and lepromatous leprosy. Intravenous injection of leukocytes from normal donors within a few months caused a remission of symptoms, histological and bacteriological findings lasting four months. Apparently, some defect of T-cell responsiveness favours invasion and disease.¹³⁴

Malaria mostly acquired in Vietnam was diagnosed in 4545 cases in the U.S.A. in 1970, but declined to 588 cases in 1972. Between 1963 and 1972, forty-two deaths nearly all from unrecognized *falciparum* infection occurred in hospitals wherein the staff was unfamiliar with malaria. The course of disease often does not portray the 'typical' precise

cyclic bouts, and is regarded as fever of unknown origin. Diagnosis depends on knowledge of where the patient had been (unde venis) and on examination of stained specimens of blood. Malaria will continue to be brought to non-endemic regions by travellers.¹³⁵ Disseminated intravascular clotting caused acute pulmonary insufficiency, renal and cerebral injury in twelve patients with *falciparum* malaria. Nine died.¹³⁶ Malarial parasites discovered within platelets by electron microscopy were thought to account for thrombocytopenia in malaria,¹³⁷ but transient thrombocytopenia is common to all acute infections.

Antimicrobial therapy

Several articles dealt with the harmful results of both proper and indiscriminate prescription of antimicrobics, as repeatedly stressed in these reviews. Questions arise if the use of these drugs at times does more harm than good, and if the risks outweigh the benefits therefrom. The death rate from infections, now about 35%, is almost the same as before the antimicrobial era, but from a different set of pathogens. The number of infections amenable to therapy is far exceeded by those that are not. The American Medical Association has authorized an investigation to determine the patterns of antimicrobial prescription in the U.S.A.¹³⁸

Since 1960, the population increased about 11%, but antimicrobial usage increased threefold. In 1971, antimicrobics purchased by hospitals cost about \$218 million, and 27% of 33 million hospital patients received one or more of them. Why? Annually at this 500-bed hospital, antimicrobial therapy cost patients \$250,000.

The chief reasons for unnecessary or improper therapy are: (1) treatment of colds and other viroses; (2) prophylaxis; (3) failure to identify the pathogen; (4) prescription by telephone; (5) combinations of drugs; (6) commercial advertising; (7) patients' demand. The chief harmful effects are (1) untoward and fatal drug reactions; (2) emergence of resistant pathogenic microbes; (3) unnecessary expense. An estimated 100,000 deaths annually are caused by antimicrobial resistant Gram-negative bacillaemias. 'A fullblown national epidemic' has ensued as an aftermath of antimicrobial usage. Factors recommended to correct the matter are: proper education of the public, medical students and physicians, and the establishment of antimicrobial surveillance committees in hospitals.¹³⁹ 'If the present inexperienced physician overuse of antibiotics continues, it must be expected that limitation' by government control will come about.¹⁴⁰

A combination of carbenicillin and cephalothin was credited as causing a favourable response in 80% of cancer patients with Gram-negative bacillary

infections.¹⁴¹ Fever may indicate actual infection, but may be an effect of the damaged tissue of neoplasms without microbic invasion. According to Kunin, such drugs often are used as 'drugs of fear'. They seldom prevent or cure infection in the immunologically suppressed or anatomically compromised host, and their prophylactic value is overrated.¹⁴²

Antimicrobial coverage was recommended because transient bacteraemia follows in 16% of nasotracheal intubations.¹⁴³ Routine prophylaxis generally is deplored as unnecessary and perhaps harmful. Intrathecal and intramuscular injections of gentamicin were given for presumed or actual Gram-negative bacillary meningitis. Yet according to the authors, the value of intrathecal therapy is unproved.¹⁴⁴ One wonders if bacilli floating in spinal fluid are harmful, and how much, if any, of the drug enters the infected meninges.

According to two articles and an editorial in the 15 July issue of the *Journal of the American Medical Association*, *H. influenzae* has acquired resistance to ampicillin, probably as a result of its widespread use. When resistant strains are encountered, penicillin and chloramphenicol or chloramphenicol alone probably will be the drugs of choice especially for meningitis and septicemia. Single doses of 100 mg of doxycycline used during epidemics, cured victims of typhus and borreliosis, but severe reactions ensued in the latter.¹⁴⁵

Methicillin caused nephropathy in thirteen children,¹⁴⁶ ampicillin caused nephritis in another, and lincomycin caused pseudomembranous colitis.¹⁴⁷ According to letters in the *Lancet* (i, 1221, 1974), clindamycin also caused colitis. Use of the latter drug should be reserved only for severe anaerobic infections. According to the *Medical Letter* of 22 November, eight cephalosporin drugs are available. They are over-used and generally are not superior to penicillins.

Iatrogenic infections

During a 3-year study in a hospital, nearly 50% of 6063 patients received one or more antimicrobics. Of these, 5.4% had reactions therefrom severe enough in many to need four or more additional days in the hospital. The administration of gentamicin, kanamycin, streptomycin and polymixin to senile patients and of ampicillin to children is hazardous. The use of prophylaxis for any condition without indication was therefore condemned.¹⁴⁸ Two deaths from anaphylaxis followed an intravenous injection of cephalothin (Keflin) given for prophylaxis during surgical operations. Both patients had received penicillin on prior occasions.¹⁴⁹ Six patients treated with corticosteroids for multiple sclerosis acquired cavitary pulmonary infections and two died.

Because oestrogen therapy favours infection of the urinary tract, oral contraceptives have increased the incidence of bacteriuria.¹⁵⁰ Candidial myocarditis occurred during immunosuppressive therapy for leukaemia.¹⁵¹ Pulmonary cavitation caused by *Aspergillus* followed immunosuppressive or corticosteroid therapy in nine patients with lymphoma.¹⁵² Disseminated infection and fungaemia occurred in forty-four patients whose resistance had been impaired by other disease or after instrumentation. Disease was transient in eight and clinically significant in eighteen.¹⁵³ Transient bacteraemia ensued in 100 patients after angiography.¹⁵⁴

After instrumentation in chronically ill patients, *Proteus* bacilli resistant to all drugs used caused 10 infections, three with abscesses and bacteraemia.¹⁵⁵ A relative increase in the incidence of Gram-negative bacillary infection occurred in hepatic abscesses and in endocarditis after antimicrobial therapy was applied.¹⁵⁶

Critique pertained to the propriety and danger of performing renal biopsy to discover streptococcal infection in asymptomatic children,¹⁵⁷ and of duodenal biopsy during enteritis.¹⁵⁸ Methods for the prevention and management of infections incident to intravenous therapy¹⁵⁹ and during cardiac surgery¹⁶⁰ were outlined.

Miscellaneous items

The Center for Disease Control (CDC) in Atlanta published a list of immunobiological agents and drugs available for distribution on request. They include antitoxins, globulins, plasmas, antiparasitic drugs, skin-test antigens and vaccines, and information about their use.¹⁶¹

A recent study reaffirmed what has been known for 50 years, namely, that polymorphonuclear leukocytosis of more than 10,000 mm³ usually signifies Gram-positive bacterial infections while about 500 mm³ of non-segmented neutrophils indicate Gram-negative bacillary infection.¹⁶² Unfortunately, frequent exceptions weaken reliance on cell counts for diagnostic aid.

Even after critiques of tonsillectomy and adenoidectomy by Kaiser 50 years ago, mine of 1940¹⁶³ and others later, the 'slaughter of tonsils' persists. Tonsillectomy is the most frequently performed surgical operation. About 100,000 children are so treated annually in the U.S.A. One may wonder if excision of tonsils leaving the lymphoid tissue of Waldeyer's ring and elsewhere in the nasopharynx intact actually serves its purpose. A diagnosis of chronic tonsillitis, at times, may be as questionable as that of chronic appendicitis. In the hope of solving the problem, another investigation and controlled study is under way by a committee of the American Medical Association.

Tuberculosis, meningococcaemia, viral infection, malaria and sinusitis among other diseases were considered as causes of recurrent fever for 8 years before a diagnosis of periodic fever was made in an otherwise healthy man.¹⁶⁴ Earlier reports on the value of scintiscanning with gallium citrate ga 67 for locating abscesses, areas of infection and inflammation were confirmed.¹⁶⁵ Although reported cases of trichinosis have declined from 393 in 1951 to 115 in 1971, two small outbreaks resulted from ingesting raw pork in New York City.¹⁶⁶

Dogs immunized against leptospirosis apparently acquired *Leptospira icterohaemorrhagiae* from rats and transmitted the infection to five persons in St Louis.¹⁶⁷ Penicillin failed to stop leptospirosis. A dog infected with *L. autumnalis* apparently was the source of seven human infections in Oregon.¹⁶⁸

Severe fetal toxoplasmosis was noted only when mothers acquired infection in early pregnancy. If infected later, fetal infection was inapparent or absent.¹⁶⁹ The February 1974 issue of the *Bulletin of the New York Academy of Medicine* contained reports of a symposium on toxoplasmosis. According to a letter in the *Journal of the American Medical Association* of 11 February 1974, dry ice applied for 30–90 min cured local lesions of cutaneous leishmaniasis.

Prototheca, a unicellular alga, caused a rare non-fatal septicaemic infection in New Zealand. The agent was present in peritoneal nodules, nasal biopsy specimen, skin and blood.¹⁷⁰ Tick typhus (Rocky Mountain spotted fever) has increased in incidence with the highest number of reported cases—668 in 1973, partly owing to better diagnosis. The death rate is about 6%.¹⁷¹

References

- EDITORIAL (1974) The specialty of infectious diseases. *Lancet*, ii, 1051.
- MONTO, A.S. & ULLMAN, B.M. (1974) Acute respiratory illness in an American community. *Journal of the American Medical Association*, **227**, 164.
- EVANS, A.S. *et al.* (1973) Acute respiratory infections in different ecologic settings: Argentine military recruits. *American Review of Respiratory Diseases*, **108**, 1311.
- MINOR, T.E. *et al.* (1974) Viruses as precipitants of asthmatic attacks in children. *Journal of the American Medical Association*, **227**, 292.
- WENZEL, R.P. *et al.* (1974) Coronavirus infections in military recruits. *American Review of Respiratory Diseases*, **109**, 621.
- MCINTOSH, K. *et al.* (1974) Coronavirus infection in lower respiratory tract disease of infants. *Journal of Infectious Diseases*, **130**, 502.
- PANUSARN, C. *et al.* (1974) Prevention of illness from rhinovirus infections by a topical interferon inducer. *New England Journal of Medicine*, **291**, 57. Editorial, *ibid.* 95.
- Vitamin C and the common cold (1974) *Medical Letter*, **16**, 85.
- SCHWARTZ, A.R. *et al.* (1974) Evaluation of the efficacy of ascorbic acid in prophylaxis of induced rhinovirus 44 infection in man. *Journal of Infectious Diseases*, **128**, 500.
- EDITORIAL. Antibiotics and respiratory illness (1974) *British Medical Journal*, **3**, 1.
- GORDON, M., LOVELL, S. & DUGDALE, E.L. (1974) The value of antibiotics in minor respiratory illness in children. *Medical Journal of Australia*, **1**, 304.
- New influenza vaccines (1974) *Medical Letter*, **15**, 90.
- STUART-HARRIS, C. (1974) Influenza vaccines (Abstract). *Annals of Internal Medicine*, **80**, 469.
- SMITH, J.W.G. (1974) Vaccination in the control of influenza. *Lancet*, ii, 330.
- GUYER, B. *et al.* (1974) The Memphis state university rubella outbreak. *Journal of the American Medical Association*, **227**, 1298.
- SCHIFF, G.M. *et al.* (1974) Serological survey for rubella and measles antibodies among first graders. *Journal of the American Medical Association*, **227**, 49.
- FLEET, W.F. *et al.* (1974) Fetal consequences of maternal rubella immunization. *Journal of the American Medical Association*, **227**, 621.
- MEDICAL NEWS (1974) Viral inhibitor tests involve 17 centers. *Journal of the American Medical Association*, **228**, 142.
- NELSON, K.E. *et al.* (1974) Current strategy for urban measles control. *Journal of the American Medical Association*, **227**, 780. Editorial, p. 798.
- DAWSON, C.R., WHITCHER, J.P. & SCHMIDT, N.J. (1974) Acute hemorrhagic conjunctivitis. *Journal of the American Medical Association*, **230**, 727.
- SPRAGUE, J.B. (1974) Epidemic keratoconjunctivitis: Outbreak of adenovirus type 8. *New England Journal of Medicine*, **289**, 1341.
- DENNIS, F.A. *et al.* (1974) Coxsackie A16 infection from lake water. *Journal of the American Medical Association*, **228**, 1370.
- CALDWELL, G.G. *et al.* (1974) Epidemic of adenovirus type 7 acute conjunctivitis in swimmers. *American Journal of Epidemiology*, **99**, 230.
- LINNEMANN, C.C. *et al.* (1974) Febrile illness in early infancy associated with ECHO virus infection. *Journal of Pediatrics*, **84**, 49.
- DILLON, M.J. *et al.* (1974) Epidemic neuromyasthenia: Outbreak among nurses at a children's hospital. *British Medical Journal*, **1**, 301.
- NORRBY, E. *et al.* (1974) Measles virus antibodies in multiple sclerosis. *Archives of Neurology*, **30**, 285.
- MONATH, T.P. *et al.* (1974) Lassa virus isolation from *Mastomys natalensis* rodents during an epidemic in Sierra Leone. *Science*, **185**, 263.
- BEISEL, W.R. *et al.* (1974) Symptomatic therapy in viral illness. *Journal of the American Medical Association*, **228**, 581.
- DNA virus infections yield to systemic ara-A (1974) *Journal of the American Medical Association*, **230**, 197.
- DENNIS, D.T. *et al.* (1974) Failure of cytosine arabinoside in treating smallpox. *Lancet*, ii, 377.
- DAWBER, R. (1974) Idoxuridine in herpes zoster. Further evaluation of intermittent topical therapy. *British Medical Journal*, **2**, 526.
- JUDELSON, R.G. (1974) Efficacy of zoster immune globulin. *Pediatrics*, **53**, 476.
- LEVIN, M.L. *et al.* (1974) Hepatitis B transmission by dentists. *Journal of the American Medical Association*, **228**, 1139.
- MAHONEY, P. *et al.* (1974) Australia antigen: Detection and transmission in shellfish. *Science*, **183**, 80.
- DICK, S.J., TAMBURRO, C.H. & LEEVY, C.M. (1974) Hepatitis B antigen in urban-caught mosquitoes. *Journal of the American Medical Association*, **229**, 1627.

36. HEATHCOTE, J., CAMERON, C.H. & DANE, D.S. (1974) Hepatitis-B antigen in saliva and semen. *Lancet*, **i**, 71.
37. SZMUNESS, W. *et al.* (1974) Hepatitis B infection. *Journal of the American Medical Association*, **227**, 901.
38. REED, W.D. *et al.* (1974) Exposure and immunity to hepatitis-B virus in a liver unit. *Lancet*, **i**, 581.
39. PAPAEOANGELOU, G., HOOFNAGLE, J. & KREMASTINOU, J. (1974) Transplacental transmission of hepatitis-B virus by symptom-free chronic carrier mothers. *Lancet*, **ii**, 746.
40. STEIGMAN, A.J. (1974) Rashes and arthropathy in viral hepatitis. *Mount Sinai Journal of Medicine*, **40**, 752.
41. KOHLER, P.B. *et al.* (1974) Chronic membranous glomerulonephritis caused by hepatitis B antigen-antibody complexes. *Annals of Internal Medicine*, **81**, 448.
42. ZUCKERMAN, G.R. *et al.* (1974) Epidemiological-clinical correlates of hepatitis B antigen subtypes. *Gastroenterology*, **66**, 408.
43. LE BOUVIER, G.L. (1973) Subtypes of hepatitis B antigen: Clinical relevance? *Annals of Internal Medicine*, **79**, 894.
44. PRINCE, A.M. (1974) Long-incubation post-transfusion hepatitis without serological evidence of exposure to hepatitis B virus. *Lancet*, **ii**, 241.
45. MEYERS, J.D. *et al.* (1974) Parenterally transmitted hepatitis A associated with platelet transfusions. *Annals of Internal Medicine*, **81**, 145.
46. ALMEIDA, J.D., GRAY, F.W. & WREGITT, T.G. (1974) Pitfalls in the study of hepatitis A. *Lancet*, **ii**, 748.
47. CHANG, F.W., FIUMARA, N.J. & WEINSTEIN, L. (1974) Genital herpes. *Journal of American Medical Association*, **229**, 544.
48. WALZ, M.A., PRICE, R.W. & NOTKINS, A.L. (1974) Latent ganglionic infection with *Herpes simplex* virus types 1 and 2. Viral reactivation *in vivo* by neurectomy. *Science*, **184**, 1185.
49. DEAN, A.G. (1974) Clinical events suggesting *Herpes simplex* infection before the onset of Burkitt lymphoma. *Lancet*, **i**, 1225.
50. STRAUCH, B. *et al.* (1974) Oropharyngeal excretion of Epstein-Barr virus by renal transplant recipients and other patients treated with immunosuppressive drugs. *Lancet*, **i**, 234.
51. VELTRI, R.W. (1974) Epstein-Barr virus linked to exudative tonsillitis. (Medical News). *Journal of the American Medical Association*, **228**, 1628.
52. CLIZER, E.E. (1974) Cytomegalovirus mononucleosis. *Journal of the American Medical Association*, **228**, 606.
53. LANG, D.J., KUMMER, J.F. & HARTLEY, D.P. (1974) Cytomegalovirus in semen. *New England Journal of Medicine*, **291**, 121.
54. ELEK, S.D. & STERN, H. (1974) Development of a vaccine against mental retardation caused by cytomegalovirus infections *in utero*. *Lancet*, **i**, 1.
55. LORD, R.D. *et al.* (1974) Assessment of bird involvement in three urban St. Louis encephalitis epidemics. *American Journal of Epidemiology*, **99**, 364.
56. SMITH, R. *et al.* (1974) Powassan virus infection. *American Journal of Diseases of Children*, **127**, 691.
57. HERNDON, R.M. *et al.* (1974) Ependymitis in mumps virus meningitis. *Archives of Neurology*, **30**, 475.
58. ZLOTNIK, I. *et al.* (1974) Transmission of Creutzfeldt-Jakob disease from man to squirrel monkey. *Lancet*, **ii**, 435.
59. SEVER, J.L. *et al.* (1974) Diagnosis of subacute pan-encephalitis. *Journal of the American Medical Association*, **228**, 604.
60. EDITORIAL. Measles and multiple sclerosis (1974) *Lancet*, **i**, 247.
61. HOTCHIN, J. *et al.* (1974) Lymphocytic choriomeningitis in a hamster colony causes infection of hospital personnel. *Science*, **185**, 1173.
62. DOUGHERTY, R.M. & DI STEPHANO, H.S. (1974) Isolation and characterization of a papovavirus from human urine. *Proceedings of the Society for Experimental Biology and Medicine*, **146**, 481.
63. SALM, R. (1974) EB virus and the treatment of lymphomas. *British Medical Journal*, **2**, 435.
64. AMSTEY, M.S. *et al.* (1973) Herpes virus cervicitis and cervical neoplasia. *Cancer*, **32**, 1321.
65. LANGENHUYSEN, M. (1974) Antibodies to Epstein-Barr virus. Cytomegalovirus and Australia antigen in Hodgkin Disease. *Cancer*, **34**, 262.
66. FLEWETT, T.H. *et al.* (1974) Relation between viruses from acute gastroenteritis of children and newborn calves. *Lancet*, **ii**, 61.
67. BISHOP, R.F. *et al.* (1973) Virus particles in epithelial cells of duodenal mucosa from children with acute non-bacterial gastroenteritis. *Lancet*, **ii**, 1281.
68. WYATT, R.G. *et al.* (1974) Comparison of three agents of acute infectious nonbacterial gastroenteritis by cross-challenge in volunteers. *Journal of Infectious Diseases*, **129**, 709.
69. SCHREIBER, D.S., BACKLOW, N.R. & TRIER, J.S. (1974) The small intestinal lesions induced by Hawaii agent of acute infectious nonbacterial gastroenteritis. *Journal of Infectious Diseases*, **129**, 705.
70. CARTER, W.A. & DE CLERCO, E. (1974) Viral infections and host defense. *Science*, **186**, 1172.
71. MAUGH, T.H. (1974) Chemical carcinogenesis: A long-neglected field blossoms. *Science*, **183**, 940.
72. STUART-HARRIS, C. (1974) Whither virology? Trends and prospects in medical research. *Postgraduate Medical Journal*, **54**, 1.
73. BREESE, B.T. *et al.* (1974) Streptococcal infections in children. *American Journal of Diseases of Children*, **128**, 457.
74. MERENSTEIN, J.H. & ROGERS, K.D. (1974) Streptococcal pharyngitis. *Journal of the American Medical Association*, **227**, 1278.
75. SILVERMAN, B.K. (1974) Comparative serologic changes following treated Group A streptococcal pharyngitis. *American Journal of Diseases of Children*, **127**, 498.
76. ANTHONY, B.F. *et al.* (1974) Classroom outbreak of scarlet fever and acute glomerulonephritis related to Type 2 (M-2, T-2) group A streptococcus. *Journal of Infectious Diseases*, **129**, 336.
77. EDITORIAL (1974) Group B streptococci: A serious threat to the neonate. *Journal of the American Medical Association*, **230**, 1117.
78. NEEFE, L.I. *et al.* (1974) *Streptococcus mutans* endocarditis. *Journal of the American Medical Association*, **230**, 1298.
79. ROSS, S. *et al.* (1974) Staphylococcal susceptibility to penicillin G. The changing pattern among community strains. *Journal of the American Medical Association*, **229**, 1075.
80. Meningococcal vaccine (1974) *The Medical Letter*, **16**, 74.
81. SMILACK, J.D. (1974) Group-Y meningococcal disease. *Journal of the American Medical Association*, **230**, 740.
82. GRIFFISS, J.M. *et al.* (1974) Recurrent meningococcal infection with an antigenically identical strain. *Journal of the American Medical Association*, **229**, 68.
83. WEINSTEIN, L. (1974) Whatever happened to the "old-time" infections? *Journal of the American Medical Association*, **229**, 196.
84. MUFSON, M.A. *et al.* (1974) Capsular types and outcome of bacteremic pneumococcal disease in the antibiotic era. *Archives of Internal Medicine*, **134**, 505.

85. BREWIN, A. *et al.* (1974) High-dose penicillin therapy and pneumococcal pneumonia. *Journal of the American Medical Association*, **230**, 409.
86. KAISER, A.B. & SCHAFFNER, W. (1974) Prospectus: The prevention of bacteremic pneumococcal pneumonia. A conservative appraisal of vaccine intervention. *Journal of the American Medical Association*, **230**, 404.
87. DORFF, G.J. *et al.* (1974) Etiologies and characteristic features of pneumonias in a municipal hospital. *American Journal of Medical Sciences*, **266**, 349.
88. PHILP, J.R. & SPENCER, R.C. (1974) Secondary respiratory infections in hospital patients: Effect of antimicrobial agents and environment. *British Medical Journal*, **2**, 359.
89. SICKLES, E.A. *et al.* (1974) Pneumonia in acute leukemia—A common and serious complication. *Annals of Internal Medicine*, **79**, 528.
90. WALZER, P.D. *et al.* (1974) *Pneumocystis carinii* pneumonia in the United States. *Annals of Internal Medicine*, **80**, 83.
91. ELLENBOGEN, C. *et al.* (1974) Bacterial pneumonia complicating adenoviral pneumonia. *American Journal of Medicine*, **56**, 168.
92. NAFTALIN, J.M. *et al.* (1974) *Mycoplasma pneumoniae* septicemia. (Letter). *Journal of the American Medical Association*, **228**, 565.
93. NOAH, N.D. (1974) *Mycoplasma pneumoniae* infection in the United Kingdom—1967–73. *British Medical Journal*, **2**, 544.
94. THOMPSON, T.R., SWANSON, R.E. & WIESNER, P.J. (1974) Gonococcal ophthalmia neonatorum. *Journal of the American Medical Association*, **228**, 186.
95. EDITORIAL. Gonorrhoea of the pharynx (1974) *British Medical Journal*, **2**, 239.
96. CORMAN, L. *et al.* (1974) The high frequency of pharyngeal gonococcal infection in a prenatal clinic population. *Journal of the American Medical Association*, **230**, 568.
97. HANDSFIELD, H.H. *et al.* (1974) Asymptomatic gonorrhoea in men. *New England Journal of Medicine*, **290**, 117.
98. VOLK, J. & KRAUS, S.J. (1974) Nongonococcal urethritis. *Archives of Internal Medicine*, **134**, 511.
99. BROOKS, G.F. *et al.* (1974) *Eikenella corrodens*: A recently recognized pathogen. *Medicine*, **53**, 325.
100. PALMER, D.L., HARVEY, R.L. & WHEELER, J.K. (1974) Diagnostic and therapeutic considerations in *Nocardia asteroides* infection. *Medicine*, **53**, 391.
101. VICTORICA, B., BAER, H. & AYOUB, E.M. (1974) Successful treatment of systemic *Chromobacterium violaceum* infection. *Journal of the American Medical Association*, **230**, 578.
102. LEINO, R. & KALLIOMÖKI, J.L. (1974) Yersiniosis as an internal disease. *Annals of Internal Medicine*, **81**, 458.
103. WEISSMAN, J.B. *et al.* (1974) Shigellosis. To treat or not to treat? *Journal of the American Medical Association*, **229**, 1215.
104. MUSER, D.M. (1973) Permanent carriers of non-typhosa salmonellae. *Archives of Internal Medicine*, **132**, 869.
105. BRADFORD, W.D. *et al.* (1974) Pathologic features of enteric infection with *Yersinia enterocolitica*. *Archives of Pathology*, **98**, 17.
106. MANI, V. *et al.* (1974) Invasive illness with *Salmonella virchow* infection. *British Medical Journal*, **2**, 143.
107. BARKER, W.H. (1974) *Vibrio parahaemolyticus* outbreaks in the United States. *Lancet*, **i**, 551.
108. AZIZ, K.M.S. (1974) Diarrhea toxin obtained from a waterbloom-producing species, *Microcystis aeruginosa* Kützinger. *Science*, **183**, 1206.
109. SHORE, E. *et al.* (1974) Enterotoxin producing *Escherichia coli* and diarrheal disease in adult travellers. A prospective study. *Journal of Infectious Diseases*, **129**, 577.
110. THOMAS, M.E.M. *et al.* (1974) Recurrent gastroenteritis in a preparatory school caused by *Shigella sonnei* and another agent. *Lancet*, **i**, 978.
111. BRADY, P.G. & WOLFE, J.C. (1974) Waterborne giardiasis. *Annals of Internal Medicine*, **81**, 498.
112. GANGAROSA, E.J. & BARKER, W.H. (1974) Cholera. Letter to the Editor. *Lancet*, **i**, 800.
113. LEIGH, D.A. (1974) Clinical importance of infections due to *Bacteroides fragilis* and role of antibiotic therapy. *British Medical Journal*, **3**, 225.
114. CHOW, A.W. & GUZE, L.B. (1974) Bacteroidaceae bacteremia: Clinical experience with 112 patients. *Medicine*, **53**, 93.
115. FREDERICK, J. & BRAUDE, A.I. (1974) Anaerobic infection of the paranasal sinuses. *New England Journal of Medicine*, **290**, 135.
116. BARTLETT, J.G. & FEINGOLD, S.M. (1974) Anaerobic infections of the lung and pleural space. *American Review of Respiratory Diseases*, **110**, 56.
117. BARTLETT, J.G., GORBACH, S.L. & FEINGOLD, S.M. (1974) The bacteriology of aspiration pneumonia. *American Journal of Medicine*, **56**, 202.
118. SWENSON, R.M. *et al.* (1974) Bacteriology of intra-abdominal infections. *Archives of Surgery*, **109**, 398.
119. Med. News. Diphtheria reported to be spreading among adults in the Northwest. *Journal of the American Medical Association*, **227**, 18.
120. MUNFORD, R.S. *et al.* (1974) Diphtheria deaths in the United States 1959–1970. *Journal of the American Medical Association*, **229**, 1890.
121. MERSON, M.H. *et al.* (1974) Current trends in botulism in the United States. *Journal of the American Medical Association*, **229**, 1305.
122. WAPEN, B.D. & GUTMANN, L. (1974) Wound botulism. *Journal of the American Medical Association*, **227**, 1416.
123. RAMACHANDRAN, S., GODFREY, J.J. & PERERA, M.V.F. (1974) Typhoid hepatitis. *Journal of the American Medical Association*, **230**, 236.
124. SITPRIJA, V. *et al.* (1974) Glomerulitis in typhoid fever. *Annals of Internal Medicine*, **81**, 210.
125. Current status of tuberculosis in the United States (1974) *Statistical Bulletin of the Metropolitan Life Insurance Company*, **55**, 9.
126. REICHMAN, L.B. (1974) Tuberculosis cure: When and where? *Annals of Internal Medicine*, **80**, 402.
127. GROTH-PETERSEN, B. (1974) Tuberculosis in 84 BCG vaccinated young adults. *Chest*, **65**, 166.
128. PRADHAN, R.P. *et al.* (1974) Tuberculosis in dialyzed patients. *Journal of the American Medical Association*, **229**, 798.
129. HORWITZ, O. & MAGNUS, K. (1974) Epidemiologic evaluation of chemoprophylaxis against tuberculosis. *American Journal of Epidemiology*, **99**, 333.
130. ISRAEL, H.L. (1974) Stop isoniazid prophylaxis. Letter. *Annals of Internal Medicine*, **80**, 672.
131. RAUSCHER, C.R., KERBY, G. & RUTH, W.E. (1974) A ten-year clinical experience with *Mycobacterium kansasii*. *Chest*, **66**, 17.
132. GRAYBILL, J.R. *et al.* (1974) Disseminated mycobacteriosis due to *Mycobacterium abscesses* in two recipients of renal homografts. *American Review of Respiratory Diseases*, **109**, 4.
133. REES, R.J.W. & MEADE, T.W. (1974) Comparison of the modes of spread and the incidence of tuberculosis and leprosy. *Lancet*, **i**, 47.
134. MOSER, R.H. (1974) Holy man and his disease. Editorial. *Journal of the American Medical Association*, **228**, 78.

135. WALZER, P.D., GIBSON, J.J. & SCHULTZ, M.G. (1974) Malaria fatalities in the United States. *American Journal of Tropical Medicine and Hygiene*, **23**, 328.
136. PUNYAGUPTA, S. *et al.* (1974) Acute pulmonary insufficiency in falciparum malaria. *American Journal of Tropical Medicine and Hygiene*, **23**, 551.
137. FAJARDO, L.P. & TALLENT, C. (1974) Malarial parasites within human platelets. *Journal of the American Medical Association*, **229**, 1205.
138. Antibiotic usage study (1974) *Journal of the American Medical Association*, **230**, 530.
139. SIMMONS, H.E. & STOLLEY, P.D. (1974) This is medical progress? *Journal of the American Medical Association*, **227**, 1023. Comments on pages 1029–1032.
140. JACKSON, G.G. (1974) Perspective from a quarter century of antibiotic usage. *Journal of the American Medical Association*, **227**, 634.
141. KLATERSKY, J. *et al.* (1974) Gram-negative infections in cancer. *Journal of the American Medical Association*, **227**, 45.
142. KUNIN, C.M., TUPASI, T. & CRAIG, W.A. (1973) Use of antibiotics. *Annals of Internal Medicine*, **79**, 555.
143. BERRY, F.A. (1974) Comparison of bacteremia occurring with nasotracheal and orotracheal intubation. *Anesthésie et analgésie*, **52**, 873.
144. RAHAL, J.J. *et al.* (1974) Combined intrathecal and intramuscular gentamicin for Gram-negative meningitis. *New England Journal of Medicine*, **290**, 1394.
145. PERINE, P.L. *et al.* (1974) Single-dose Doxycycline treatment of house-borne relapsing fever and epidemic typhus. *Lancet*, **ii**, 742.
146. SANJAD, S.A., HADDAD, G.G. & NASSER, V.H. (1974) Nephropathy, an underestimated complication of methicillin therapy. *Journal of Pediatrics*, **84**, 873.
147. RULEY, E.J. & LISI, L.M. (1974) Interstitial nephritis and renal failure due to ampicillin. *Journal of Pediatrics*, **84**, 878.
148. CALDWELL, J.R. & CLUFF, L.E. (1974) Adverse reactions to antimicrobial agents. *Journal of the American Medical Association*, **230**, 77.
149. SPRUILL, F.G., MINETTE, L.J. & STURNER, W.Q. (1974) Two surgical deaths associated with cephalothin. *Journal of the American Medical Association*, **229**, 440.
150. TAKAHASHI, M. & LOVELAND, D.B. (1974) Bacteriuria and oral contraceptives. *Journal of the American Medical Association*, **227**, 762.
151. VANKIRK, J.E., SIMON, A.B. & ARMSTRONG, W.R. (1974) Candida myocarditis causing complete atrio-ventricular block. *Journal of the American Medical Association*, **227**, 931.
152. RAMSAY, G.C. & MEYER, R.D. (1973) Cavitary fungus disease of lungs. *Radiology*, **109**, 29.
153. YOUNG, R.C. *et al.* (1974) Fungemia with compromised host resistance. A study of 70 cases. *Annals of Internal Medicine*, **80**, 605.
154. SHAWKER, T.H., KLUGE, R.M. & AYELLA, R.J. (1974) Bacteremia associated with angiography. *Journal of the American Medical Association*, **229**, 1090.
155. EDWARDS, L.D. *et al.* (1974) Outbreak of nosocomial infection with a strain of *Proteus rettgeri* resistant to many antimicrobials. *American Journal of Clinical Pathology*, **61**, 41.
156. DE LA MAZA, L.M., NAEIM, F. & BERMAN, L.D. (1974) The changing etiology of liver abscess. *Journal of the American Medical Association*, **227**, 161.
157. FLOYD, K.M. (1974) Ethics of renal biopsy. *Annals of Internal Medicine*, **80**, 117.
158. MEYER, J. (1974) Virus particles in duodenal biopsy specimens. (Letter). *Lancet*, **i**, 136.
159. MAKI, D.G., GOLDMAN, D.A. & RHAME, F.S. (1974) Infection control in intravenous therapy. *Annals of Internal Medicine*, **79**, 867.
160. KLUGE, R.M. *et al.* (1974) Sources of contamination in open heart surgery. *Journal of the American Medical Association*, **230**, 1415.
161. JOHNSON, R.H. & ELLIS, R.J. (1974) Immunologic agents and drugs available from the Center for Disease Control. *Annals of Internal Medicine*, **81**, 61.
162. TODD, J.K. (1974) Childhood infections. *American Journal of Diseases of Children*, **127**, 810.
163. REIMANN, H.A. & HAVENS, W.P. (1940) Focal infection and systemic disease. The case against the routine removal of teeth and tonsils. *Journal of the American Medical Association*, **114**, 1.
164. REIMANN, H.A. & MCCLOSKEY, R.V. (1974) Periodic fever. *Journal of the American Medical Association*, **228**, 1662.
165. BLAIR, D.C. *et al.* (1974) Localization of infectious processes with gallium citrate ga 67. *Journal of the American Medical Association*, **230**, 82.
166. IMPERATO, P.J. *et al.* (1974) Trichinosis among Thais living in New York City. *Journal of the American Medical Association*, **227**, 526.
167. FEIGIN, R.D. *et al.* (1974) Human leptospirosis from immunized dogs. *Annals of Internal Medicine*, **79**, 777.
168. FRASER, D.W. *et al.* (1974) Leptospirosis caused by serotype Fort-Bragg. A suburban outbreak. *Annals of Internal Medicine*, **79**, 786. Editorial. p. 893.
169. DESMONTS, G. & COUVREUR, J. (1974) Congenital toxoplasmosis. *New England Journal of Medicine*, **290**, 1110.
170. COX, G.E., WILSON, J.D. & BROWN, P. (1974) Protothecosis: A case of disseminated algal infection. *Lancet*, **ii**, 379.
171. MEDICAL NEWS (1974) Rocky Mountain spotted fever case numbers rise. *Journal of the American Medical Association*, **230**, 1503.