ANNUAL REVIEW

Infectious diseases: Annual review of significant publications

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Introduction

As in previous years, advances in knowledge of infections accrued, especially about viruses, the diseases they cause and protection against them, and in reactions of immunity in general. Hepatitis and herpes viruses claimed much attention, respiratory tract infections less than usual. The relation of EB and other viruses to cancer still is obscure. Venereal diseases continued to increase in incidence. New and expensive antimicrobial drugs were widely used, but few exceeded the value of older ones. Antimicrobial-resistance increased apace. Many reports dealt with the dangers of iatrogenic and nosocomial infections.

Viral infections

Hepatitis

Hepatitis B, as an occupational hazard, involved ten hospital employees after exposure to a patient who had received many blood-transfusions.¹ Four of five surgeons were infected during operation on a patient. Three had concurrent arthritis.² More articles on the subject appeared in the July 23 *Journal of the American Medical Association* and in the July *Archives of Internal Medicine*. Hepatitis occurred in 30% of 200 drug addicts.³ According to two articles in the *Lancet* of June 30, sexual intercourse and domestic contact are likely sources of infection. Infection with hepatitis B virus seems to be as universal as that of cytomegalovirus or herpes virus.⁴

Among more than 2 m blood samples from volunteer donors, 0.10% contained HB Ag. The ratio of subtype ad to ay was 5.8 : 1, and lower in the northern U.S.A. Hb Ag was three times higher in paid blood donors than in volunteers.⁵ HB Ag appeared in 79.5% of patients at some time after exposure to infection. Fifty-six per cent of normal donors had subtype ad HB Ag and 75% of patients with post-transfusion hepatitis had subtype ay suggesting that healthy carriers present little danger of

transmitting infection. Subtypes may reflect epidemiological features, not biological differences of strains.⁷ Immunity often follows early exposure to the virus.⁸

Hepatitis probably is a systemic disease. Therapy failed in nine comatose patients. In one, most organs were damaged and HB Ag was present in each.⁹ Injected heat-inactivated B antigen may meliorate the disease¹⁰ and eventually a vaccine may be prepared.¹¹ Radioimmunoassay detected twice as many infections with hepatitis B virus as other tests.¹² Infection was induced experimentally in chimpanzees.¹³

Hepatitis A. Further evidence supports the identity of a virus recovered from marmosets inoculated with blood from patients with hepatitis A to that of hepatitis A.¹⁴ Inoculation resulted in characteristic evidence of the infection.¹⁵ Convalescent serum from patients neutralized the infectivity of the agent in marmosets.¹⁶ Virus particles appeared in stools during the acute phase of disease.¹⁷

Herpes hominis

Except for pain and tenderness, herpes virus type 2 penile lesions may be mistaken for other chancres. Virus was present in 6% of urethral swabs, in one accompanied by *T. pallidum*.¹⁸ Type 1 virus caused intrauterine infection of an infant. Six instances have been observed resulting in congenital malformations, cerebral injury, mental retardation and other defects.¹⁹ Six adults had herpes hepatitis subsequent to infection elsewhere chiefly of the oral mucosa. Because of its bad prognosis, therapy with cytosine arabinoside or idoxuridine was recommended.²⁰ Among twenty patients with herpes virus encephalitis treated with idoxuridine, thirteen showed apparent improvement, nine are well and two died. Of nine untreated patients, six survived but only one recovered completely.²¹ Herpes hominis virus, the commonest cause of sporadic necrotizing encephalitis, affected seven patients. Of four treated with

idoxuridine, three died. In one instance, as much virus was in the brain after a full course as initially. Two treated with cytarabine have chronic disease.²²

Labial lesions seemed to respond and recurrences were prevented by applying fluorescent light to lesions treated with neutral red dye.²³ Therapeutic photoinactivation of herpes virus may be hazardous and lead to changes that result in oncogenesis.²⁴ BCG vaccination apparently prevented recurrences of genital herpes type 2 infection incident to menses.²⁵ Repeated application of ether or chloroform is recommended as the safest treatment for ether-sensitive labial herpes.²⁶ Controversy continues about the relation of herpes viruses to cancers. A latent virus may become active in dysplastic cells.^{27, 28} Patients with cervical carcinoma had antibody to type 2 herpes virus twice as often as in normal women.²⁹ A recently published book³⁰ and a review in the September 27, October 4 and 11 *New England Journal of Medicine* summarize knowledge about herpes and varicella-zoster viruses.

Meningoencephalitis

Besides measles and smallpox, vaccinia virus also may be a cause of subacute disseminated encephalomyelitis years after vaccination.³¹ Measles virus may be a cause of multiple sclerosis.³² As yet, no evidence of any viral infection has appeared in brain tissue from a patient.³³ Measles antigen in infected neurons and glial cells may be involved in the cytolysis of sub-acute sclerosing panencephalitis.³⁴ The increase in the incidence of SSPE in New Zealand may be related to vaccination against poliomyelitis. Either SV40 or measles virus may have been contaminants.³⁵ Slow viruses were even considered as a cause of schizophrenia.³⁶ Knowledge of conventional and unconventional slow viruses was summarized in *Science* of June 29 and July 6.

Powassan virus, present in rodents, caused non-fatal encephalitis in a resident of New Jersey.³⁷ ECHO virus caused a small outbreak in Britain.³⁸ Mumps, ECHO 2 and California encephalitis viruses were implicated as causes in one child.³⁹ The question of anamnestic reaction arises. California arbovirus caused meningoencephalitis in sixty-six children in Minnesota between 1967 and 1972. All survived but 15% had sequelae.⁴⁰ Type 1 poliomyelitis in eleven unvaccinated students in October 1972 in Connecticut emphasized the need for vaccination.⁴¹ Paralytic poliomyelitis type 3 developed after a month in an orally vaccinated person in 1963. Ten years later in a suit against the U.S. government, \$2 million was awarded because of negligence in pretesting the vaccine for safety.⁴²

House sparrows and pigeons probably disseminated the St Louis encephalitis virus during an epidemic in Houston.⁴³ Sparrows also harbour salmonellae.⁴⁴

Rabies. Uncertainty persists about the value of vaccination. Although serious sequelae are rare, the low incidence of rabies in the U.S.A. makes the risk of reaction to the vaccine greater than the risk of rabies. Among 116 persons receiving duck-embryo vaccine, all had local reactions, 33% had constitutional symptoms and one had an anaphylactic reaction.⁴⁵ A human cell culture of rabies vaccine evoked antibody without causing an untoward general reaction.⁴⁶ Antiserum (Lederle Laboratory) is available commercially.⁴⁷ It may interfere with active immunity induced by vaccine.⁴⁸

A laboratory worker contracted the infection probably by inhaling aerosolized 'fixed' virus.⁴⁹

Viral respiratory tract infections

Upper respiratory tract viral infections occur in the tropics in any season. In Bangkok, parainfluenza (40%), respiratory syncytial (13%) and adenoviruses (13%) were the chief causes. A2 influenza appeared in August 1965 and dominated for 2 months.⁵⁰ Elsewhere, viral infections, especially respiratory syncytial and parainfluenza 3, predominated as causes of pneumonia in infants.⁵¹ Viral infections often account for exacerbations of chronic bronchitis⁵² and do not require antimicrobial therapy.

Interferon applied intranasally prevented rhinoviral infection and viral shedding in inoculated volunteers.⁵³ Inexplicably, vitamin C reduced the severity of colds in girls, but not in boys.⁵⁴ Sceptical letters about its value appeared in *Lancet* of April 28 and in an editorial.⁵⁵ Both glyceryl guaiacolate and terpin hydrate are useless as expectorants.⁵⁶ Large dosage of the latter injured the liver.⁵⁷

Influenza affected three newborn infants. One had bilateral pneumonia on the first day of infection.⁵⁸ Vaccination of patients who have a demyelinating disease is hazardous.⁵⁹ A new vaccine (1972-73) effectively induced serum and nasal antibodies.⁶⁰ Prophylaxis with amantadine seemed to prevent nosocomial infection⁶¹ but resistant strains of virus A appeared in treated mice.⁶² The hope of averting pandemics rests on the improvement of vaccines as discussed in the June 8 and 15 issues of *Science*.

Coxsackie virus

An outbreak of Coxsackie virus B5 in a boys' summer camp probably had its source in lake water during bathing. Thirteen boys had pharyngitis. Conjunctivitis, pleurodynia, meningitis and dysentery occurred in one each.⁶³ Evidence of Group B Coxsackie virus infection appeared in fifteen of twenty-one children with the haemolytic-uraemic syndrome, and the virus was recovered from two.⁶⁴ Adenovirus type 2 caused haemorrhagic cystitis in seventeen children and three adults.⁶⁵ As in the case of mumps, Coxsackie B virus caused acute pancreatitis in two patients.⁶⁶

Cytomegalovirus usually is invasive when host-resistance is impaired, but it caused nine cases of heterophil negative mononucleosis in otherwise healthy persons. Viruria was present in each. The infection is commoner than is generally believed.⁶⁷ The virus was recovered from the cervix and demonstrated in human semen where it may remain for months without causing symptoms.⁶⁸ Infection diagnosed by IgM antibody occurred in fourteen healthy adults and in sixteen with underlying disease.⁶⁹

Viral dysentery caused two institutional outbreaks. Volunteers were infected by ingesting stool filtrates of patients.⁷⁰ It probably is caused by an ether-stable, noncultivable, 30 nm-sized pox-like virus⁷¹ or a parvovirus.⁷² Intestinal biopsy of volunteers after ingesting the Norwalk agent showed minor villar changes and multivesiculate intracellular bodies. In the absence of inflammation,⁷³ the term gastroenteritis is inappropriate.

Miscellaneous. Infectious mononucleosis continues to be misdiagnosed. Clinical, epidemiological, haematological and serological criteria for diagnosis must be observed before diagnosis is established.⁷⁴ The transfer factor, probably the EB virus, persisted in the throat for months after the active infection.⁷⁵ Cytarabine failed for treating varicella-zoster infection⁷⁶ and provoked adverse effects.⁷⁷ ECHO 19 virus caused fatal hepatic necrosis in three neonates.⁷⁸ According to Hammon, the cause of dengue haemorrhagic fever is uncertain. A viral mutation or selection, two viruses or other reasons may account for changes in its epidemiological and clinical characteristics.⁷⁹ A nonfatal case of Lassa fever contracted in Africa was observed in London.⁸⁰

Knowledge about drug therapy of viral infections was summarized.⁸¹ According to one opinion, there is no convincing evidence of the therapeutic value of pyrimidine, cytosine arabinose or purine nucleoside derivatives for varicella-zoster, herpes hominis encephalitis or cytomegalovirus.⁸²

Measles

Fifty-one million doses of measles vaccine distributed after 1963, reduced the incidence of the disease from 480,000 to 75,000 in 1968, deaths from 408 to 24 and encephalitis from 337 to 19. The risk of vaccine encephalitis is 1 : 1000.⁸³

Three articles in the *May Journal of Pediatrics* discuss the occasional failure of measles vaccination. Combined measles-mumps vaccine gave satisfactory antibody response in nearly all vaccinated children without significant side-effects.⁸⁴ Bacteria seldom invaded the pneumonic lungs of African children. When they did, penicillin therapy aided in the severest cases, but prophylactic administration was deemed unnecessary.⁸⁵ Several instances of combined

measles and varicella pneumonia are recorded. In an unusual fatal case in an infant, measles pneumonia appeared during varicella pneumonia. Interferon of the first infection probably failed to protect against the second.⁸⁶

Rubella

Although vaccination seemed to end one epidemic,⁸⁷ routine vaccination of most children in a neighbourhood failed to prevent an outbreak of more than 1000 cases 9 months later.⁸⁸ Some victims of rubella spread the disease to many susceptible persons, others apparently infect only a few. Virus transmission is maintained in a population by spreader to spreader contact. Concurrent minor viral respiratory tract disease may increase dissemination of rubella.⁸⁹ Pregnant women who are not sero-susceptible should not be vaccinated. Vaccinated ones should receive contraceptive agents for three months.⁹⁰

Viruses and cancer

By the age of 10, 70–80% of persons in England had antibody against a 'new' polyoma virus. No illness occurred, but the agent may be oncogenic.⁹¹ Ten of seventy-four patients with functioning allografts excreted polyoma virus and inclusion-bearing cells in the urine. The prevalence of BK antibody was about the same as that found in the general population.⁹²

Although evidence connecting EB virus with Burkitt's lymphoma 'is now almost complete',⁹³ 'it is still premature to assume that EB virus causes Burkitt's tumour in any country . . .'.⁹⁴ Virus antibody during Burkitt's lymphoma in Africans and its absence in one-third of American patients suggests that different agents are causal or that the suspected virus is an unlikely cause.⁹⁵

RNA virus particles were seen in, and cultured from, three renal cancers. Neutralizing antibody appeared in the blood.⁹⁶ Malignant gliomas developed in hamsters inoculated with a papova virus from a patient with leukoencephalopathy.⁹⁷ It still is uncertain if the supposed cancer viruses of man are causes or commensals.⁹⁸ Hilleman summarized problems regarding interferons, vaccines and chemotherapy of viral diseases including cancer. The only effective vaccine for cancer in any species of animal is one for Marek's disease, a malignant neoplasm of chickens.⁹⁹

Bacillary infections

An outbreak of diphtheria in the summer of 1970 in Texas involved nearly 200 patients, chiefly children, of whom two died, and 169 detected healthy carriers. Bacilli of the *intermedius* type dominated;

mitis and gravis forms were less common. The types were not correlated with the severity of disease, nor were there differences in previously immunized or unimmunized patients.¹⁰⁰

Multiple drug-resistant typhoid bacilli in the Mexican epidemic have spread elsewhere. Resistance also was transferred by the R factor to *Esch. coli*, and to other salmonellae. Cycloserine and gentamicin were antibacterial *in vitro*.¹⁰¹ In India¹⁰² and in Germany,¹⁰³ trimethoprim-sulfamethoxazole was curative for typhoid. Relapses did not occur. The drug is useful for strains resistant to chloramphenicol or ampicillin. Actual invasion of *Esch. coli* from cheese, not absorption of toxin alone, caused dysentery in twenty-eight or thirty-seven persons. All recovered without antimicrobial therapy.¹⁰⁴ Besides *Esch. coli*, *Salmonella* also may induce cholera-like stools, probably of toxic origin.¹⁰⁵ Person-to-person spread of *Yersinia enterocolitis* affected six hospital employees.¹⁰⁶ During 5 years, the incidence of ampicillin-resistant shigellae increased from none to 85%.¹⁰⁷ Lomotil therapy for shigellosis prolonged the fever and caused other harmful effects.^{107a}

Cholera

Gastric hypochlorhydria increases the susceptibility to cholera, salmonellosis, and shigellosis, especially in poorly nourished populations.¹⁰⁸ In 1892, Pettenkofer got cholera by ingesting vibrios after neutralizing his gastric juice with sodium bicarbonate.¹⁰⁹ Two articles in the *Lancet* of June 2 concern the ineffectiveness of cholera vaccine. In 1972, forty cases occurred in Australia, two in Germany and in England.¹¹⁰ The occurrence of 150 cases and eighteen deaths in Naples in August 1973 induced much unnecessary preventive effort including vaccination. The ratio of overt to inapparent attacks was 1 : 25. A single case of unknown source occurred in Texas. A brief summary of new knowledge was published.¹¹¹

Anaerobes, especially clostridia and cocci, appeared in blood cultures from 264 of 1307 patients with a death-rate of 31%.¹¹² Bacteroides and streptococci caused 19% of empyemas in a 20-year period with a death rate of 19%.¹¹³ Such infections are often overlooked because refined methods for identifying anaerobes seldom are applied. Ubiquitous saprophytic anaerobes may be colonizers or pathogens, usually in injured or degenerate tissues. Penicillin is the drug of choice for therapy and clindamycin for bacteroides. The matter is discussed in a monograph.¹¹⁴

Miscellaneous bacillary infections

In a 3-month period, thirty-nine persons in Utah contracted tularaemia chiefly from deerflies. A rabbit

epizootic concurred.¹¹⁵ The first evidence of plague infection contracted from a carnivore occurred after skinning a bobcat in Arizona.¹¹⁶ Gram-negative bacilli caused osteomyelitis in sixteen patients or 28% of all cases.¹¹⁷ Minocycline apparently cured a dermal granuloma of 5 years' duration caused by *Serratia*.¹¹⁸ Antipertussis vaccine was not very effective in Britain where *B. pertussis* is the major cause of whooping cough.¹¹⁹ Vaccination to prevent pseudomonal infection in cancer patients had limited value and many untoward reactions ensued.¹²⁰ Other Gram-negative bacillary infections are mentioned in the section on nosocomial disease.

BCG given to monkeys as an inhaled aerosol afforded greater protection against virulent *M. tuberculosis* than did parenteral injection. Inhaled aerosol vaccine induced weak dermal tuberculin reactivity.¹²¹ Forty-five infections with *Myco. intracellulare* emphasized the importance of this disease and the need for aggressive therapy.¹²²

Inapparent infections of leprosy occur as in almost all other infections. Among twenty-six persons living in an endemic area for 2 months, none responded to a test of immune response, but 24% of those exposed for a year responded and more than 50% in contact with victims did.¹²³ Application of the transfer factor after chemotherapy apparently augmented the treatment of lepromatous leprosy.¹²⁴ *M. leprae* multiplies in the foot-pads of mice, and widely scattered lepromas appeared in armadillos 15 months after inoculation.¹²⁵ Trachoma, rampant in Asia and Africa and among Amerinds responded favourably to therapy with doxycycline for a total of 28 doses in 40 days.¹²⁶ The causal microbe may be related to Gram-negative bacilli.

Coccal infections

Pneumococcal infections

Interest revived in the capsular swelling test. Few of the higher numbered types among the 82 types cause typical lobar pneumonia. They are invasive and cause 'atypical' pneumonia when host-resistance is low.¹²⁷ More than 26 different pneumococcal serotypes, mostly of the higher numbered types, associated with 123 cases of pneumonia, make it unlikely that specific immunization will be practicable.¹²⁸ The cocci can be typed directly in sputum within minutes and in an hour or two in peritoneal exudate after mouse inoculation without prior culture. Antimicrobials given before specimens are taken obscure diagnoses. Pneumococci were identified in 92% of previously untreated patients, but were absent in 69% of treated ones.¹²⁹ Patients with sickle cell anaemia are subject to repeated attacks of pneumococcal pneumonia, often hard to distinguish from pulmonary infarction.¹³⁰ Prior administration

of tetracycline and chronic disease were factors in causing tetracycline-resistance of pneumococci in 5.7% of 400 patients.¹³¹ Blood-culture discovered bacteraemia in thirty-one of 708 ambulatory febrile children in a clinic, mostly with pneumococci and *H. influenzae*.¹³²

Staphylococcus aureus, an omnipresent transient or persistent colonizer, rapidly becomes resistant to most antimicrobials. At times, it causes widespread epidemics especially as nosocomial infections in hospitals, and during influenza epidemics.¹³³ In one patient it caused typical scarlet fever, vasculitis and fasciitis.¹³⁴

Renal injury after Group A streptococcal infection is commoner than believed, but usually is asymptomatic. Among 248 infected children, fifty-four showed evidence of glomerulonephritis by biopsy.¹³⁵ Nongroup A haemolytic streptococci, often of endogenous rather than of nosocomial origin, caused puerperal illness in most of seventy-three women. In three, scarlet fever, meningitis and pelvic abscess ensued.¹³⁶

Paediatricians called attention to the importance of Group B streptococcal infections in infants in three papers in the April 1973 *Journal of Pediatrics*. Forty-four infants had meningitis, others had septicemia or respiratory tract disease. The maternal vagina was the probable source. Allergic, clinical and immunological features of meningococcosis were described in two papers in the June 30 *British Medical Journal*.

Gonorrhoea

The incidence in the U.S.A. increased from 670,000 reported cases in 1971 to 758,000 in 1973¹³⁷ and continues to increase. As a consequence the case-rate of ophthalmia neonatorum has risen to 265/100,000.¹³⁸ The cocci were in the pharynx of 150 patients, in 21% of homosexual men and 10% of women. Penicillin and tetracycline were effective in treatment, but spectomycin failed.¹³⁹ Allergic reaction to penicillin followed in 0.66% of 27,673 patients.¹⁴⁰

Endocarditis

The mortality rate from staphylococcal endocarditis remains about the same, 14% in patients less than 60 years old and in 71% of the rest. Classic signs often are absent.¹⁴¹ Staphylococcal and streptococcal infections developed in twenty-eight heroin addicts.¹⁴² Vancomycin-streptomycin was effective in treating enterococcal endocarditis.¹⁴³ Whether 'synergism' is responsible is doubtful. Penicillin-gentamicin therapy cured four other patients with enterococcal endocarditis and two with meningitis.¹⁴⁴ Seven endocardial infections with *Lactobacillus plantarum* are on record. One instance followed

dental scraping.¹⁴⁵ The mortality rate of Gram-negative anaerobic bacillary infection was 46%. In one instance, 18 months of therapy with tetracycline-erythromycin failed,¹⁴⁶ as one would expect. Fatal candida endocarditis and systemic involvement followed injury to the tricuspid valve by catheter insertion and multiple antimicrobial therapy.¹⁴⁷

Miscellaneous infections

Mycoplasmas

Among sixty-two male college students with acute urethritis, gonococci probably were causal in only eight and T-strain mycoplasma in forty-six. Antimicrobial therapy cleared symptoms in the latter.¹⁴⁸ Tetracycline had no obvious beneficial effect in five children with encephalitis and radiculitis.¹⁴⁹ Genital mycoplasma salpingitis, post-partum fever and low birth-rate as a result of infection were reviewed.¹⁵⁰ T-strain mycoplasma was a colonizer more often in unmarried than in married women.¹⁵¹ It commonly was present in the genital tract of sexually active normal men probably as a commensal.¹⁵² The problem was discussed in the *Journal of the American Medical Association* of October 15, 1973. *M. pneumoniae* vaccine protected 87% of vaccinees against infection and 66% against pneumonia.¹⁵³

Rickettsioses

More than 98% of cases of tick typhus or tick-borne pox (Rocky Mountain spotted fever) occur elsewhere than in the region named. In southeastern U.S.A., the incidence increased from 194 cases in 1959 to 432 in 1971. Antimicrobial treatment of victims is easier to accomplish than the elimination of ticks.¹⁵⁴ Colorado tick fever may be mistaken for tick typhus.¹⁵⁵

Mycoses

Histoplasmosis in thirty-two children posed differential diagnostic problems. Fever, malaise, chest pain, and weight-loss occurred. Pneumonia was present in eleven, nineteen had lymphadenopathy and ten had hepato- or splenomegaly.¹⁵⁶ A man had systemic disease and a penile lesion worsened by steroid therapy. He apparently transmitted the infection to his wife.¹⁵⁷ Second attacks occurred in six persons, two with pulmonary infiltrates. As in tuberculosis, persons whose skin reacts to the dermal test are at risk.¹⁵⁸ During 2 weeks, airborne dust from a bird roost, as on previous occasions, infected 40% of persons in a school.¹⁵⁹

Inhaled contaminated cotton dust probably caused fatal Coccidioidomycosis in a mill worker in Georgia, a nonendemic region.¹⁶⁰ Twenty-eight of eighty patients in whom *Cryptococcus neoformans* was present in sputum had pulmonary disease caused by that

agent. The majority of patients recovered without antimicrobial therapy.¹⁶¹

Others

Entamoeba histolytica eats inflammatory cells as well as erythrocytes. Leukocytes therefore are not defensive against invasion.¹⁶² Therapy with combined emetine, chloroquine, metronidazole and tetracycline reduced the mortality rate of amoebic hepatic abscess to 2.3%. Aspiration was needed only in 17% of 2322 patients.¹⁶³

Despite chloroquine prophylaxis, six of eighty Danes who visited India had malaria 7–9 months later.¹⁶⁴

The cat may be the definitive host of *Toxoplasma gondii*. Other small animals and birds are intermediate hosts.¹⁶⁵ According to another view, ingestion of raw meat exceeded the importance of contact with animals, particularly cats, as a cause of toxoplasmosis, the cardinal evidence of which was lymphadenopathy.¹⁶⁶

New artificial lakes in Africa greatly increase the incidence of schistosomiasis by creating suitable milieus for snails.¹⁶⁷ The discovery of salmonellae as parasites of schistosomes may account for the frequency of salmonellosis in patients with schistosomiasis.¹⁶⁸ Cutaneous leishmaniasis appeared in ten marines who had served in Panama.¹⁶⁹ Leptospirosis in 150 military personnel in South Vietnam exhibited fever alone. Without serological tests, forty-four cases would have been unrecognized as such. Mild cases are commoner than is generally believed.¹⁷⁰

Antimicrobial drugs

According to the Director of the U.S. Food and Drug Administration, antimicrobial drugs, despite their great value, kill more than 30,000 persons a year. 'Over-the-counter' sales total about \$1 billion annually.¹⁷¹

As I continue to do, Kunin called attention to the over-use, especially of expensive drugs. In one hospital, therapy was not needed, or the choice of the drug was wrong, for 51.5% of patients,¹⁷² and in another report 60% of treated patients had no evidence of infection.¹⁷¹ Similar critique appeared elsewhere.¹⁷³ In another study, no consistent logic appeared for ordering bacteriological studies, nor were their results heeded. Surprisingly, in one-third of cases, cultures were made while patients were receiving antimicrobials.¹⁷⁴ About 2,400,000 kg (2640 tons) of antimicrobial drugs made in 1972 would suffice to treat two illnesses for every person in the U.S.A. Production of antimicrobials increased 320% and their cost 130% between 1960 and 1970.¹⁷²

Large amounts in the blood of injected antimicrobials do not ensure sufficient amounts in infected tissues where they are needed. In interstitial

spaces, the amounts are lower but persist longer.¹⁷⁵ Intravenously injected antimicrobials, as with other substances, increased the amount of serum fibrinogen which may be mistaken for evidence of infection.¹⁷⁶ Question concerns the value of topical application, especially of intrathecal injection for meningitis, and how much, if any, of the drug enters the meninges. Although injected drugs entered brain abscesses in effective amounts, disease persisted in six patients until pus was aspirated.¹⁷⁷ Penicillin, penicillin/sulphasoxazole, erythromycin and ampicillin gave equally good results in treating acute otitis media in children.¹⁷⁸

A guide for the use of antimicrobics for patients with impaired renal function was prepared.¹⁷⁹ Large doses of penicillin may arrest marrow cells and cause pancytopenia.¹⁸⁰ Among 13 brands of penicillins for oral application and 14 brands of ampicillin, inexpensive penicillin V is the drug of choice for treating non-serious Gram-positive coccal infections.¹⁸¹

Carbenicillin, an expensive penicillin that cross-reacts with others, should be used only for treating pseudomonal, enterobacterial and indole-positive proteus infections so as to restrict the emergence of resistant strains.¹⁸² The same applies to clindamycin for anaerobic infections.¹⁸³ Carbenicillin caused granulocytopenia in two patients.¹⁸⁴ Clindamycin, at present, is the drug of choice for treating bacteroides infection.¹⁸⁵ In several instances, the drug has caused colitis¹⁸⁶ and mucocutaneous fever.¹⁸⁷ Its effect on acne is doubtful.¹⁸⁸ Cephalexin probably will be of most value for treating urinary tract infections.¹⁸⁹ Calf's liver contains an antimicrobial substance against Gram-negative bacilli.¹⁹⁰

As usual many 'new' agents are available including Rosamycin, Cefoxitin, Vibramycin, Minocin, Cloxyquin, Cephacetrile, Cefazolin, Ticarcillin, Cotrimoxazole, Cuprimixin, and Isoconazole.

Iatrogenic infections

The increasing incidence of aspergillosis, toxoplasmosis and endocarditis during neoplastic diseases in relation to immunosuppressive therapy was discussed in several papers in the January 1973 *American Journal of Medicine*. Salmonella sepsis occurred in seven patients receiving immunosuppressive therapy.¹⁹¹ Several drugs induced hepatitis; methyl dopa, for one, caused death according to two papers in the March issue of the *Journal of Infectious Diseases*. Osteomyelitis appeared in five patients receiving haemodialysis and corticosteroid therapy.¹⁹² Antimicrobial therapy rarely prevents or cures infection in immunologically suppressed patients. The drugs used were regarded as 'drugs of fear'.¹⁷² BCG therapy for cancer occasionally causes severe illness and tuberculous infection.¹⁹³

Infections during other forms of therapy. Meningitis developed in five patients under treatment with cephalothin.¹⁹⁴ Prior antimicrobial therapy was a factor in causing episodes of Gram-negative bacillary or mycotic pneumonias in sixty-eight leukaemic patients, and a death-rate of 65%.¹⁹⁵ Similar circumstances pertained to seven cases of salmonella sepsis¹⁹¹ after platelet transfusions. Cytomegalovirus infections and pneumonia followed marrow transplantation in twenty of fifty patients, with fourteen deaths.¹⁹⁶ The incidence of hepatitis during isoniazid therapy was 1%. Three of fourteen patients died.¹⁹⁷ Antimicrobial prophylaxis not only failed to prevent postoperative wound infections but induced infections with drug-resistant bacteria.¹⁹⁸

Mechanical factors. Transient bacteraemia with commensal bacteria followed nasotracheal intubation in 12% of children, and in 65% after exodontia.¹⁹⁹ Sigmoidoscopy induced similar bacteraemia in 9% of instrumented patients.²⁰⁰ A fatal case of clostridial sepsis followed a barium enema.²⁰¹ Among 122 patients receiving nutrition parenterally, tube-tips harbouring *Candida* or staphylococci caused bacteraemia in five. Fourteen others had Gram-negative bacillary or enterococcal bacteraemia of other origin.²⁰² Methods of control were outlined.²⁰³ Vials of multiviral vaccine probably contaminated with *Myco. chelonii* caused recurrent abscesses in forty-seven children.²⁰⁴

Nosocomial infections

Twenty-six cases of pseudomonal pneumonia in patients with serious underlying disease were hospital-acquired. Despite antimicrobial therapy, twenty-one died.²⁰⁵ In a review of 224 pneumonias, one-third were caused by Gram-negative bacilli, but specific causes could not be determined in 44%. The death-rate was 50% with or without the administration of gentamicin. Disseminated mycotic superinfection followed in seventeen treated patients.²⁰⁶ Pseudomonal osteomyelitis and arthritis involved four of five patients, three of whom were receiving antimicrobics.²⁰⁷ Serratia caused destructive arthritis in three debilitated patients.²⁰⁸ Opportunistic streptococcal infections occurred in forty-four patients of whom twenty-four had neoplastic disease.²⁰⁹ Staphylococci caused endocarditis in twenty-eight heroin addicts, three with panophthalmitis, and five died.²¹⁰ More than simple person-to-person spread accounts for nosocomial epidemics of salmonellosis. A hospital environment was extensively contaminated by eight infected patients, but others escaped infection. Spread occurs chiefly by contaminated food and drink.²¹¹ Within a day, ECHO virus infected four infants in an intensive-care unit.²¹² A patient with Lassa fever in a Liberian hospital spread the infection to three other patients and seven staff members

of whom four died. Eight others probably were inapparently affected as described in two papers in the November *American Journal of Tropical Medicine and Hygiene*. The mode of contagion was undetermined. Knowledge of iatrogenic^{213, 214} and nosocomial²¹⁵ infections was summarized.

Miscellaneous

Immunity

Two articles and an editorial in the April 1973 *Annals of Internal Medicine* indicate that a defective cellular immune response may result from chemotactic dysfunction of monocytes. The immunoglobulins may be normal. Administration of a transfer factor may restore immune responsiveness in candidiasis. The transfer factor, a dialysable leucocytic extract, may soon be available for the treatment of infectious diseases when there is a defect in cell-mediated immunity or anergy to one or more specific antigens.²¹⁶ Knowledge of the transfer factor was summarized editorially in *Lancet*, ii, 79, 1973. The importance of immunoglobulins A, D, E, G and M, and the differences between B and T lymphocytes involved in immune reactions were outlined.²¹⁷ Marrow transplants may restore immunity.²¹⁸ Deficient antibody, humoral and cellular activity are not alone responsible for poor defence against infections. A nurse with agammaglobulinaemia and lymphopenia had no infections for 14 years. Her serum had normal opsonizing ability.²¹⁹

Follow-up study of seventy-four women entering hospitals for pyelonephritis between 1950 and 1960 disclosed repeated episodes within 3 years in twenty-nine (40%) and within 6 months in sixteen (23%). Hypertension affected ten, but most were in good health.²²⁰ Practical aspects of urinary tract infections were summarized.²²¹

Among seventy military personnel in Vietnam with chronic and recurrent diarrhoea, *Strongyloides* or *Giardia* were present in twenty-five. Favourable responses to appropriate drugs occurred.²²² Question often arises if *Lamblia* grow as commensals in abnormal tissue or are pathogenic.

Pets as sources of infection of man and diseases they transmit are listed respectively as follows: dogs or cats—visceral or cutaneous *larva migrans*, pasteurellosis, leptospirosis, cat-scratch fever, toxoplasmosis; birds—psittacosis, ptilosis; turtles and snakes—salmonellosis; monkeys—measles, arboviruses, amoebae and others; raccoons and dogs—rabies.²²³

For diagnostic purpose, gallium-67 injected intravenously localizes in septic focal lesions in various areas detected by gamma camera scintiphography.²²⁴

The American Type Culture Collection in Rockville, Md., preserves 16,000 strains of microbes for

distribution to investigators.²²⁵ For longer, but non-viable preservation, precambrian rocks in the Grand Canyon contain fossilized spheroid and filamentous microbes.²²⁶

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