INFECTIOUS DISEASES

Annual Review of Significant Publications

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AS USUAL in recent years, interest in antimicrobics and in viral infections predominates. A number of new antimicrobics, not all of which are better than the ones at hand, are under clinical trial. Unwanted side-effects of antimicrobial therapy, in addition to known ones, were reported on. Surprisingly, some pneumococci became resistant to tetracycline. Several chemical compounds have an antiviral and an antitrichinal action. Fewer papers about respiroviruses were published than in the previous year, but knowledge of the clinical and epidemiologic features of the specific infections was amplified. The relation of viruses to cancer received much attention. Further doubt was cast on the value of vaccination in preventing typhoid and cholera; on the value of antitoxin in preventing and treating tetanus, and on the effect of antitoxin in the treatment of botulism. Increasing attention was focused on pathogenic acid-fast bacilli that differ from *M. tuberculosis*; on microbes of the *Mima-Herellea* group; and on the rising incidence of venereal infections.

Antimicrobics

Despite advice available in text-books, medical journals and at conferences, the unnecessary use of antimicrobial agents continues. Criticism in regard to the selection of drugs, overreliance on sensitivity tests, combinations of drugs and attempted prophylaxis, and a discussion of the indications for the use of drugs and of antimicrobial-resistance appeared in Jawetz's paper that should be widely read and heeded¹.

The U.S. Food and Drug Administration on the advice of a panel of authorities² wisely proposed a ban on commercially prepared combinations of a variety of drugs that include antimicrobics for the treatment of colds. Unfortunately, the proposal was rejected by the Pharmaceutical Manufacturers Association, the American Medical Association³ and by many physicians as undesired interference with the

practice of Medicine⁴. Apparently, many physicians still are uninformed about the uselessness and dangers of antimicrobial therapy or prophylaxis against viral infections of the respiratory tract, and about the disadvantages of polypharmacy. Topical application of antimicrobics in general is condemned as unnecessary, useless, and dangerous as causing sensitization. Some agents, however, such as neomycin are effective and relatively safe when used in deodorant preparations or for dermal⁵ and ocular infections.

When treating diseases amenable to antimicrobics, it is best to give the smallest amount of a single antimicrobial that will suppress or kill the invaders. Treatment of most infections with multiple antimicrobics adds the risk of superinfection, and excessive amounts or prolonged use of a single drug may be equally dangerous. The rate of superinfection was 0.0 per cent when one to two million units of penicillin were injected daily, but was 28 per cent after 10 to 20 million units. Semisynthetic penicillins, for unknown reasons, favored more superinfections than penicillin G⁶. Large doses of tetracyclines or chloramphenicol similarly increased the incidence of superinfections.

Suggestion was made to treat osteomyelitis, purulent arthritis and fulminating infections of soft tissue of the extremities caused by antimicrobial-resistant pathogens by perfusing relatively toxic but effective bacitracin into the affected part hoping to obviate systemic toxicity⁷. Tetracycline injected intra-arterially was used for the same reason⁸.

As stated at a conference, streptomycin failed to prevent infection in 18 of 20 volunteers when given one to 24 hours after inoculation with *P. tularensis*. Chloramphenicol was given to four volunteers inoculated with *S. typhosa* 24 hours later and for seven days. Typhoid developed after a week in two, but not in two treated for 28 days. In the latter, typhoid

antibody failed to appear. Antimicrobics given prophylactically reduced the incidence of bacteriuria and bacteraemia during genito-urinary surgery. None of 43 patients treated prior to cardiac surgery and for four to eleven days afterward had any infection⁹.

Broad-Spectrum Antimicrobics. Chloramphenicol, because of its possible hæmotoxic effect, should not be used when penicillin, tetracyclines or erythromycin are effective. There is no justification for giving chloramphenicol prophylactically to surgical patients, or for viral and *H. influenzae* infections. The agent is specific for typhoid and with few exceptions should be restricted to treatment of that disease. It is less effective against other salmonellas, and is inferior to the newer penicillins for staphylococcoses¹⁰. Before chloramphenicol was used extensively in a closed population, one per cent of colon bacilli were resistant. After 36 hours of treatment, 76 per cent of strains in treated patients and eight per cent of those in untreated ones were resistant⁹.

Pneumococci remain sensitive to penicillin, but surprisingly, some have become resistant to tetracycline¹¹. Infection with tetracycline-resistant Type 7 cocci caused pneumonia in ten patients in a hospital; five of these were treated successfully with other effective drugs and five died¹². Resistant Types 6 and 14 pneumococci caused pneumonia in patients elsewhere; in one while the drug was being given¹³. With this new knowledge, care must be taken if tetracycline is used routinely for the treatment of pneumonias of undetermined cause. Strains of hemolytic streptococci collected in 1930 were sensitive to tetracycline, but 20 per cent of strains isolated in 1961 were resistant¹⁴.

New Antimicrobics

Newly introduced agents, such as Cephalothin, Gentamycin, Lincomycin, ones still named by number, and other matters were considered in 176 papers at a conference in October, 1963⁹.

Semisynthetic Penicillins. The relative value of old and of newly synthesized penicillins was reviewed. They should be given orally whenever possible, but never applied topically in the form of lozenges, ointments or aerosols¹⁵. Ampicillin and nafcillin are active *in vitro* against a variety of bacteria¹⁶. If clinical trials are successful, they eventually may replace other broad-spectrum drugs. Ampicillin was said to have rid three of seven carriers of *Salmonella*¹⁷. Excepting *Salmonella* and *Proteus*, a variety of other gram-negative bacilli inactivated penicillin G, methicillin, oxacillin and ampicillin¹⁸. Ampicillin

was effective in the initial treatment of urinary tract infections with *Proteus*. For *Esch. coli* infections it was less effective than cycloserine, and the majority of klebsiellas resisted the drug. It probably is no better than other agents for acute salmonellosis. Untoward effects occurred in 19 per cent of patients and cross-sensitization probably happens with all penicillins¹⁹. Ampicillin is bactericidal for pneumococci, hæmolytic streptococci, staphylococci and enterococci, whereas tetracycline and chloramphenicol are bacteriostatic. Ampicillin was effective against *Esch. coli* and *P. mirabilis*, but less so against other gram-negative bacilli than agents already in use²⁰. Nafcillin, cephalothin, cloxacillin and oxacillin were superior to methicillin against penicillin-resistant staphylococci²¹. Methicillin and oxacillin failed to cure two patients with staphylococcal endocarditis²². Sodium diphenicillin was said to be eight times as active as methicillin²³. Penicillin N, formerly called cephalosporin N, had greater activity against gram-negative bacilli than penicillin G and was successful in controlling infections with *Proteus* and *Salmonella*²⁴. Ancillin was effective against staphylococci *in vitro*, but not particularly effective in the treatment of severe staphylococcal infections²⁵. It was superior to methicillin, but as active as oxacillin and nafcillin²⁶. Obviously, final evaluation of these newer penicillins awaits further trial.

Penicilloyl-polylysine, a nonimmunogenic compound, was said to be a reliable agent to detect sensitivity to penicillin by the skin-test. A strong dermal reaction indicated a 9-fold greater risk of a systemic reaction to penicillin than a negative reaction²⁷.

Other New Drugs. The colistins were recommended for use against infections caused by *Pseudomonas*. They are less effective against *Esch. coli*, *Aerobacter aerogenes*, *Salmonella*, *Shigella*, *Hemophilus* and *Brucella* and not at all against *Proteus*²⁸. Colistin and polymyxin E are identical²⁹.

Gentamycin was bactericidal and more active against *Esch. coli*, *Pseudomonas*, *Klebsiella* and *Proteus* than other antimicrobics, especially for urinary-tract infections. A small amount entered the blood and it may be weakly effective for septicæmia, pneumonia and meningitis. Resistance to it developed *in vitro*³⁰. Gentamycin eliminated shigellas from the urine and stool in urinary tract infections³¹. Rolitetracycline was said to be less irritant than tetracycline and more suitable for intravenous or intramuscular therapy³².

Griseofulvin should be used only for the treatment of proved superficial mycotic infections. Noninfectious dermal lesions are not affected and infections with *Candida albicans* may be made worse by therapy³³. Ethionamide, derived from isonicotinic acid was active against *M.tuberculosis*, has toxic side-effects and induces bacterial resistance rapidly³⁴. Metronidazole (Flagyl) cured 203 of 300 patients with vaginal trichomoniasis without adverse reaction, but should not be given during pregnancy or to uninfected husbands³⁵.

Cyclopin, netropsin and helenin are the only agents of mycotic origin that experimentally are active against viruses³⁶. Stoxil, a brand of idoxiuridine, is available in an ointment for the treatment of herpes simplex keratitis; its value has been questioned.

Unwanted Effects. Tetracyclines cause a variety of undesirable effects. They may discolor the nails³⁷ and teeth, inhibit odontogenesis³⁸ and when given in the last trimester of pregnancy or to premature infants, depress skeletal growth³⁹. Doses of 2.4 to 6 g. per day for pyelonephritis caused fatal hepatic disease in six pregnant women⁴⁰. Tetracycline enhanced the invasiveness of tetracycline-resistant staphylococci in guinea-pigs⁴¹. Kanamycin, when injected intravenously, in one instance, caused cardiac and respiratory arrest, fortunately relieved by neostigmine⁴². Amphotericin B caused nephrotoxic tubular injury and deposition of calcium⁴³. After an anaphylactic shock from penicillin, evidence of cerebral injury persisted in two adult patients, for whom the use of penicillin was not indicated in the first place⁴⁴. In spite of danger, potentially toxic kanamycin, polymyxin B and colistin were used successfully in treating renal infections in uremic patients⁴⁵. Disseminated candidiasis caused death of 26 of 29 patients who had been treated with antimicrobics or corticosteroids before the onset of mycosemia⁴⁶.

Among surgical patients, infections occurred in 25 per cent of those who were treated prophylactically with antimicrobics as compared with 8.7 per cent in untreated patients. The incidence of staphylococcal infections was 12 per cent in treated patients and 3.2 per cent in controls. In general, the incidence of superinfections with resistant bacteria was three times higher in treated patients. On the other hand, potential infection with *Clostridia* should be prevented by penicillin G or tetracycline, but treatment should not be continued for more than four days⁴⁷.

Viral Respiratory Tract Infections

Further study allowed a nosologic arrangement of various of the commonest of all minor infections. About 70 viruses are implicated. Infants and children generally are affected more often and more severely than adults, who are partly immune from previous infections. Adeno-myxo-, rhino (ERC)-, REO-, or respirosyncytial (RS)-viral infections may occur in epidemic form separately⁴⁸ or together in various combinations in a community^{49,50}. Two viruses may cause disease in a person and antibodies against more than one may appear in the blood. The cause could not be determined in one-third of adult patients⁵¹, indicating the existence of unknown viruses awaiting recognition. Similar features characterize epidemics among infants and children^{49,52}. No specific therapy has been discovered.

Viral infections caused 50 per cent of exacerbations of illness in victims of chronic bronchitis. RS virus accounted for 17 per cent; myxoviruses and adenoviruses fewer⁵³. Similar findings were noted in Scotland^{53a}. The excessive number of vaccines injected prophylactically in newly inducted recruits against a variety of other diseases probably explained the higher incidence of acute respiratory tract infections among them as compared with civilians. Infections were reduced by 20 per cent when the immunizing procedures were postponed⁵⁴.

Polyvalent vaccines prepared with antigens of several myxo- and adenoviruses failed to prevent infections in children. More respiratory tract infections occurred in vaccinated children than in control ones⁵².

Rhinoviruses caused the common cold, but less severely than adenoviruses in adults⁵⁵. Children were less often infected⁵⁶. Most of them had mild disease, but a few bronchitis, croup or pneumonia⁵⁷. Inoculated volunteers who possessed specific antibody or had been vaccinated were less susceptible to experimental infection than others⁵⁸.

Respiratory-Syncytial (RS) Virus. Epidemics occurred in winter. Infants and children were affected more often and more seriously than adults. Infection occurred even in those who possessed specific antibody. As in other viral diseases the clinical spectrum ranged from inapparent infection to rare fatal pneumonia^{48,59}. Prophylaxis fails unless vaccine contains antigens specific for several types of RS virus⁶⁰.

Reoviruses Types 1, 2 and 3 seldom cause overt disease. A few cases of mild meningoence-

phalitis, dermal eruption and one of pneumonia were described^{60a}.

Influenza. The annual incidence of influenza among college students during a nine-year-period varied from 5 per cent to 63 per cent. The spectrum of disease ranged from the symptoms of the common cold to viral pneumonia. Paradoxically, more students who had influenza A2 in 1957, or had been vaccinated, were infected in 1960 than were those previously unexposed to the antigen⁶¹.

World-wide outbreaks of influenza after 1961 were caused by A2 virus that had changed antigenically since 1957. Although a contemporary A2 variant was added to vaccine used in 1963-64⁶², and 42 million injections were given, there was little or no evidence of its prophylactic value⁶³. Question was raised whether or not general vaccination should be recommended "without better scientific evidence to justify the major costs to the public than are entailed"⁶⁴. Pretreatment with a new agent (Dupont Exp.—105) reduced serologic evidence of influenza in 30 per cent to 50 per cent of subjects.

Encephalitis lethargica during influenza in 1918-19 rose in incidence at the time, declined after 1920 and has not complicated subsequent influenza infections. Parkinson's disease as a sequel became prominent after 1930⁶⁵.

Parainfluenza viruses caused 18 per cent of all acute respiratory tract infections in general practice. Croup was the commonest clinical manifestation in younger children. Older children and adults had milder illness with cough and hoarseness or influenza-like disease^{65a}.

ECHO viruses seldom attack the respiratory tract. In one instance, ECHO virus, Type 25 was the cause⁶⁶.

Respiratory tract viruses in general were discussed at a symposium, the report of which appeared in two places⁶⁷. Crystalline aggregates of influenza, Coxsackie, Columbia SK and Poliovirus were observed in neutrophil cells. These cells may provide a site for the growth of viruses, favour their hæmatogenous dissemination⁶⁸, as presumably occur in typhoid and tuberculosis, and explain the neutropenia of viral infections.

Viral Pneumonias. Little was added to knowledge excepting mention of the occurrence of viral pneumonia during epidemics of RS virus^{48,49}, parainfluenza, adenovirus⁴⁹ and rhinoviral infections⁵⁷. Adenovirus Type 4 caused 80 per cent of 88 pneumonias among recruits⁵⁰.

Mycoplasma Pneumoniae Pneumonia. Of importance is the extrication of *Mycoplasma pne-*

umoniae (Eaton agent) pneumonia that responds to tetracycline therapy, from the group of viral pneumonias that do not^{69,70,71}. The disease had occurred in 1938, but was confused then with other viral pneumonias⁷². Recent surveys indicated that from 5 per cent to 40 per cent of populations had been infected with *Myco.pneumoniae*^{69,70}. Adults seemed to be involved oftener than children. It caused ten per cent of pneumonias among recruits⁵⁰. Infection occurred in 23 of 42 antibody-free inoculated volunteers, three of whom had pneumonia and myringitis. An attenuated strain may serve as a vaccine⁷³. Several other species of *Mycoplasma*, including *Myco.pharyngis*, *salivarium* and *hominis* inhabit the pharynx as commensals, easily mistaken for *Myco.pneumoniae*^{73a}. In experimentally infected hamsters, *Myco.pneumoniae* localized primarily on the epithelium of large bronchi and persisted there for more than ten weeks^{73b}.

Picornia (entero-) Viruses

Coxsackie Viruses. Viruses of Group B, Types 2, 3, 4 and 5 were implicated in an epidemic among military personnel in the summer of 1960. Infection caused disease of different nature in different victims. Pleurodynia predominated. A few instances of encephalitis, encephalomyocarditis, herpangina, fever alone, diarrhoea, orchitis and pneumonia occurred⁷⁴. In an outbreak of 43 attacks with virus B5, adults had myalgia, pleurodynia or pericarditis; children had hepatomegaly, splenomegaly, dermal eruption, pharyngitis and pneumonia⁷⁵. Virus Group A, Type 21, caused symptoms of the common cold in inoculated volunteers whose blood at the time contained no specific antibody⁷⁶. Virus Group B, Type 2, caused a three-month summer epidemic involving 142 patients with the same gamut of complaints mentioned and in addition, orchitis and epididymitis, but not encephalitis. Virus was present in 34 inapparently infected household contact persons, and in 13 per cent of the population at risk, children especially⁷⁷. Group B, Type 5 virus caused acute enteritis followed by encephalitis in children⁷⁸. Group A, Type 16 virus caused fatal encephalomyocarditis in an infant⁷⁹. A maculopapular exanthem, urticaria and lymphadenopathy were caused by viruses B5 and A9^{80,81}. The viruses indeed are multi-tropic.

ECHO Viruses. A small epidemic of meningoencephalitis and paralysis was caused by a virus named "Giles" that together with Price virus, was classed as ECHO, Type 30 by the

Committee on Enteroviruses⁸². ECHO viruses Type 2⁸³ and 16 caused dermal eruptions⁸¹. A direct fluorescent-antibody staining method served to identify Coxsackie and ECHO viral infections rapidly⁸⁴.

Two kinds of viruses unrelated to known ones were studied. One group of "Caldwell" enteroviruses, was isolated from children with lymphocytic meningitis in Kansas, Denmark and elsewhere⁸⁵. Another called "Frater" obtained from Canadian and Scottish children with meningitis probably is a member of the ECHO group⁸⁶.

Encephalopathy accompanied cat-scratch disease in two patients^{87,88}. The first case of encephalomyelitis caused by Apeu virus was described⁸⁹.

Adenoviral Infection. An ophthalmologist who had keratoconjunctivitis caused by adenovirus, Type 8, was the source of infection in 26 of his patients. An outbreak in a community affected 14 children and adults. The event would have been unnoticed except for the deliberate attempt to discover it. The disorder usually is named pink-eye. The virus seems to be endemic and its spread and invasiveness is favoured by poor sanitation and by primary bacterial infection⁹⁰. Adenovirus Type 12 was associated with, or was the cause of, familial outbreaks of a pertussis-like disease with high lymphocytosis⁹¹. Serologic evidence indicated a widespread distribution of Type 12 virus in England⁹². The oncogenic ability of Types 7 and 12 adenoviruses in experimentally inoculated animals raises apprehension if live viruses are used as vaccines.

Reovirus, Type 1 caused severe myocarditis in newborn mice^{91a}. Specific antibody for Reoviruses, Types 1, 2 and 3 exist in many animals, birds, fish and plants probably because they have characteristics in common with a variety of plant-insect viruses^{91b}.

Bats were infected experimentally with Japanese B and St. Louis viruses. They may serve as reservoirs of infection⁹³.

Viral Enteric Infection. An outbreak of viral dysentery occurred among students as usual. No virus was isolated nor did antibodies against known enteroviruses appear in the blood⁹⁴. Three unclassified RNA enteroviruses were recovered from stools of children with dysentery in Mexico. Antibody against two of the strains was present in the blood of persons in Mexico and the United States, suggesting that the infections were endemic and had occurred previously⁹⁵. Enteroviruses did not cause a significant number of diarrhoeal diseases in Texas. *Shigella*,

Salmonella or *Esch.coli* were isolated from 22 per cent of infants⁹⁶. In epizootic diarrhoea of mice, intracellular spherical bodies resembling viral particles were in the enteric epithelial cells⁹⁷.

Although enteropathogenic bacilli were isolated from 14 per cent of 1,000 infants with diarrhoea in Argentina, the cause was undetermined in the majority of cases. No viral studies were mentioned⁹⁸. The cause of "traveller's diarrhoea", common in Mexico, southern Europe and elsewhere, is unknown. According to clinical description⁹⁹, the disorder is identical to viral dysentery.

Poliomyelitis. Oral vaccines of three types of virus have been approved and licensed for general use by the U.S. Public Health Service. Viraemia followed oral vaccination in five of 14 persons who received Type 1 strain and in six of 13 with Type 2¹⁰⁰. Nasal and oral secretions of 19 of 124 persons in contact with patients contained poliovirus. The findings indicated the possibility of air-borne transmission¹⁰¹. Monkeys subjected to stress were more resistant to experimental infection than control animals¹⁰². Simian virus 40 no longer contaminates vaccine prepared by culture in monkey-renal cells. The virus was not carcinogenic in early vaccines¹⁰³.

Horstmann summarized knowledge about the epidemiology of poliomyelitis. If polioviruses are suppressed by vaccination, the possible emergence and spread of other pathogenic enteric viruses does not seem imminent¹⁰⁴.

Viral Hepatitis. More than 2,000 cases of viral hepatitis were reported in England, chiefly in children in 1960-61. The number was said to reflect a world-wide wave of incidence. Evidence of contact infection was noted, and air-borne transmission was considered possible¹⁰⁵ although it had never been proved.

Death from serum hepatitis was said to follow one of every 150 blood transfusions in persons more than 40 years old. The mortality-rate of hepatitis after transfusion in that age group was about 20 per cent. For prevention, a suggestion was made to inject gamma-globulin after each transfusion¹⁰⁶. The recommendation is impracticable; there is only limited evidence that serum hepatitis can be prevented by gamma-globulin and the supply is meagre. Better screening of donors and stopping the excessive use of transfusions are better preventive measures^{107, 108}.

Gamma-globulin was of value in preventing epidemic viral hepatitis. The incidence of infection was 0.1 per cent in soldiers who

received it and 1.1 per cent of untreated ones, a protection-rate of 91 per cent. Dosage of 0.04 ml/kg sufficed to maintain immunity for five months¹⁰⁹. Gamma-globulin seems to suppress, not prevent hepatitis^{109a}. As was shown before, strict bed-rest and special diet had but little effect on the speed of recovery¹¹⁰.

About 78 persons in contact with monkeys had hepatitis¹¹¹. The inference is obvious.

Measles

Live measles vaccine with human immune-globulin provided immunity against measles for more than two years¹¹². While gamma-globulin reduced the frequency of disease after antimeasles vaccination, it also impaired the antibody response. The injection first of dead, then of live virus and gamma-globulin may have advantage¹¹³. The reaction to the tuberculin skin-test was depressed during the incubation period of vaccine-induced measles and for 18 days afterward¹¹⁴. Vaccination has caused death in children with agammaglobulinemia. The prevention of measles will reduce the incidence of encephalitis and permanent cerebral injury which ranged from one in 400 to one in 1,000 cases with a death-rate of 11 per cent to 32 per cent^{114a}. Measles virus was isolated from the washed leucocytic fraction of blood of ten of eleven patients in the first 24 hours of the exanthem and of one of eight patients in the second 24 hours. The procedure may be of value in the isolation of other viruses¹¹⁵.

Rabies. The rabies problem was reviewed with regard to the use of vaccine and hyperimmune serum. The role of active immunization with vaccine is uncertain and inferior to that of antiserum if antiserum is administered within 24 hours after infection¹¹⁶. 26 of 86 cats inoculated with virus died, almost all with negri bodies in the brain and virus in the salivary glands. The glands were free of virus in three of eight cats with "dumb" rabies¹¹⁷. In a newspaper report, a man was infected by a bite from his rabid son.

Rubella is often confused with other exanthematic infections as discussed in three papers in the British Medical Journal of November 23rd, 1963. The virus was isolated from the throat and blood of patients. Second attacks occur, probably caused by different antigenic types of rubella virus. If different types exist, vaccine to be effective must contain several specific antigens. Encephalitis occurred in ten victims in the 1962 epidemic in Britain. The virus was similar antigenically to other English

and American strains¹¹⁸. Specific neutralizing antibody was found in 19 lots of commercial gamma-globulin in titers from 256 to 2,048. The titer in serum from convalescent patients was 4,096, and may persist for years¹¹⁹.

Smallpox. Variola in Tanganyika apparently is milder than classic smallpox and the causal virus differs from it and from alastrim¹²⁰. Vaccinia-immune-globulin prepared from the serum of adults recently vaccinated is available for use. It gives rapid immunity after known exposure to smallpox and may be of value in treatment of progressive vaccinia, eczema vaccinatum or optic infection¹²¹. Plague has also occurred recently in Tanganyika.

Vaccinia. Vaccination in the first trimester of pregnancy may infect the fetus, or induce premature labor or abortion^{122, 123}. A pox-virus was isolated from a milker's nodule and probably is the cause¹²⁴.

The first epidemic of dengue since 1953 in the Western hemisphere occurred in Puerto Rico and Jamaica.

Antiviral Chemicals. N-methylstan β -thio-semicarbarzone (methisazone) reportedly was successful in preventing smallpox in exposed persons. Three mild attacks occurred among 1,100 treated persons as compared with 78 cases and 12 deaths in control subjects. The effectiveness of the agent was said to exceed that of vaccination or the use of immune globulin¹²⁵. If the results are confirmed the method is the greatest advance against smallpox since the days of Jenner. The effect of the drug on other viral infections is under study.

Cytosine arabinose had antiviral activity in cell-cultures against the DNA viruses of herpes simplex and vaccinia, but not for RNA adenoviruses. It was more active than 5-iodo-2'-deoxyuridine (IUDR)¹²⁶. IUDR also prevented cytopathogenic effects of varicella-herpes zoster virus¹²⁷, but induced resistance of herpes virus to it¹²⁸. Virus-specific processes accompany the reproduction of picorna viruses and certain chemicals inhibit the mechanism. Specific chemical inhibition of the synthesis of viral nucleic acid may provide a means for the control of viral infections¹²⁸.

A virus-inhibiting substance against Sindbis virus was present in the pharyngeal washings of patients with influenza¹²⁹. No viruses could be detected in the female genital tract. A viral-inhibitor of obscure nature may be active¹³⁰, bringing to mind the lysozyme that Fleming found before his discovery of penicillin.

Viruses and Cancer. Knowledge of the relationship between viruses and cancer is

empirical. Virus-like particles present in neoplastic cells suggest an association, but the criteria needed to substantiate a causal relation are lacking. Further information may accrue from the study of nucleic acids and their infectiousness¹³¹. A major task is to assign functions to the many genes present in tumor-inducing viruses that contain either DNA or RNA. Some action may transform normal cells into malignant ones¹³². Viruses may continue to live in tumors in an altered state. Viral nucleic acid is present in some tumor cells in an integrated or extra-chromosomal state. It is possible that a virus-cell relationship may exist in tumors induced by viruses^{132a}. Inoculation of SV 40 virus in monkeys may incite tumors months later and these may disappear¹³³. The new terminology involved and the complexity of the problem is evident in this excerpt: "When a preparation containing the DNA of the bacteriophage ϕ X174 in its replicative form together with DNA from *Esch.coli* is treated with exonucleases, the replicative form retains its characteristic physical properties, while the bacterial DNA is degraded"¹³⁴.

Adenovirus, Type 12 inoculated by various routes caused transplantable sarcomas and death of newborn hamsters¹³⁵. The tumors were suppressed if animals were injected with 5-iododeoxyuridine within two hours of inoculation¹³⁶. Viruses 7 and 18 also are oncogenic. A wound-tumor virus of plants is similar in structure to ECHO virus Type 10 and shares a common antigen¹³⁷. A possible antigenic relationship of Reoviruses to plant-insect viruses was mentioned on a previous page.

Virus-like particles visualized by electron microscopy were described in lymphocytes from patients with acute leukemia by several observers^{138,139,140}. Whether they are "passenger viruses" or have an etiologic relation to leukemia is unknown. The occurrence of eight cases of leukemia among children in a small community suggested infection with a transmissible leukemogenic virus as the cause¹⁴¹.

Bacillary Infections

Tuberculosis. The hope of eradicating tuberculosis is dim. While recovery is said to happen in 95 per cent of properly treated new infections, tuberculosis still kills 10,000 victims annually in the United States. In 1961, 50,000 new active cases were found. There probably is a reservoir of about 300,000 victims with active infection, and 30 million healthy carriers who disseminate tubercle bacilli. Previously treated persons have a high relapse-rate and

are a major problem in eradicating the disease¹⁴². They developed chronic disease and died of tuberculosis about three times as often as untreated ones¹⁴³. According to Myers, the prognosis of primary infection in childhood is good, regardless of the intensity or lack of treatment. Before the antimicrobial era, between two and three per cent of infants had infection resulting in meningitis or miliary spread¹⁴⁴. Controversy persists as to the merit of the tuberculin skin-test versus skiagraphy in the "case-finding" procedure. The skin-test disclosed a prevalence-rate of three per thousand among infants in a low socio-economic area at a cost of about \$500 (£180) per active infection¹⁴⁵.

Reports of the ominous prevalence of drug-resistant tubercle bacilli vary greatly depending on the source of the bacilli and the procedures used to measure resistance. An estimated seven million persons harbor drug-resistant bacilli. Among 482 patients, 44 per cent with new infection and 67 per cent of those previously treated had tubercle bacilli resistant to one or more of the three antituberculous agents in use. Among bacilli isolated from 514 patients in Great Britain, 82 per cent were resistant to one or more of three drugs; 74 per cent to isoniazid, 63 per cent to streptomycin and 53 per cent to para-aminosalicylic acid¹⁴⁶.

According to two co-operative investigations published in the March, 1964, issue of the *American Review of Respiratory Disease*, there has been no significant increase of resistance in recent years. Among strains isolated from newly diagnosed untreated patients in 1961-62, less than 5 per cent resisted streptomycin, isoniazid and paraaminosalicylic acid. Primary resistance presumably depends upon the presence of naturally resistant bacilli in the microbic population. Further study obviously needed to determine the prevalence and danger of resistant bacilli and how to restrain their emergence.

In a critical evaluation, the effect of adjuvant corticosteroid therapy in hastening the healing of pulmonary tuberculosis was not proved¹⁴⁷. Ethionamide used with other drugs was effective in therapy¹⁴⁸.

A committee report outlined the procedure recommended for the application of isoniazid under various circumstances for the prevention of tuberculosis¹⁴⁹. The method apparently is good, but of unproved value. Even though isoniazid was said to have reduced the number of extrapulmonary complications by 80 per cent, Jensen in Denmark instead favours the

vaccination with BCG of all exposed tuberculin-negative children and hospital personnel. If vaccinal complications arise, treatment with isoniazid and PAS is indicated¹⁵⁰.

A British Committee studying the effects of vaccination for about nine years reported an incidence of tuberculosis in unvaccinated adults of 1.9 per 1,000, as compared with 0.4 for those vaccinated with BCG and 0.43 after vole vaccine¹⁵¹. On the other hand, over a 13-year period, among 531 vaccinated inmates in an institution, 12 developed tuberculosis and four died. Of 494 control subjects, eight became tuberculous and two died^{151a}. Apparently, the matter is unsettled.

Among 198 victims of tuberculous meningitis, 122 recovered and were well for 15 years, and 42 are slightly incapacitated. So favourable a rate of recovery has not been generally attained. The dubious procedure of daily intrathecal injections of antituberculous drugs and, surprisingly, of purified derivative of tuberculin was recommended for every patient¹⁵². Intrathecal therapy of any kind is dangerous and its value is unproved.

In fatal tuberculosis, the incidence of genitourinary infection declined from 21 per cent to 4.3 per cent partly owing to the antimicrobial control of military disease. Less than 20 per cent of caseous lesions had been diagnosed during life¹⁵³.

An accident akin to the 1930 BCG tragedy in Lübeck occurred. In Japan, 62 of 209 infants injected with contaminated pertussis vaccine were given tuberculosis¹⁵⁴. An infant with hypogammaglobulinemia died after vaccination with BCG. Widespread dissemination of BCG and *Pneumocystis carinii* pneumonia were found at necropsy¹⁵⁵.

Unclassified acid-fast bacteria, easily mistaken for *M. tuberculosis*, may be commensals, secondary invaders, or the cause of disease resembling tuberculosis called mycobacteriosis. Acid-fast bacilli in the sputum or elsewhere are morphologically alike and must be identified by special methods. An unclassified antimicrobial-resistant bacillus was present for years in a suspected tuberculous patient whose skin reacted positively to the PPD test. The patient eventually recovered¹⁵⁶. Victims of such infections should not be sent to tuberculosis sanatoria and should be not treated with antimicrobics. In a tuberculosis service of a hospital, about four per cent of patients had infection with a photochromogenic bacillus named *M. kansasii*. Antituberculosis drugs were relatively ineffective in therapy, and surgical

resection was not always successful¹⁵⁷. In another tuberculosis service, 32 patients with "atypical pulmonary tuberculosis" caused by mycobacteria were described. Photochromogenic bacilli of Group I were present in 13; non-photochromogens of Group III in 16; scotochromogens of Group II and "rapid growers" of Group IV in the rest¹⁵⁸. The microbes are regarded as "unclassified", yet they are classified, tentatively at least, into four groups. Variant forms of acid-fast bacilli derived from a prototype *M. tuberculosis* in my laboratory have some characteristics of these atypical forms. Descriptions of them will be published eventually.

Salmonella derby caused outbreaks of disease in 40 hospitals in Northeastern U.S. chiefly among patients whose resistance was impaired. About 50 per cent of persons from whom *Sal. derby* was isolated were asymptomatic. The source presumably was in raw or undercooked cracked eggs. Rigid enforcement of isolation procedures failed to restrain the spread of infection¹⁵⁹. The epidemiology of salmonellosis was the subject of a symposium¹⁶⁰.

Twenty-three cases of typhoid occurred among 175 persons in a camp in Pennsylvania in July, 1963¹⁶¹. An epidemic of typhoid involving 700 victims who had been vaccinated during previous months¹⁶² cast further doubt on the value of attempted immunization. *Salmonella paratyphi B, Type 5*, caused 52 infections in Manchester, England, in 1961. Most victims were young adults and the disease was of moderate severity. The physician in charge doubted the therapeutic value of chloramphenicol. Paromomycin failed to affect the outcome or reduce the carrier state¹⁶³. Ampicillin in large doses brought about recovery in 65 patients with paratyphoid B infection in three days, as compared with six days in 80 patients treated with chloramphenicol. The carrier-rate persisted in 41 per cent and 52 per cent respectively¹⁶⁴. The management of typhoid and its complications was reviewed by Woodward¹⁶⁵.

Esch. coli 0126:B16:NM caused diarrhoeal disease in 30 per cent of 383 infants and infected 18 per cent of family members and neighbors. It was present in the pharynx suggesting that air-borne transmission occurs¹⁶⁶.

During four years, 692 patients in a hospital had bacteraemia caused by gram-negative bacilli. In 24 per cent, the course was complicated by hypotension and shock, especially in elderly patients with infection of the urinary tract, diabetes or other chronic illness. The death-rate from bacteraemia alone was 20 per cent

and from bacteraemia and shock 82 per cent. Vasopressor therapy had little or no favourable effect. Corticosteroids were beneficial at times¹⁶⁷.

Cholera. The early loss of 365 mEq. of bicarbonate by diarrhoea accounted for the acidosis of cholera. Rapid restoration of fluid and electrolytes obviously is essential in treatment. Renal tubular necrosis may occur¹⁶⁹. *Vibrio El Tor* differs from *V. comma*. The disease in Southeast Asia in 1961 usually was sporadic and the death-rate low¹⁷⁰. Enteroviruses played no role in inciting cholera although Thai C18 virus was present in times¹⁷¹. The value of vaccination is doubtful. No definitive field study with comparable control procedure has yet been made. Evidence, however, suggests that vaccination against *El Tor* vibrios may be effective. Cholera is a unique disease characterized chiefly by increased permeability of the enteric mucosa and toxemia, but no fever or inflammation. Therapy with tetracycline was said to shorten the duration of cholera and eliminate vibrios from stools¹⁷³. The effects were similar to those reported in 1945 after the use of streptomycin which, like sulphonamides, proved to be of no value¹⁷⁴. One wonders if any conventional vaccine or bacteriophage will be successful in prevention¹⁷⁵ or treatment¹⁷⁶.

Tetanus. Views on the management of tetanus have changed. The incidence of death was no greater in victims who had been treated prophylactically with antitoxin after injury than in those who had not. A severe anaphylactoid reaction followed in five minutes after an intradermal skin-test with antitoxin¹⁷⁷. Prior immunization with toxoid and antimicrobial therapy are of value¹⁷⁸. Tetanus immune-human-globulin 250 units, injected intramuscularly at the time of injury gives protection without depressing the immunity evoked by toxoid¹⁷⁹.

Controlled studies in India failed to disclose a beneficial effect of antitetanus serotherapy. Considering its uncertain value and its disadvantages, its continued use was questioned. A physician, at present however, may be held legally responsible unless treatment with antiserum is administered, but also if an allergic reaction thereto ensues. Intrathecal injection of antiserum was condemned. The actual cost of treating a patient with tetanus was estimated at a minimum of \$2000 (£700). The money could be applied better to general immunization with toxoid¹⁸⁰.

Tetanus, like other infections, has a spectrum of graded degrees of severity. Inapparent, mild, severe, and fatal cases occur. In one study in

South America, 60 per cent of cases were benign and victims recovered spontaneously. Antitoxic serotherapy was of doubtful value. Thirty-six of 84 patients died. Modern methods of prophylaxis and treatment were described by Kloetzel¹⁸¹ and in Eckmann's monograph¹⁸².

Considering the presence of *Cl. tetani* as an enteric commensal in about five per cent of persons, it is surprising how seldom tetanus follows intestinal surgery. Tetanus occurred in a patient with an intestinal infarct. The bacilli passed through the intact wall and were demonstrated in the peritoneal exudate¹⁸³. *C. welchii* caused peritonitis after gastrectomy¹⁸⁴.

Twelve outbreaks of botulism accounted for 46 cases and 14 deaths in 1963¹⁸⁴. Contaminated smoked fish, liver paste, canned mushrooms and raw whale meat were the sources. Type E bacilli, of recent recognition, were found in canned tuna fish¹⁸⁵, salmon roe¹⁸⁶ and in white fish. Although there is no proof that antitoxic serum has therapeutic value, if used it should contain antibodies against the toxins of each of five types of bacilli. Toxoids may be of value in prevention. Attention to proper handling and sterilization of food is of more importance. The problem was discussed at a symposium¹⁸⁷.

Coccal Infections

Group A streptococci were present in the throat of 90 per cent of children with febrile pharyngitis. Cocci were absent in 90 per cent of those with mild afebrile pharyngitis and the antistreptolysin titer rose in only 4 per cent. About 50 per cent of children with two of three features of fever, exudate or pharyngitis had streptococci in the throat¹⁸⁸. Evidently, severe sore throat with fever usually is of streptococcal origin. Mild afebrile pharyngitis usually is caused by viruses and needs no antimicrobial therapy. In cervical adenitis of 34 children, hemolytic streptococci were present in 25, staphylococci in five, *M. tuberculosis* and a scotochromogenic tubercle bacillus in one each¹⁸⁹.

Rheumatic Fever. An eight-year study of the clinical behaviour of 441 victims of acute rheumatic fever confirmed some current views and refuted others. Many patients never suffered permanent cardiac injury. Cardiac disease, if present, may disappear, especially if rheumatic fever does not recur. Carditis developed insidiously and almost exclusively in patients without arthritis and often was not discovered. Prolongation of the PR interval in electrocardiograms was not a useful indic-

tion of severity in the acute phase nor a guide to prognosis. In 11 of 12 fatal cases, no evidence of active or recurrent acute rheumatic inflammation was found. Among 431 patients treated prophylactically, there were 48 recurrences; two in those who received benzathine penicillin; in 16 treated with sulfadiazine, and in 30 with oral penicillin¹⁹⁰.

Persistent fever in 60 adults with rheumatic cardiac disease was caused chiefly by pulmonary infarction. Rheumatic activity accounted for 20 per cent; pneumonia, chronic cardiac failure, endocarditis and pulmonary arteritis for the rest. Cardiac failure or pulmonary arteritis alone may cause fever¹⁹¹.

Russian investigators isolated adenoviruses and other viruses from the blood and myocardium of 36 patients¹⁹². Their relationship to rheumatic fever was not established. They may have been commensals or secondary invaders.

Current methods of the diagnosis, treatment and prevention of rheumatic fever were discussed in detail. The majority of sore throats are not caused by hæmolytic streptococci and routine therapy with penicillin is not recommended. If streptococci are causal, a single intramuscular injection of benzathine penicillin, 600,000 units for children, double the amount for adults, is recommended. There was no advantage in the repeated injection of other forms of penicillin¹⁹³.

Endocarditis. The prognosis for subacute endocarditis is better than for acute endocarditis is caused by pyogenic cocci that usually occurs in hearts previously uninjured and often is diagnosed too late¹⁹⁴. Antimicrobial therapy has greatly reduced the incidence of late rheumatic cardiac disease, of involvement of the mitral valve and of endocarditis caused by nonhemolytic streptococci. The incidence of acute endocarditis caused by other pathogens in previously normal hearts has increased¹⁹⁵. Among 85 cases, 17 infections were acquired in a hospital, chiefly in old persons with other postoperative infections. Nine were caused by staphylococci, three by gram-negative bacilli and the rest were of unknown origin¹⁹⁶. *Herellea* caused endocarditis in two patients¹⁹⁷. Victims of subacute bacterial endocarditis who are, or who become, sensitive to penicillin present therapeutic problems. The usual dermal test with penicillin is unreliable. Desensitization to penicillin seldom is successful and is dangerous. Antihistaminics rarely prevent or control reactions and there is no proof that corticosteroids are of value¹⁹⁸.

Staphylococci. Penicillin-resistant staphylococci thus far, have caused serious trouble chiefly in debilitated patients in hospitals. They invaded the home as well^{199, 200}, but gradually disappeared within five years^{200a}. A newly classified multiantimicrobial-resistant strain caused epidemics in six hospitals in 1962²⁰¹. The presence of a carrier-disseminator in a surgical operating suite, even though conventionally masked, gowned and shod is a hazard to patients. Air-borne cocci apparently caused infection in several patients. Staphylococci escape through the mesh of face-masks²⁰². The majority of 155 victims of staphylococcal enterocolitis had had abdominal surgery performed, and others were not operated upon. Most of them had been treated previously with penicillin or broad-spectrum agents. With the use of new bacteriophages, 93 per cent of strains were "typed"²⁰³.

Among a group of infants, the deliberate implantation of an attenuated staphylococcus of low virulence limited the invasion and spread of other strains of virulent staphylococci probably by a mechanism of interference. The principle might be of value if applied to other infections. The matter was presented in several papers in the June, 1963, American Journal of Diseases of Children and commented on editorially by Dubos²⁰⁴.

Among 175 strains of *Staphylococcus albus* obtained by blood-culture, 50 per cent resisted penicillin; 41 per cent ampicillin; 10 per cent methicillin; 5 per cent oxacillin and 2 per cent nafcillin. Among other albus strains, 60 per cent resisted chloramphenicol; 48 per cent tetracycline and 29 per cent erythromycin. These resistant cocci cause therapeutic difficulties. The development of resistance was ascribed to the presence of small numbers of inherently resistant cocci that supplanted sensitive ones²⁰⁵.

Meningitis. Meningococcal meningitis has been fairly well controlled excepting in Africa where epidemics still occur²⁰⁶. Some strains of Group B meningococci in England²⁰⁷ and in America²⁰⁸ have become resistant to sulphonamides. Prophylaxis with those drugs failed to reduce the carrier-rate. No evidence of resistance to penicillin has yet been reported. Sulphadiazine was successful in the treatment of chronic meningococcemia²⁰⁹.

Meningitis caused by a mixture of bacteria, viruses or fungi is serious, especially in young children. Mixed infection occurred in 20 of 534 cases. Therapy with broad-spectrum antimicrobics was successful in seven who recovered completely. Six others had neural sequels²¹⁰. About 25 per cent of children who recovered

from severe attacks of purulent meningitis had neural or neuropsychiatric sequelae²¹¹.

Cryptococcus neoformans meningitis may occur where pigeons abound. Forty-two cases were described of which 21 occurred in patients with other disease. Therapy with amphotericin B almost always caused improvement and treatment often had to be continued for several years. Relapse occurred in many after treatment stopped²¹². Pigeons and starlings are more important as sources of ornithosis and histoplasmosis than of cryptococcosis. A classification of the meningitides and their laboratory features and treatment were presented in detail²¹³.

Venereal Diseases

According to Moore, the alarming increase of syphilis since 1957 can be stemmed and the disease eradicated²¹⁴. To do so, the infection must be controlled epidemiologically. All victims should be reported to Health Officers, the chain of contacts promptly traced, the source detected and eliminated. Factors that impair the control of venereal diseases are the general decline of moral principles, the over-reliance on antimicrobics for prevention and cure, the increase of promiscuity when the chances of pregnancy are reduced by the use of hormones taken orally^{214a}, and the treatment of infections by private physicians instead of at official health agencies.

About 124,000 cases of all stages of syphilis were reported in the United States in 1962, the greatest number since 1957. Perhaps three-fourths of cases are not reported officially²¹⁴. Similar increased incidence of venereal infections took place in Britain²¹⁵. American private physicians treat more than three-fourths of all venereal diseases. A survey disclosed that only 11 per cent of primary and secondary cases, and three per cent of cases in the late stage of syphilis and only 11 per cent of gonorrheal infections were reported²¹⁶.

Gonorrhœa. Penicillin G was successful in combating gonococci sensitive to it, but failed when the cocci were more resistant. The coexistence of other penicillinase-producing bacteria also interfered with therapy²¹⁷. A patient with gonorrheal urethritis was treated with large doses of penicillin but urethritis persisted. Two weeks later arthralgia, fever, chills and a maculopapular eruption occurred. The spinal fluid was normal. The next day there was photophobia, headache and cloudy CSF contained gonococci²¹⁸. The patient probably had gonococcemia and it is possible that

spinal puncture incited meningeal invasion. A hæmorrhagic vesico-pustular eruption, arthralgia and fever were observed in 14 victims of gonococcemia. The dermal lesions probably were septic infarcts like those of meningococcemia²¹⁹. Men, regardless of possible immunity from prior urethritis, were experimentally infected by gonococci obtained from asymptomatic women who serve as reservoirs of the disease²²⁰.

Among 200 soldiers with urethritis, three were found to be infected with *N. catarrhalis* which, like the *Mima-Herellea* bacteria, cause infections mistaken for gonorrhea²²¹. Bacteria of the *Mima-Herellea* group have received increasing attention since 1942. They are commensals and were present on the skin of 25 per cent of normal persons²²². During 14 months, these gram-negative bacteria were present in 77 specimens sent to a laboratory. They caused bacteræmia, cellulitis, urethritis, arthritis, otitis, conjunctivitis, cholecystitis, urinary tract infections and pneumonia chiefly in debilitated and aged patients^{223, 224}. Because many physicians are unacquainted with these microbes, a scheme for their identification was outlined. They are sensitive to a number of antimicrobics²²⁴. It may be difficult to decide if mimas are the primary pathogens, secondary invaders or saprophytes.

Pasteurella multocida was isolated from six patients. Two had been bitten by cats, two by dogs and two had bronchiectasis²²⁵.

Histoplasmosis. *H. capsulatum* caused both severe acute and mild chronic meningitis. Five victims were described, and in some the characteristic evidence of infection was absent. Therapy with amphotericin B, caused remission in two²²⁶. Twenty-six cases of neural involvement in patients aged four months to 75 years old were reviewed²²⁷. Tests of immunity as regards dermal reactions and circulating antibody were of value in acute pulmonary histoplasmosis, but less so in disseminated disease²²⁸. Skin tests may increase the specific antibody titre for longer than six weeks²²⁹ and may cause diagnostic confusion. Therapy with amphotericin B is of value, but corticosteroids induce dissemination²³⁰. *H. capsulatum* found in bat guano in Malaya proved its existence in southeast Asia²³¹. Infection in man also had been observed in Indonesia.

Since I pointed out the clinical and pathologic similarities between sarcoidosis and histoplasmosis in a patient and the possible causal relation of the fungus²³², about 12 similar cir-

cumstances involving other mycoses were described²³³.

Coccidioidomycosis. The first evidence that *coccidioidomycosis* may be transmitted from person to person was described. The fungus growing in a plaster-cast on a patient with coccidioidal osteomyelitis infected six hospital attendants²³⁴. A worker in Georgia was infected by handling bales of cotton from an endemic area in California²³⁵. Monkey to monkey transmission occurred²³⁶. Dermal lesions usually are manifestations of systemic dissemination. A case of primary infection of the skin appeared on the foot as the result of a puncture wound four weeks before. A chancre with nodular lymphangitis and suppurative inguinal lymphadenopathy were described. The lesions healed in three months without antimicrobial therapy²³⁷. Six other instances of primary dermal infection were observed; two in presumably immune persons^{237a}.

Trichinosis occurred in 60 of 117 persons who ate ham salad in a hospital. The incubation period ranged from 9 to 35 days. A rise in the titer of the trichinal flocculation test was helpful in diagnosis. The skin-test gave a positive result in only 46 per cent of cases. The degree of eosinophilia correlated well with the severity of symptoms²³⁸. Infected bear meat caused outbreaks of trichinosis in Alaska. The skin-test made with a properly prepared antigen was superior as an aid in diagnosis to commercially available ones²³⁹. Two patients with trichinosis were said to be cured with thiabendazole, a new broad-spectrum anthelmintic²⁴⁰.

Malaria. Malaria suppressed by therapy may appear as overt disease years afterwards. Vivax infections relapsed 6 to 14 months after treatment ceased and ovale malaria after four years. Quartan plasmodia may remain latent for 20 years²⁴¹. Quartan malaria occurred in a woman in Pennsylvania who had never been in an endemic area nor received a blood-transfusion. The source was a mystery²⁴².

The current perspective of malaria, specific antibody determined by fluorescence, cross-reactions and other aspects were discussed at a symposium published in the *Journal of the American Medical Association* of June 15, 22 and 29, 1963. In a panel discussion, the cultivation of plasmodia, antigenic features and vaccine prophylaxis were considered²⁴³.

Miscellaneous

Sixteen years after infection with *Wuchereria bancrofti*, a skin-test with the antigen gave a

positive reaction in 20 of 25 military men. Minor degrees of lymphatic obstruction and increased size of their affected limbs persisted in 24. Single infections did not lead to elephantiasis²⁴⁴. Autochthonous dirofilariar infections were observed in 13 patients in the United States²⁴⁵.

A newly recognized infection of minks apparently was transmitted to a man who raised the animals. At necropsy, peculiar lesions resembling those of myeloma were described²⁴⁶.

As a result of rapid global travel, the question "unde venis?"²⁴⁷ is important for the diagnosis of unexpected exotic diseases. Travellers visiting the American Southwest may contact coccidioidomycosis, as happened at one time to the late Professor John Fulton; the Midwest, histoplasmosis; and the Northwest, Rocky Mountain spotted fever. Elsewhere in the world dengue, hemorrhagic fevers, yellow fever, smallpox, amebic or bacillary dysentery, cholera, plague, leishmaniasis, and malaria are endemic. Bathers may acquire schistosomiasis²⁴⁸. Fungi were present in the deep ice of the Antarctic. Whether they were endemic or were seeded there by explorers is unknown²⁴⁹. Three scientists infected with Bolivian hemorrhagic fever recovered²⁵⁰. The hemorrhagic fevers of Argentina and Trinidad probably are identical, but the virus is unrelated to other arbo viruses. Clinically, the infection resembles the hemorrhagic fevers of Asia²⁵¹.

Listeriosis apparently has increased in incidence or is recognized oftener in Germany where about 100 cases were observed^{252, 253}. *L.monocytogenes* may be commensal or may cause disease with a variety of visceral and neural symptoms. The pathogenesis of leprosy was the subject of a study-group²⁵⁴.

According to Aas, bacterial allergy rarely, if ever, causes asthma. No beneficial effects followed treatment with bacterial vaccines²⁵⁵. It is possible that intensive oft-repeated immunizing procedures, known to induce hyperglobulinemia, may lead to amyloidosis. In a group of 76 persons injected with many antigens during 7 to 13 years, no illness occurred, but there was a high incidence of lymphocytosis and abnormal hepatic function tests, while abnormal serum electrophoretic patterns appeared in 50 per cent of subjects. Gingival biopsy also disclosed changes²⁵⁶. Decades ago amyloidosis was observed in Wadsworth's horses immunized with pneumococci, and in 1935 I described its occurrence in a patient after prolonged vaccine injections²⁵⁷.

Modern therapy of lymphomas prolongs life, but renders patients susceptible to infection with commensal opportunistic microbes. Septicæmia with gram-negative bacilli or staphylococci and perirectal infections were the chief causes of death²⁵⁸. *Pneumocystis carinii* pneumonia caused death in 33 patients, all but three of whom had other underlying disease. One had leukæmia²⁵⁹. Leukæmia also favoured the invasion of toxoplasmas²⁶⁰. According to the skin-test, from 12 per cent to 22 per cent of veterinary students gave evidence of having been infected at some time with toxoplasmas²⁶¹.

Antimicrobial therapy has not reduced the incidence of death from terminal pneumonias significantly. During poliomyelitis and in chronic pulmonary diseases, infections with staphylococci and gram-negative bacilli were common causes of death²⁶². Bacteria that enter the lungs normally are destroyed and ejected by the activity of alveolar macrophages and the mucociliary stream. Acute infection induces œdema, exudate and polymorphonuclear leucocytosis²⁶³. In kidneys of rats with pyelonephritis "cured" with antimicrobics, bacterial protoplasts survived for three months without reverting to the original causal enterococci²⁶⁴. Perhaps this explains the nature of certain latent infections and why they may relapse.

Unchlorinated water in swimming pools may

contain a variety of pathogenic bacteria and viruses that cause sore throat, colds, conjunctivitis, diarrhoea, and perhaps vaccinia from recently vaccinated persons²⁶⁵. In critical tests, two "antiseptic" creams and a hexachlorophene jelly applied to the hands after washing with soap failed to lessen the bacterial flora²⁶⁶. Routine shaving of the perineum and catheterization before minor gynaecologic surgery are unnecessary. No complications occurred in 147 patients neither shaved nor catheterized. The risk of infection is increased by those procedures²⁷⁷.

The value of hyper-immune, human, gamma globulin for the treatment and prevention of infections was reviewed. It was valuable for vaccinia, of slight help for mumps and as substitute for antitoxin for tetanus, warranted for varicella, in the experimental stage for rubella and rabies, controversial for pertussis, and of doubtful or of no value against bacterial infections. In malaria, it caused a diminution of trophozoites and gave protection²⁶⁸.

Interferon acts intracellularly to prevent the synthesis of viral nucleic acid. It has a non-specific, broad-spectrum prophylactic action against viruses, but is of no benefit once an infection has started. There is little promise for its use in clinical medicine²⁶⁹. Corticosteroids administered during viral infections inhibit the production and action of interferon²⁷⁰.

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