Annual Review

INFECTIONOUS DISEASES

Annual Review of Significant Publications*

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MEDICAL interest, as usual, has changed with the times. In the past two decades antimicrobics held the stage during their developmental period when hundreds of them were tested. Therapeutically effective and nontoxic ones were used extensively and their value was established. Unfortunately, overenthusiasm and carelessness led to their indiscriminate, wasteful and harmful use. Persons were inadvertently sensitized, allergic and toxic reactions occurred and antimicrobial-resistant bacteria emerged or were evolved. Some of these resistant bacteria were unimportant previously, but now have replaced sensitive ones that were the chief causes of disease and death in the preantimicrobial era.

During the past few years, owing to advances in cultural and serologic technique, research in virology accounted for a huge number of publications. More than 3,000 papers from world-wide sources on poliomyelitis, influenza and related diseases were annotated last year in bulletins published by the National Foundation for Poliomyelitis in New York City and by the American Institute of Biologic Sciences in Washington. Limitation of space in this review permits discussion of only a few of these and of advances in other infections.

Entero-Respiro-Viruses

The discovery in the past decade of more than 100 kinds and subtypes of viruses that may inhabit the body normally, and at times cause disease, has given rise to nosologic and nomenclatural confusion. So-called enteroviruses may reside in the nasopharynx and cause respiratory tract disease, and respiro- or rhino-viruses often are present in the enteric tract and may cause disturbance there. ECHO (enteric, cytopathogenic, human, orphan) virus Type 28, for example, causes colds and rarely is found in the bowel. Many of the viruses also invade the neural system, the skin, mucosal and serous membranes, the heart and elsewhere to cause a variety of diseases. New ones are being discovered.1 Many terms such as REO, Coe,
Respiratory Tract Infections

Viruses far exceed pneumococci, hemolytic streptococci, H. influenzae and diphtheria as causes of respiratory tract infections. Respiroviruses were the subject of several reviews.\(^{34, 37, 38}\) of seven papers in the June 1962 American Journal of Public Health, and of an international conference at the National Institutes of Health in Bethesda, in October 1962, the report of which will be published. The viruses of measles, varicella and variola also may be included as respiroviruses,\(^{39}\) but because of their dermal manifestations they are regarded otherwise. Viral diseases of the respiratory tract comprise two-thirds of all acute infections. They cause 37% of lost work-days and 67% of absences from schools.\(^{40}\)

Adenoviruses seemed to affect military recruits chiefly,\(^{41, 42}\) but civilians also were involved. Among families, chiefly in children, 37% of respiratory tract infections were caused by adenoviruses 1, 2, 5 and 6.\(^{43}\) Among 99 children, virus 7 caused pulmonary disease in 76, enteric disturbances in 34 and meningeal symptoms in 20.\(^8\) Severe pneumonias occurred in infants.\(^{44}\) In an epidemic in Finland, symptoms of enteric disturbances were dominant in infants and of the respiratory tract in older children, often with pneumonia.\(^7\) Meningoencephalitis also occurred. The incidence and severity of infections in military personnel.\(^{45}\) A hexavalent vaccine failed to evoke a significant antibody response in many children. An agglutination test was devised to identify adenoviruses quickly.\(^{46}\)

Among 407 recruits, Coxsackie virus Type A21 (Coe virus) caused respiratory tract disease in 61%.\(^{47}\) It usually affected the upper area.\(^{48}\) Volunteers were infected experimentally.\(^{49}\) B5 virus caused similar illness in children as did ECHO viruses.\(^{19, 20, 21}\)

Asian (A2) and B strains of influenza viruses caused serious illness in 40 children and pneumonia in 20.\(^{48}\) Elsewhere, among 133 children with influenza B, pneumonia occurred in only three. Inapparent infections were detected serologically. Virus was present in the enteric tract.\(^{49}\) Serums obtained from natives who lived in Alaska during the pandemic of 1918 nearly all had antibodies in high titre against A/swine influenza virus. This supported evidence that the agent of the pandemic was the prototype of present A viruses.\(^{50}\) It cannot be certain, however, that later infections with similar viruses may have been implicated. Recently isolated Type B viruses are different antigenically from those of previous years. Subgroups B1 and B2 probably exist.\(^{51}\)

Lesions observed bronchoscopically during influenza viral pneumonia disclosed inflammation increasing distally in the tracheobronchial tree. The columnar cells were vacuolated, oedematous and deciliated. Epithelial cells were desquamated to the basement membrane or were said to be pseudo-metaplastic. Epithelial necrosis occurred during the first 24 hours of illness.\(^{52}\) According to other investigators, influenza virus causes viral pneumonia characterized by foci of oedema and bleeding, not by true inflammation.\(^{53}\)

Vaccine. In September 1962 anti-influenza vaccine was recommended officially for all persons in the United States because of a predicted recurrence of Asian influenza. The alarm was unnecessary. No serious outbreak took place and other viruses also were prevalent. Epidemics cannot be foretold at long range, nor what virus or variant virus will be rampant. To be consistent, immunization against all possible invaders would be necessary. There is a limit, however, to the number of antigens in a vaccine and to the effectiveness of each diluted component, while the possible interference of one with another must be considered.\(^{54, 55, 56}\) Combined influenzal and adenoviral vaccine was successful in controlling influenza, but only partly so for adenoviral disease. Immunization resulted in a compensatory increase in the number of mild, afebrile attacks.\(^{57}\) Annual vaccination of persons in industrial groups in the absence of a threatened epidemic did not justify the results or the cost.\(^{58}\) Parainfluenza (an unfortunate term) or other myxoviruses caused 6% to 19% of infections in children\(^{48, 59, 60}\) and also affected adults.\(^{37, 61}\)

The respiratory syncytial (RS) virus caused severe respiratory tract disease, often pneumonic, in 30% of a group of infants in 1962\(^{62}\) and milder attacks in adults\(^{60}\) in whom it probably causes a large proportion of colds and mild viral pneumonias.\(^{63}\) Antibody against RS virus commonly found in an English population suggested that infection had been widespread and frequent.\(^{62}\)

Numerous coryza viruses recovered from victims of the common cold belong to the ECHO 28-rhinocoryza (ERC) group. Twenty serotypes were isolated which may account for repeated attacks of colds in one person in a year. Immunity is short and seems to be type-specific. A polyvalent vaccine, therefore, to be effective would have to contain 20 specific antigens. The viruses caused mild colds in adults, but children usually were sicker with fever, croup, bronchitis and viral pneumonia.\(^{64}\) Two papers on the subject appeared in the Lancet of February 9, 1963. Cold weather and chilling of the body cannot be blamed for intensifying respiratory tract infections.\(^{60}\) Yet in my personal experience undue chilling has incited many 'colds', at least three with viral pneumonia that was recognized only by skiagraphy.

The causative agents of acute respiratory tract infections were determined in 40% of 667 children in 1959-60. The respiratory syncytial virus, adenoviruses and parainfluenza viruses predominated in childhood and were less common in adults in contrast with 'cold' (coryza and Salisbury) viruses that affected adults oftener. Mycoplasma (Eaton agent) and influenza viruses affected people of all ages.\(^{28}\) A number of viruses remain to be discovered.

Viral Pneumonias. Most viral pneumonias are the severe forms of mild respiratory tract infections as outlined in 1938, when the nature of the lesions and the discovery of causal viruses were predicted.\(^{66}\)
Yet the use of the ambiguous term primary atypical pneumonia persists and now, curiously, is restricted to the Eaton agent pneumonia. Some physicians disregard viruses as causes. Viral pneumonias exceed all others in incidence, but often are undiagnosed. Current problems of the pneumonias in general were reviewed elsewhere.

Adenoviruses were isolated from 61% of 118 recruits with respiratory tract infections and 25% of these had viral pneumonia. In an epidemic in Russia, 29% of sick children had pneumonia and three died. In Finland, pneumonia was present in 21% of adenoviral infections. Parainfluenza viruses, respiratory syncytial virus and the Eaton agent accounted for 48% of lower respiratory tract infections in children. Combinations of these agents were present in 17%. Eaton agent caused 50% of pneumonias in adults. In retrospect, the elusive agent isolated from the first case of severe viral pneumonia described in 1938 may have been a mycoplasma. A committee has agreed to name the microbe Mycoplasma pneumoniae to separate it from other mycoplasmas. Among volunteers inoculated with the Eaton agent, 12 had mild infections, three had pneumonia and 12 had acute myringitis. Rhino-coryza viruses caused pneumonia in infants and mild non-pneumonic disease in adults. The virus of herpes zoster caused pneumonia in a patient with Hodgkin’s disease who had had varicella in childhood. Dermal lesions resembled those of varicella.

Thirteen more cases of pneumonia caused by Pneumocystis carinii were described, all imposed upon other underlying disease, especially lymphomas, and if therapy with steroids, cytotoxic agents or roentgen rays had been applied. The microbe is an opportunistic invader.

Treatment. Antimicrobics used prophylactically during minor respiratory tract infections failed to reduce the incidence of bacterial invasions. During viral infections new signs or symptoms thought to be warnings of complications such as otitis media, seldom are caused by bacteria requiring antimicrobial therapy. Purulent bacterial complications, when they do occur during unnecessary antimicrobial prophylaxis or therapy, may be more difficult to manage than those in untreated patients. Antimicrobial therapy is not needed for acute sinusitis unless sensitive bacteria are the cause. Treatment with virugon (A.B.O.B.) had no influence in the treatment of respiratory viral infections, including varicella or mumps.

Viral Encephalomyelitis

St. Louis virus caused an outbreak of encephalitis in Florida. Nine of 76 observed patients died. Many mild or inapparent attacks no doubt were unrecognized. Mosquitoes were suspected as vectors.

Venezuelan equine encephalitis was discussed in four papers in the November 1962 American Journal of Tropical Medicine. The report of a large outbreak in 1943 in Venezuela was questioned since a number of purported victims were not proved to be infected. No instances of the disease in man or in equines has been acquired naturally since 1944. The virus is endemic, resides in rodents and mosquitoes, and often causes inapparent infection in man. Animals were infected experimentally by inhalation of aerosolized virus. This result recalls rabies in men who visited a cave inhabited by bats, but were not bitten.

Infection with Japanese encephalitis virus was detected serologically in 5% of 300 American personnel in Korea; 22% of reactors had had a mild systemic illness. The ratio of inapparent infection to overt encephalitis was 1 to 25.

A victim of myalgic encephalomyelitis observed in Switzerland prompted a review of its occurrence elsewhere in widely scattered epidemics. A mysterious epidemic, possibly of myalgic encephalitis, neuromyasthenia or Iceland disease, affected 1,800 persons in the State of Maryland in the winter of 1963. Fever, cough, respiratory tract infection, enteric disturbance, dizziness and irritability were followed by weakness and depression. No causal agent was isolated.

Encephalomyeloradiculitis and erythema nodosum occurred in a child with cat-scratch disease. Human rabies is rare in the United States despite the widespread distribution of the virus in animals. Bites by startled, goaded, or injured wild animals rarely cause rabies. Animals that have been raised from birth in pet shops, or very young ones, or those that are restricted to areas free of rabies are not likely to be rabid. Species that are the most dangerous reservoirs of rabies are the dog, fox, cat, skunk, and easily-bitten farm animals such as the cow, horse, and hog. A bite by a bat, if unprovoked, may cause rabies. On the other hand, bites by the chipmunk, gopher, hamster, rabbit, squirrel, mole, and other rodents carry very little risk of rabies infection. The use of vaccine without good indications of rabies is discouraged. When hyperimmune serum and steroids are given in addition to vaccine, the response to the vaccine may be suppressed unless two supplemental doses of vaccine are given 10 and 20 days after completion of the usual schedule.

Polioymelitis. The value of vaccination against poliomyelitis is so well publicized that an extensive review here is unnecessary. The great decline in the incidence of paralytic disease in the United States from 13,850 cases in 1953 to 988 in 1961 was attributed largely to the widespread use of inactivated vaccine. Yet a few failures have been described. Sixty-two of 137 paralyzed victims had had three or more injections of Salk vaccine. Vaccination did not appear to prevent infection in about 50% of Amerindian children. Three of four children in an English family who had been vaccinated acquired poliomyelitis. Perhaps the vaccines failed to evoke antibody or were defective or not antigenically specific. Studies disclosed intratypic differences among strains of Type 1 virus.

In a six-year study the superiority of oral vaccine over Salk vaccine was made evident by higher
conversion rates and greater amounts of antibody attained. Many children who had received inactivated vaccine lacked antibodies.90 Untoward effects from live vaccine have been observed. Neurologic sequelae,81 paralysis82 and illness within 12 to 48 hours after injection were described. Oral vaccine seemed to have induced infection with Type III vaccine in 11 instances and in seven with Type I vaccine. Even so, in view of the fact that 15 to 31 million doses were fed, the small risk involved justifies the continued use of vaccine.93 Some of the infections could not be ascribed to the vaccine with certainty.

Other viruses also may induce paralysis. In 706 patients with suspected poliomyelitis, diagnosis was confirmed in 62%. In 10% Coxsackie A and B, ECHO, mumps, herpes simplex and St. Louis viruses were causal.94

Measles. Ender’s measles vaccine is effective in preventing infection in almost all vaccinees. Live and inactivated preparations are now available for general use. Three-quarters of children vaccinated with living virus had fever and a rash two weeks afterward, sometimes severe.96 Fewer and milder reactions occurred when human immune globulin also was injected.96 Neutralizing antibody persisted undiminished for a year, and probably lasts much longer.97 The matter was reviewed in the American Journal of Public Health, Supplement, of February 1962, and elsewhere.95, 96, 98, 99 The status of vaccines and detailed recommendations for their use also were outlined.100, 101

Measles antibody, measurable in the spinal fluid of 75% of victims of multiple sclerosis but not in normal persons, raises a question as to the possible relation of the two diseases.102

Rubella. The isolation of the virus of German measles from patients whose blood later contained a specific neutralizing antibody was reported by investigators in Boston103 and Bethesda.104 The virus also was found in army recruits.105 Antibody was demonstrable in most persons who had had rubella. Effort is under way to make a vaccine.106 The matter of congenital disturbances induced by rubella in early pregnancy was reviewed in a monograph.107

Smallpox. Eleven cases of smallpox were described. In eight the severity of disease apparently was not lessened by previous vaccination. The nature of the exanthem varied in different victims.108 An epidemic in Brazil was characterized by a predominance of benign attacks that could be regarded as alastrim or variola minor.109 Perhaps mild cases and inapparent attacks should be regarded as parts of a spectrum of one disease.110 A new book on smallpox was published.111

Antivaccinal gamma globulin obtained from recently vaccinated persons may act quickly to prevent smallpox because the immunity evoked by vaccine may appear too late. Trials of the agent indicated its effectiveness.112

Cat-scratch disease contracted from a kitten involved five members of a family in a two-month period.113 Lymphadenopathy of 18 months’ duration may ensue.114

Hemorrhagic fevers of viral origin are more widespread than first was believed when U.N. troops in Korea were involved. The diseases probably are caused by related viruses and have been known by different names in the U.S.S.R., South-eastern Europe, Japan, China and South-western Asia. Arthropods are vectors.115

Herpes Simplex. An epidemic of herpetic stomatitis affected 10 of 13 children in an orphanage. The incubation period lasted about seven days. Herpes simplex virus was isolated and specific antibody was demonstrated in eight. No inapparent attacks were detected.116 Medical personnel who touch oral secretions of patients that carry the virus are apt to acquire digital herpetic lesions after about five days. Malaise, fever and regional lymphadenopathy may last three weeks.117 Virus can be isolated from the lesions and is detectable within three hours by electron microscopy.118 Herpes simplex encephalitis occurred in six patients.119 Several chemical compounds were effective in the treatment of herpetic keratitis in patients120 and in rabbits121 representing the first successful chemotherapy of a viral infection. Topical application of 5 iodo-2-deoxyuridin, however, had no influence in the treatment of cutaneous herpes simplex.122

Mumps. Mumps is commoner than is generally believed. About 40% of infections are inapparent. Contagion often occurs among school children who in turn infect their families at home. Those who escape probably were immunized by previous overt or inapparent attacks.123 Mumps is a multirropic virus and may cause fatal nephritis, diabetes124 or meningoencephalitis.

Mumps-like parotitis, orchitis and meningoencephalitis were caused by a Group B arbovirus,125 Coxsackie and lymphocytic chorion meningitis viruses.126 Such infections may be mistaken for the first or for a recurrent attack of mumps.

Viral Hepatitis. The cyclic recurrence of epidemic viral hepatitis in the United States was illustrated by the record of a decline from 50,000 cases in 1954 to 15,000 in 1957 and a resurgence to 72,000 in 1961.127 The number would have been greater if all undiagnosed, or unreported, or mild and inapparent attacks had been included statistically. The same was true in an epidemic among military personnel attributed to polluted water when 96 cases were diagnosed in 28 days.128 Hepatitis may be transmitted to others 7 to 17 days before symptoms of the disease or jaundice appear129 as had been known to occur. The cockroach may be a vector of the virus.130

The incidence of serum hepatitis increased in proportion to the number of transfusions of blood from 1.4% after 1 unit, to 8.3% after 6 units.131 During ten years, blood from a donor who had had hepatitis and probably had persistent viremia was used to treat 95 patients, 53 of whom were traced later. Of these, nine became icteric after 24 to 64 days.132 In 1886 an epidemic of hepatitis
was ascribed to the lymph contained in smallpox vaccine. Disease appeared from several weeks to a couple of months after vaccination. A similar accident occurred in troops immunized with anti-yellow fever vaccine in 1942. Two physicians and a dentist who had minor dermal lesions acquired hepatitis as an occupational disease from their patients. The hemovirus of hepatitis was isolated from more than 95% of sick victims and from persons with clinically inapparent infections. Now that three serotypes of virus are at hand, vaccine eventually may be prepared.

**Cytomegalic Inclusion Disease.** The virus of this disease was widely distributed among children, but infection usually was inapparent except in patients with other debilitating conditions. Viruria was present and the virus was recovered from the liver of children with hepatosplenomegaly. The disease is chronic and leaves neural and other defects as sequelae. The virus may be another cause of hepatitis. Evidence of the infection was present post-mortem in adults debilitated by neoplasms, anaemia, antimicrobics and steroids. Inclusion bodies were present in most of the visceral organs and elsewhere.

**Interferon.** Interferon is a by-product of infection of cells with a virus and is mediated by some natural cellular substance. It inhibits replication of a virus and may be a factor in the suppression of growth or invasiveness of one virus against another. Interferon may have some practical value in therapy or prophylaxis. It has a broad antiviral spectrum, is non-toxic to cells, is non-allergenic and quite stable. On the other hand, interferon does not affect all viruses, and its activity is brief. To be of value, it must be applied at the proper time. Reports of the control of vaccinal keratitis and of the prevention of reaction to vaccination appeared in two papers in the Lancet of April 28, 1962. The matter was reviewed elsewhere in detail.

Much investigation is devoted to the possible causal relation of viruses to cancer in man. Specimens of various malignant growths from 84 patients were tested in cell-culture systems and by injection into animals, but no significant viruses were isolated. The occasional presence of viruses of simian origin in tissue cultures may be misleading. Precautions to be observed in handling continuously cultured cells and viral vaccines were outlined by a committee.

**Antimicrobics**

In the United States, 1,600 tons of antimicrobics, including 648 billion units of penicillin, were made in a year. It has been estimated that 90% is prescribed needlessly. A sub-committee of the U.S. Senate is investigating means to furnish information to physicians and laymen about their proper use to curtail the wastage of the drugs by indiscriminate therapy. Antimicrobics have reduced the seriousness and death rate of infections that are amenable to treatment. The mortality rate of pneumonia in general was reduced from 8 to 22 per 100,000 between 1930 and 1954, owing chiefly to the cure of pneumococcal infections. Since then, unfortunately, the mortality rate of pneumonias of other cause has increased steadily to about 30 per 100,000 in 1962 because of the increased incidence of infections caused by antimicrobial-resistant bacteria.

As a result of the iatrogenic disturbance of microbial ecology, infections by resistant bacteria have increased fivefold. In other words, one set of pathogens was controlled only to be replaced by another. Chief among these are gram-negative bacilli, staphylococci and fungi. Esch. coli, aero-bacter and pseudomonas caused an increased number of deaths among 173 middle-aged women and elderly men, especially when their resistance was impaired by other factors. In about half of them, bacteraemia became overt clinically while they were receiving antimicrobics for other reasons. Infections were severer when they were acquired in hospitals and when steroids had been given. Only about 50% of the invading bacilli were sensitive to antimicrobics. Combined drugs were of no advantage in therapy; combination of penicillin and streptomycin was least beneficial. Important determinants in the outcome were the nature, severity and treatment of the underlying disease.

Enterococci and pseudomonae resistant to penicillin, streptomycin and neomycin, usually were sensitive to erythromycin and chloramphenicol. Esch. coli, Klebsiella and proteus that had acquired resistance to streptomycin, chloramphenicol and tetracycline returned to degrees of sensitivity after the use of these drugs was restricted. Hemolytically streptococci increased their resistance to tetracycline. The matter of resistant gonococci is disputed, but pneumococci and meningococci still are sensitive.

The favourable effects of colistin on gram-negative bacillary infections were discussed in three papers in the Lancet of October 13, 1962. In other studies more strains of Esch. coli, Klebsiella and pseudomonas were found to be sensitive to colistin sulphate and polymyxin B than to other antimicrobics. Among 48 patients with gram-negative bacillary infections, colistin temporarily controlled urinary tract infections in 26, but cured only a few. Untoward effects were minimal but relapses were common. The drug may cause serious neuro- and nephro-toxic trouble, especially during renal dysfunction. Colistin sulphate is three times as active as colistin methane sulphonate (colistimethate). When given in the usual dosage, both cause fewer side-effects than polymyxin B. Colistin is relatively ineffective against Salmonella and Shigella.

Amphotericin B was credited with the cure of 15 of 30 patients with cryptococcal meningitis; ten had a relapse but were retreated successfully, and five failed to respond. About half of the patients had underlying illness, especially Hodgkin's disease or diabetes. Long-term corticosteroid therapy preceded meningitis in seven. A high incidence of untoward reactions occurred during intrathecal
therapy. Intrathecal therapy of any sort generally is condemned.

Antimicrobics for Prophylaxis. The administration of penicillin to prevent subacute bacterial endocarditis during exodontia is of uncertain value and failed in two instances. The drug suppresses sensitive bacteria, but permits the growth of resistant non-hemolytic streptococci and other bacteria, the chief causes of the disease. If prophylaxis is indicated, soluble penicillin should be given within minutes before or immediately after operation. Among children receiving penicillin to prevent recurrent rheumatic fever, alpha streptococci resistant to 2 units/ml were present in the oropharynx of 17 of 21. None appeared in control subjects. Should the cocci cause subacute bacterial endocarditis in these patients, treatment would be difficult. Penicillin-resistant staphylococci also appeared during prophylactic management. Prophylactic endeavour failed to influence the occurrence of many gram-negative bacillary infections. The incidence of post-operative pulmonary infections and wound infections was not reduced by penicillin. Prophylaxis had no appreciable effect on the incidence of sepsis, or on the course of appendicitis. Reliance on prophylaxis may mask and delay recognition of infection or the need for surgical intervention. After infection is obvious, treatment may be clouded by inappropriate antimicrobial therapy. These therapeutic faults and harmful reactions to antimicrobics were frequent bases for malpractice suits.

Unwanted Effects. Various pathogens appeared in the sputum of 5.4% of patients with pneumonia after therapy with tetracycline or chloramphenicol, in 19% after combined penicillin and streptomycin, and in 47% after penicillin plus tetracycline or chloramphenicol, but in none treated with penicillin alone. About one-third of patients superinfected with staphylococci or gram-negative bacteria during therapy had clinical illness therefrom. The results emphasize the danger of prescribing unnecessary combinations of drugs. Orally-administered antimicrobics listed in the order of frequent causes of allergic reactions were penicillin, sulphanethoxypyridazine, novobiocin, chloramphenicol, erythromycin, chlorotetracycline, sulphamethoxazole, tetracycline and triacetyl-oleandomycin. Penicillin given orally caused 28 reported anaphylactoid reactions with three deaths. According to other statistics, more than 1,000 reported deaths have been ascribed to anaphylaxis from penicillin. About 4% of people reacted positively to the skin test with a penicillin derivative. In those who react to the test and subsequently are given penicillin, the chances of an allergic reaction are increased 10- to 400-fold. The usual skin or conjunctival tests used to discover hypersensitivity are unreliable and, in rare instances, have caused death. As a substitute, an indirect serologic basophil dermal granulatation test was successful in detecting circulating antibodies to penicillin and to other drugs.

Tetracyclines may accumulate in toxic amounts when renal excretion is impaired. Photosensitivity may be induced. Acidosis, glycosuria and other untoward effects may follow the use of deteriorated tetracycline. Erythromycin and triacyt oleandomycin may harm the liver. Tests disclosed clinically inapparent jaundice in 50% of patients treated with esters of erythromycin for more than 10 days. Despite warnings of hemotoxicity, chloramphenicol that in total amount averaged 64 g. caused no trouble in 95 patients with severe infections. Amphotericin B given successfully for coccidioidomycosis caused nephrocalcinosis. Treatment, therefore, is justified only when the infection is disseminated.

Antistaphylococcal Therapy. The introduction of new compounds of penicillin served to keep a step ahead of agents to which staphylococci have become resistant. Yet, if they are used unwisely, cocci also resistant to them may appear during therapy as they already have in vitro. Methicillin (Staphcillin) and oxacillin (Prostaphlin) affect the cocci, whether or not they make penicillinase. The drugs were inferior to penicillin in their action on penicillin-sensitive cocci. Oxacillin was five to eight times more active than methicillin and was well absorbed when given orally, though less so than phenicillin. Oxacillin-resistant strains resisted other penicillins. BRL 1621, Orbenin or Cloxacillin given orally was said to enter the blood in amount greater than oxacillin. Penicillin G still is the drug of choice except for strains resistant to it.

Nearly all tested strains were sensitive to the new agents, but they were not eliminated regularly and were replaced by other staphylococci and by gram-negative bacilli, some of which caused serious superinfections. For the treatment of serious infections, penicillin G in combination with methicillin or oxacillin should be given initially pending the results of sensitivity tests, after which the appropriate agent should be used.

Penicillin-resistant staphylococci were present in 10% of the population of a community and in 20% of hospital employees. More than twice as many resistant strains were isolated from children after they had been given antimicrobics, than were present before. Penicillin interferes with the formation of the cell walls of staphylococci and causes lytic disruption.

Group A streptococci were not eliminated from the nasopharynx by penicillin owing to the presence of penicillin inactivating coagulase-positive staphylococci. Oxacillin destroyed both staphylococci and streptococci. The staphylococcidal effect of a new agent, Fucidin, was described in three papers in the Lancet of May 5, 1962. Resistance to it developed quickly in vitro.

Bacillary Infections

Dysenteries. E. coli, Shigella, Salmonella and parasites were isolated from 14 of 29 Puerto Rican children with diarrhoea. Enteroviruses were recovered from 15, of which seven were unidentified. Several different microbes present in more than
one-third of children confused aetiological diagnosis. Only 13% of children in Guatemala had diarrhoea caused by Shigella. Salmonella and coliforms seldom were encountered. Viruses probably caused many of the infections. An extensive outbreak of diarrhoea caused by *E. coli* 0111: B4 occurred among children. Carrier rates rose to 4.8% to 10% in healthy persons at the time. All strains had acquired resistance to neomycin as compared with those studied three years previously. The fluorescent antibody test was superior to older methods for identification. An outbreak of shigellosis spread among poor people in Kansas by inter-household and neighbourhood contagion. The spectrum of severity of illness ranged from inapparent infections to prostration and death. Bacteremia was detected in a patient with *S. sonnei* dysentery.

Immuno-fluorescent studies in dogs injected with *E. coli* toxin disclosed toxin widespread in the peripheral and visceral vascular system, in polymorphonuclear leukocytes and elsewhere that may account for bacteremic shock.

The chief cause or causes of 'traveller's diarrhoea' that troubles many tourists are unknown. In Mexico, where the disorder is known as 'Montezuma's revenge', Shigella, Salmonella, amebas and flagellates seldom were responsible. Coxsackie viruses were isolated from the stools of only two of 35 patients. Other unknown viruses may have been implicated. In an outbreak of 'viral' dysentery among my medical students in January 1963 no pathogenic bacteria and no viruses were recovered from stool samples.

**Typhoid.** Typhoid occurred sporadically and in small groups in England, the United States and elsewhere. Many victims had been infected in Switzerland during an epidemic probably caused by polluted water. Typhoid in another instance was derived from a carrier and afflicted members of three generations of a family, their friends and some visitors over many years. Thirty-one vaccinated persons were infected by contaminated food. Similar failure of immunization occurred in another outbreak as it did among British soldiers in World War II. Perhaps the immunity evoked by vaccine was weak or short, the vaccine may have been of the wrong antigenic structure or deteriorated, or the infections were massive.

The mortality rate of 251 patients treated with chloramphenicol was 8% as compared with 23% of those treated symptomatically. Relapses occurred in 11% of treated ones and in 4% of untreated ones, indicating that chloramphenicol was bacteriostatic or suppressed the development of immune bodies. Surprisingly, *S. typhosa* was killed by penicillin in test-tube culture, while chloramphenicol only inhibited its growth. Large doses of penicillin for two weeks served to rid four of six carriers of the bacilli. Contrary to previous ideas, antimicrobics were able to enter mammalian cells and to inhibit growth of intracellular bacilli as well as extracellular ones. Infected cells can clear themselves of microbes, sometimes by ejection, but viable ones may survive in the presence of antimicrobics and multiply when the drugs are withdrawn. Perhaps that behaviour accounts for relapse in treated patients and for the failure to stop the carrier state. The actual cause of death and destruction of intracellular microbes is unknown. A new book on typhoid was published.

Contaminated dried egg albumin caused salmonellosis in 300 persons in a city. Since the substance was distributed widely elsewhere in cream pies, an estimated 10,000 persons were infected.

Several forms of therapy were tested on 27 carriers of Salmonella. Intensive therapy with chloramphenicol, tetracycline and penicillin combined cured three of four patients who had gallstones. In the presence of stones, cholecystectomy and antimicrobial therapy cured all of 11 patients. Cholecystectomy alone succeeded in only four of nine. Immersion of gallstones in solutions of antimicrobics failed to sterilize the interior portions. A single oral dose of streptomycin or penicillin increased the susceptibility of mice to experimental infection with *S. enteritidis*, and with a strain of *staphylococcus*, probably by changing the enteric microflora.

*H. influenzae* meningitis is commonest in early childhood, but adults also are affected, particularly if they have diabetes, alcoholism, pneumonia or cranial injury with rhinorhoea. About 60 instances have been reported. The mortality rate is lower than that from other bacterial meningitides and has been lessened by antimicrobial therapy. A sulphonamide drug with streptomycin or chloramphenicol was recommended for treatment.

In one patient, ECHO 9 virus also was present in the spinal fluid and its antibody appeared in the blood, obviously a dual infection.

**Diphtheria.** Contrary to general belief, diphtheria still occurs and has caused outbreaks of disease in Germany and elsewhere, especially among vagrants. The incidence of infection has risen since 1945, especially in children. Most victims had not been immunized with toxoid. Severe attacks often were complicated by infection with *haemolytic streptococci* and *staphylococci* for which penicillin therapy was successful. Immunized persons who had diphtheria had mild attacks.

Diphtheria may be mistaken for viral or streptococcal pharyngitis.

**Tetanus.** The desirability of mass immunization with tetanus toxoid was re-emphasized. Toxoid rarely causes troublesome reactions as compared with antitoxic serum that causes serum sickness in 5% to 15% of persons. Reactions also occurred in 1.68% of persons treated with penicillin. The ability to respond to a booster injection of toxoid persists as long as 18 years after the initial one. Tetanus-immune-human-globulin affords protection when administered in the first four or five critical days. Among 3,295 patients with tetanus, no circulating toxin was detected in the blood or spinal fluid. There was no difference in the mortality rate whether 5,000 or 60,000 units of anti-
toxic serum were injected.\textsuperscript{19a} The value of antitetanus serum for therapy is doubtful.

The experiments of Abel 25 years ago seemed to refute Ranson's theory that tetanus toxin travels through nerves. Subsequent studies, however, indicate that toxin may enter nerve trunks from muscles, then progress along the bundles of neural fibres.\textsuperscript{19b} Isotope-labelled proteins were shown to pass along the axons of the sciatic nerve of the rat 4 to 16 days after injection at an estimated rate of 1.5 mm. per day.\textsuperscript{19c} After a latent period of two days, tetanus toxin injected into the cerebral cortex of dogs caused convulsions that persisted a month.\textsuperscript{19d}

In four instances gas gangrene was caused by the intramuscular injection of liver extract, a sulphonamide compound and other agents.\textsuperscript{19e} Because clostridies are anaerobes, oxygen delivered under pressure was said to be beneficial in the treatment of 26 patients with gas gangrene.\textsuperscript{19f} Oxygen also was said to relieve the hypoxia that presumably occurs in typhus and typhoid.\textsuperscript{19g}

Botulinus toxin disturbed the inhibitory control of the mono- or poly-synaptic spinal reflex arc in a manner similar to that of tetanus toxin.\textsuperscript{200} Anthrax toxin was fatal to guinea-pigs that were not immunized with specific antiserum. Toxin was present in the blood during the terminal stage of infection.\textsuperscript{201}

Only six instances of septicemia caused by fusobacteria are on record. Another resulting from a human bite was added. Penicillin or tetracycline were recommended for therapy depending upon the sensitivity of the microbe.\textsuperscript{202}

A pasteurella-like germ, II-D bacilli, caused endocarditis in four patients, each more than 39 years old.\textsuperscript{203} Past. pseudotuberculosis caused mesenteric lymphadenitis in a boy. Serologic evidence of recent infection in three siblings was thought to be evidence of a familial outbreak. A pet was suspected as the source of infection.\textsuperscript{204}

Studies reported on in two papers of the March 1963 issue of the American Journal of Tropical Medicine indicated that plague bacilli isolated from wild rodents may be the same as classical Past. pestis morphologically and biochemically, but differ in degree of invasiveness. Apparently, as would be expected, strains of Past. pestis differ or variant forms exist.

\textbf{Tuberculosis.} The reported incidence of tuberculosis in the United States has reached the lowest point ever recorded, and chemotherapy has reduced the death rate 70% since 1950. Necropsy of treated patients disclosed that only 15% of them died from progressive tuberculosis. The commonest causes of death were of other nature.\textsuperscript{205} Despite the advantages gained, the hope of eradicating tuberculosis is not great. About 25% of patients fail to respond to antimicrobial therapy, the incidence of drug-resistant bacilli seems to be increasing, many victims escape detection and treatment, and a large reservoir of infection exists in countries where tuberculosis has not been controlled.

It was said that many patients currently admitted to municipal hospitals in the United States are infected with drug-resistant tubercle bacilli. In untreated newly diagnosed patients from 5% to more than 15% of bacilli were resistant. The incidence varied from place to place and sensitivity varied at different times in tests in the same laboratory. Techniques varied so much that a reliable estimate of the prevalence of resistant strains could not be made.\textsuperscript{206} Nevertheless, the matter may be ominous. Among 109 patients under treatment for two years, bacilli resistant to two drugs were present in 71, and ones resistant to three drugs in 38. Of the 71, 22 died and six of those who recovered still carried the germs. Bacilli disappeared in 43. Of the 38 patients, 20 died, two survived and 16 recovered minus the resistant bacilli. Tetracycline, isoniazid and viomycin were useful in such cases, and surgical resection at times was essential.\textsuperscript{207}

Controversy about the value of vaccination with BCG persists. According to one report, 90% of more than 200 million persons have been immunized. The tuberculin sensitivity thus educated lasts about seven years.\textsuperscript{208} According to other views, the death rate from tuberculosis in Denmark where vaccination was used generally is as low as that in Holland where few were vaccinated.\textsuperscript{209} Other methods of control are satisfactory. Isoniazid in doses of 5 ug./kg. of body weight daily for a year was said to have prevented 70% of the serious manifestations of tuberculosis in Alaskans.\textsuperscript{210}

Unclassified mycobacteria provide a diagnostic and therapeutic dilemma. They cause tuberculosis-like disease and resist antimicrobial therapy.\textsuperscript{211} Microscopic lesions caused by a non-phototrophic were the same as those of M. tuberculosis.\textsuperscript{212} It still is uncertain if some or any of the atypical forms are separate strains or are variant forms of M. tuberculosis.\textsuperscript{213} Studies on this problem are under way in my laboratory.

So far, M. leprae has resisted attempts at cultivation, and reported successful ones have been doubted. Hopefully, the recent success by growing the bacilli in the cool (69° F.) footpads of mice will provide a solution to the problem. The bacilli multiplied, but were reduced 30 to 60 times in numbers by vaccination with BCG and with heat-killed tubercle bacilli.\textsuperscript{214}

\textbf{Urinary Tract Infection.} Among 10,000 school children only 56 had an infection of the urinary tract, an incidence of 1.1% in girls and 0.04% in boys. In college students, about the same percentage occurred in women, and none in men. Nearly half of them had some pertinent complaint, but only two were aware of infection. Pyelography disclosed abnormalities in 22% and cystography in 44%. Proteinuria occurred too seldom to be of diagnostic value. Esch. coli accounted for 84% of the infections.\textsuperscript{215} Observations on 110 patients with infections of the urinary tract disclosed that uncomplicated acute pyelonephritis caused by E. coli responded well to therapy. Infection complicated by obstructive uropathy responded well
after the defect was removed. Chronic bacteriuria in elderly patients and asymptomatic bacteriuria, especially in elderly women, was eliminated during therapy, but recurrences were the rule.\cite{219, 220}

During indwelling catheterization, bacteriuria often was prevented by lavage with 0.25% acetic acid as well as with solutions of neomycin and polymyxin. Prophylaxis with chloramphenicol given parenterally failed.\cite{214, 215} Acidification of the urine with ingested organic acids often stops infection, but relapse may occur.\cite{214, 215} Among 102 catheterized women, 90 had mild urinary tract infection afterward, but none had residual disturbance in nine later years.\cite{220}

*Bacteremias.* A three-month study disclosed bacteremia in nine of 88 febrile patients. One had a neoplasm, eight others had a haemorrhagic disease. Two infections were caused by staphylococci, one by pneumococci and the rest by gram-negative bacilli. After appropriate antimicrobial therapy six patients recovered. Fever caused by infection may be mistaken for fever associated with the primary disease.\cite{223}

*Rheumatic Fever.* Among 600 children with pharyngitis who harboured group A streptococci and were treated with penicillin, none got rheumatic fever. Only two of 600 untreated ones did and one had acute nephritis. Penicillin therapy suppressed specific immunity against streptococci. Immunity followed infection in 70% of untreated patients and disappeared in 66% after four years.\cite{224, 225}

In a city where prophylaxis was not applied there was no seasonal variation in the prevalence of group A streptococci in the throats of 260 children. Of these, 146 harboured group A cocci at least once during nine months and the overall prevalence rate was 16.6%. Rheumatic fever did not occur in any.\cite{226} Although penicillin is used to prevent streptococcal infections and subsequent recurrences of rheumatic fever, unfavourable effects may result. Penicillin-resistant staphylococci were present in 48% of treated children, but in only 9% who were not.\cite{227} Resistant streptococci also appear.\cite{228}

Rheumatic fever has become rarer and milder in Britain and the United States during 40 years. In one study of 139 patients only two were severely ill and none died.\cite{229} Nodules, epistaxis, pericarditis, pleuritis, pneumonia and cardiac failure seldom occur now and the mortality rate from rheumatic cardiac disease in adults has diminished.\cite{230, 231}

The incidence and severity of rheumatic fever began to decline before the antimicrobial era because of other factors.

Early therapy of rheumatic fever did not reduce the danger of cardiac injury as previous statistics seemed to show. Patients with rheumatic arthritis in whom the incidence of carditis is low seek prompt treatment. Patients with minimal or no arthritis more often have inapparent carditis in the early state and therapy may be delayed.\cite{232} Cortisone had no advantage over aspirin. Bed-rest alone gave results as good as drug therapy in patients who had no recurrent attacks. The incidence of carditis and the disappearance of murmurs was similar whether treatment was given for six or for 12 weeks.\cite{233, 234}

*Staphylococci.* Advances in the therapy of staphylococcal infection were described in the section on antimicrobics. Phage typing of staphylococci is of epidemiologic value to determine source of infection, the prevalence and distribution of strains and their route of spread. It does not measure virulence and has no prognostic value.\cite{235}

Typing may even be confusing. During the testing of cloned populations of staphylococci, new types evolved after one exposure to phage.\cite{236}

Staphylococci were seen inside of circulating phagocytes during severe bacteremia.\cite{237, 238} The complex relationship of staphylococci and man as regards production of coagulase and toxin, virulence and mutability cannot be satisfactorily explained.

The change in the ecology of staphylococci in the past 20 years was induced by the increased number of persons susceptible to infection, the unmasking of obscure staphylococcal infections by the control of other disorders, and by the emergence of antimicrobial-resistant strains.\cite{239}

*Streptococci.* Among 59 patients with subacute bacterial endocarditis treated with penicillin, 28 lived for 6 to 13 years; 22 are well but six have congestive cardiac disease. In eight who lived longer than five years death was caused by a ruptured aortic valve in one, cardiac failure in three and a vascular rupture in three, and one died after a cardiac operation. Less than 10% of men more than 60 years old survived. Infection recurred in six patients 3 to 10 months after therapy; in four the initial treatment probably was inadequate.\cite{240}

In one series of cases non-haemolytic streptococci caused 67% of endocarditis before 1943. Because rheumatic cardiovascular disease has diminished in incidence, streptococci were the cause of only 46% of valvular infections since then. Staphylococci, gram-negative bacilli, yeasts and fungi have assumed importance.\cite{241}

Five sporadic cases of haemolytic streptococcal pneumonia occurred during or after minor viral infections of the respiratory tract. Pleural effusion characteristic of this kind of pneumonia appeared in each. Procaine penicillin was used for therapy and the response was slow.\cite{242} In severe disease such as this, quick-acting crystalline penicillin should be used.

*Typhus.* Epidemic typhus happened among nomadic Arabian tribes during the first five months of 1961. The clinical behaviour was typical in 44 patients observed in a hospital. The complement-fixation, hemagglutination and Weil-Felix tests were of diagnostic value in 42 patients. Tetra- cycline and chloramphenicol were effective in therapy, and the addition of a steroid hormone did not change the course of disease. Only two patients died.\cite{243} Three persons apparently were infected by the inhalation of rickettsiae of murine typhus. Early treatment with chloramphenicol seems to be curative, but as in typhoid, relapse occurred in each one. Therapy, therefore, should
be continued for at least 12 to 14 days or until the patient has been afebrile for 48 hours.\textsuperscript{240} The indirect fluorescent antibody test gave specific results in the diagnosis of scrub typhus.\textsuperscript{241} After infection persons become carriers of rickettsias ten times more often than carriers of \textit{S. typhosa} after typhoid, but are more difficult to detect. Chloramphenicol enters leukocytes in tissue-culture, but merely inhibits the growth of rickettsias unless treatment is prolonged. Cells can clear themselves of rickettsias without antimicrobial aid. They are eliminated by inanition or senescence, by extrusion or by some action of immunity or of interferon.\textsuperscript{182}

Serologic evidence of Q (Query) fever was detected in calf in Ontario and Quebec where human infections have occurred.\textsuperscript{242} Tetracycline controls the infection if given within the first three days.\textsuperscript{243} Two attacks of Q fever occurred ten years apart in one patient. Two other patients had specific myocarditis, but recovered.\textsuperscript{244} Seventy-one patients with psittacosis or ornithosis entered Chicago hospitals in 11 years. Antibodies to psittacosis were demonstrated in 41% of persons who had been in contact with parakeets as compared with 6% who had not.\textsuperscript{245}

\textbf{Miscellaneous.} Contrary to previous report, therapy with chloroquine gave no benefit in 100 victims of infectious mononucleosis. Steroids should be used only for the severest cases.\textsuperscript{246} Antibodies against toxoplasma were prevalent in a population and confused diagnosis of diseases of other origin especially infectious mononucleosis. Significant increases in the titres of the toxoplasmal dye test and haemagglutination test were detected in three of 92 patients suspected of having mononucleosis. Toxoplasmas were isolated from the lymph nodes of three patients and from the blood of another.\textsuperscript{247} ‘Glandular’ fever or relapsing lymphadenitis occurred in a patient whose lymph node contained toxoplasmas. Mosquitoes were suspected as the source of infection.\textsuperscript{248} These observations suggest that toxoplasmosis may resemble infectious mononucleosis clinically, or that the microbes as commensals may have been activated, or an anamnestic reaction was evoked during mononucleosis. Infectious mononucleosis is a specific disease not to be confused with febrile lymphadenopathy of diverse origin.\textsuperscript{249}a

\textbf{Histoplasmosis.} Infection with \textit{H. capsulatum} affects 70 million persons in the United States, but is inapparent in most of them. In some, an influenza-like illness occurs and in a few, pulmonary involvement. The disseminated form is rare and often fatal. Pencarthritis, endocarditis and meningitis occurred. Amphotericin B was effective for severe infections and when given before pulmonary surgery. Amounts more than 25 mg./kg. three times a week for 16 weeks may cause serious harm.\textsuperscript{250} Families that moved into an endemic area were infected, probably by inhalation of contaminated dust.\textsuperscript{251} A skin test gave a positive reaction in 30% to 50% of children in Maryland which is east of the main endemic region.\textsuperscript{252} The test gave evidence of infection in 15% of Liberians.\textsuperscript{253}

\textbf{Venereal Diseases.} Syphilis increased 130% in incidence among teenagers in the United States between 1956 and 1960. Each year since 1959 has shown a 50% increase over the previous year in the general population. It is probable that the actual number of cases is more than twice the number of reported ones. According to an estimate, only 25% of venereal infections treated by private physicians are recorded officially. Private treatment of victims has hampered the application of epidemiologic methods of detecting victims and the source of their infections, of widespread serologic testing, and of adequate follow-up endeavour that serves to detect and provide treatment of relapses and reinfecions. Treatment is of secondary importance to overall control and eradication of the disease.\textsuperscript{254} The decline of morals and changing views on sexual habits, no doubt, aggravate the problem. The private physician’s responsibility was portrayed in a special communication.\textsuperscript{255} Acute penile lesions are not always syphilitic. Among 35 military men, herpes simplex virus caused one-third of infections and chancroids one-fourth. Fusospirals, condyloma acuminatum and trauma were other causes. Mycoplasm (PPLO) was present in 50% of cases.\textsuperscript{256, 257}

Uncertainty exists about the occurrence of antimicrobial-resistant gonococi, but evidence indicates that the germs still are sensitive in varying degrees. When gonococi resist penicillin or if patients are sensitive to it, tetracycline may be administered instead. The results were about the same as for penicillin. Failure of treatment after 30 days with either drug was recorded in about 11% of patients.\textsuperscript{258} Mimea bacteria may cause gonorrhea-like infection and resist therapy.\textsuperscript{258} The cause of Reiter’s syndrome, often considered as a venereal disease, is elusive. Data concerning 35 cases were reviewed. Mycoplasma (PPLO) were obtained from the synovial fluid of three of 18 patients, and from the genito-urinary tract of 14 of 35. One or another or combinations of the triad of urethritis, conjunctivitis and arthritis may recur for months or years, with or without mucocutaneous lesions. Treatment with sulphonamides and antimicrobics failed.\textsuperscript{249}

\textbf{Miscellaneous} Several years ago the existence of acute amebic hepatitis was doubted. Report by physicians in Athens now describes four cases of chronic non-suppurative amebic hepatitis. Granulomas and spheroids resembling amebas were present in the liver. Question as to the possible later development of cirrhosis was raised.\textsuperscript{261} Kala azar has been recognized in north-eastern Africa since 1900. The disease was said to differ somewhat from that in China because it does not affect infants so often. Therapy with antimonial compounds was not ideal, since 20% of treated patients died.\textsuperscript{262} A simple rapid flocculation test was said to be of value for the diagnosis of schistosomiasis. The means for
the test consists of a few drops of blood, a stable suspension of antigen, charcoal and a plastic-coated card.²⁶³

Contrary to much opinion, clonorchiosis rarely causes symptoms.²⁶⁴ Similarly, both human and animal filariasis may be inapparent clinically, but may give rise to tropical pulmonary eosinophilia as an allergic reaction to the antigens of filarias.²⁶⁵ Filarial worms were seen in tissue from a swollen inguinal lymph node in a person who had never been far from New York City. The source was undetermined.²⁶⁶ Systemic blastomycosis was treated successfully in 21 of 23 patients with 2-hydroxystilbamidine. Amphotericin B also was effective.²⁶⁷

Although Giardia lamblia often is suspected as a cause of enteric disturbance, the records of 430 patients with giardiasis gave little evidence of its pathogenicity. It is a commensal in the duodenum, but may cause ulceration in debilitated persons and in states of malabsorption.²⁶⁸ Similar uncertainty pertains to listeriosis that is widespread in man, animals and birds.²⁶⁹ Listeria often is commensal and is invasive only when host resistance is impaired.

Interest recently revived about the longevity of microbes. The reported presence of living bacteria in coal and in mummies exhumed in Siberia is doubtful. On the other hand, Cl. tetani were said to have survived in vitro for 40 years and a virus for 38 years. Anthrax spores were reported to be viable after 68 years,²⁷⁰ and fungi were recovered from ancient Mexican tombs.

A symposium about microbial warfare was reported in *Military Medicine* of February 1963. The chances of causing a widespread epidemic of any disease, fortunately, do not seem very great. It will be of interest to see if a new apparatus, the biotelescanner, will be of practicable value to detect the causative agents of infection and changes in such microbes at a distance, to detect vectors and hosts of pathogens, to screen people for antibodies and to investigate endemic and exotic diseases.²⁷¹ It may be of value if applied to lunar or Martian exobiology.

In a co-operative study no important benefit could be discerned from the use of cortisol (hydrocortisone) in the treatment of patients severely ill with various infections.²⁷²

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