Annual Review

INFECTIOUS DISEASES
ANNUAL REVIEW OF SIGNIFICANT PUBLICATIONS
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Viruses and viral diseases were the subjects of continued intensive study in the past year. Attempts to prepare vaccines for the prevention of specific infections, especially of the respiratory tract, have not had much success because of the complexities involved. No important curative agents were discovered, nor has a causal relation of viruses to cancer in man been proved. Many new antimicrobial agents, or old ones with new names, were tested. As causes of disease and death, gram negative bacillary infections now displace those formerly caused by gram positive cocci, as a result of iatrogenic impairment of host-resistance and other factors. The incidence of venereal diseases and of tuberculosis increased. Meningococcal meningitis, the one disease for which antimicrobial prophylaxis seemed to have the most value, caused serious epidemics despite efforts to control it.

Antimicrobics

New Antimicrobics. According to Garrod, there is little to be gained by the increasingly unprofitable search for new antimicrobics from natural sources. Some of the recently advertised ones are the same as, or similar to, ones in use. Synthetic or semisynthetic ones may hold more promise.

Two new broad spectrum antimicrobics especially for the control of gram negative bacillary infections were discussed in three papers in the Journal of the American Medical Association of September 14th, 1964. Gentamycin is active against Pseudomonas, less so against Proteus and Staphylococcus. It resembles streptomycin, neomycin, kanamycin and paromomycin chemically, its antibacterial action is about the same and it occasionally causes deafness. Cephalothin (Keflin), a semisynthetic broad spectrum agent has a similar range of action and is less toxic even in patients with renal failure. It was ineffective against Pseudomonas and enterococci. It differs chemically from penicillin and can be used against penicillin-resistant staphylococci, and for patients sensitive to penicillin. It is not absorbed when given orally. Neutropenia may be induced.

Sodium colistimethate (Colymycin) 2 to 2.5 mg./kg. every 12 hours injected intravenously cured five of eight patients infected with Pseudomonas. Smaller dosage was necessary when the renal function was impaired. It may be neurotoxic, cause apnea and must be used with caution in the presence of chronic debilitating disease, renal impairment, hypoxic states, and if muscle relaxants, corticosteroids, narcotics or sedatives are given at the same time.

The activity of nafcillin, ancill, and cloxacillin was reduced in media containing serum, but cephalosporin was unaffected. Several observers found no differences in the results of therapy with ampicillin, nafcillin, oxacillin, methicillin and cephalothin. The action of lincomycin and pristinomycin was said to be similar to that of streptomycin, streptogramin, spectinomycin, synergin, and mikamycin. An antagonism between lincomycin and erythromycin interfered with their effect on staphylococci. Lymecycline was said to be as effective as tetracycline for treating chronic bronchitis. Hamycin was active against Cryptococcus neoformans and H. capsulatum in inoculated mice. Ethambutol may be effective against tubercle bacilli refractory to other agents. Several years must pass before the value of any of these agents can be judged. As if the names for new products mentioned so far are not confusing enough, these also have been coined: quinacillin, everinomycin, almacetin, pediamycin, viractin, monicamycin, enteromycin, seligomycin, xanthomycin, rubiflavin, antimycin, oligomycin, tolfanate and others. There is no limit for new alphabetic combinations.

Antimicrobial Therapy. The administration of huge amounts of antimicrobics given "just to be sure" is deprecated. But recent studies showed that penicillin in doses of 20 to 60
million units (12 to 36 grams) a day given intravenously cured many gram negative bacillary infections. The amount in the serum reached 737 units/ml. Cerebral irritation occurred in patients with renal failure or central nervous disease. Obviously, the sensitivity of gram negative bacilli to penicillin should be determined. Those inhibited by 78 units/ml. or less are classed as sensitive; resistant ones resist 625 units/ml. and are uncontrollable18.

Thirteen patients with bacterial endocarditis were treated successfully with propicillin (phenoxypenicillin) or ampicillin given orally. Infections with Str. viridans responded better than those caused by Str. fecalis14. Penicillin given prophylactically during cardiac catheterization had no influence on the incidence of subsequent bacteremia. Its use therefore is unwarranted19.

The therapeutic effect of penicillin combined with sulfonamides is unpredictable. Increased, indifferent or decreased antimicrobial effect may follow. If the combination is used, full doses of each are indicated. Semisynthetic penicillin alone or combined with penicillin G and other antimicrobics was said to be of therapeutic value against infection with isoniazid-resistant tubercle bacilli27.

Acute pericarditis occurred as a hypersensitive reaction to penicillin16, and oxacillin caused hepatitis19. Huge doses of penicillin caused severe anemia in two patients20. Pencilloyl-polysylaine introduced as an agent to detect sensitivity to penicillin, itself caused a generalized eruption after the injection of a skin-test dose21.

Airborne contamination with penicillin of many products made in large pharmaceutical plants is a serious problem. It would be difficult to recall such products now on the market and to destroy the ones in reserve. Chloramphenicol suppressed the formation of antibodies in vitro and in experimental animals. Therapeutic doses in eight patients suppressed antibody formation after the injection of tetanus toxoid in six and was hemotoxic in four22. Chloramphenicol applied to the conjunctiva caused pancytopenia in a patient whose niece had succumbed to aplastic anemia after oral therapy22. The reason for the topical use of the agent is unclear.

Amphotericin B should be used only when actually needed. The blood urea was increased in amount in 93% of 81 patients during treatment. The renal function was persistently reduced in 7 of 16 patients who received more than 4 g., and in six of 36 who were given less. Tubular lesions and deposits of calcium occasionally were found. Other untoward effects also occur. The subject was discussed in two papers in the Annals of Internal Medicine of August, 1964. Actinomycin D was teratogenic in rats25.

Broad spectrum antimicrobics decrease the rate at which colon bacilli are killed by human serum, probably by inhibiting bacterial metabolism and impairing the lytic action of serum. The matter may be of therapeutic import21. The same amount of antimicrobics entered the blood after intraperitoneal injection as from injection by other parenteral routes. The method may be used in place of intravenous and intramuscular injection25.

In regard to indiscriminate antimicrobial therapy, Harris wrote that something has weakened clinical judgment: physicians who prescribe digitalis or quinidine (which are poisons) with the utmost caution, pounce avidly on chloramphenicol and other antimicrobics for minor illnesses. They would always make tests of sensitivity before injecting tetanus antitoxin, but not before giving penicillin whose danger in causing a reaction is as great25. Antimicrobics-induced diseases were described in a book27.

Viral Infections

Respiratory Tract Infections. Sir Christopher Andrewes, who with Smith and Laidlaw, discovered the virus of influenza in 1933, has also contributed to the knowledge of common colds. In a review, he points out the complex, poorly understood epidemiology of these ubiquitous infections. Respiratory tract viruses no doubt spread from person to person by the airborne route, but various determinant factors operate to cause epidemics. Meteorologic changes seem to be important at times, but a wide range of stresses, including chilling, may disturb the host-parasite relationship enough to permit the invasion of microbes. The operation of viral interference and of interferon itself probably play a role28. By indirect methods, droplets bearing the viruses were expelled in greatest amount by sneezing. Most of them fell to the ground and about 10% were small enough to be airborne. Saliva contained very little virus. Viruses die soon after shedding29. Four papers on airborne infections pertaining especially to those acquired in laboratories and in hospitals appeared in the October, 1964, American Journal of Public Health. Methods for their control were outlined.

Rhinoviruses. Fifty-three types of rhinovirus are known and there are many others. Rhinoviruses of 46 types were isolated from 10% of infected adults and from 5% of children. Children were more severely affected, and half...
of them had viral pneumonia. Adult volunteers inoculated with rhinovirus usually had coryza, but several had tracheobronchitis. The multiplicity of specific types and the constant changes in the human population explain why some persons have repeated colds in a season. Little hope was held for the preparation of effective vaccines. Hilleman discussed the problem of vaccination against a variety of viral infections. Perhaps the introduction orally of viruses into the enteric tract in specially coated containers may elicit immunity without causing respiratory tract symptoms or illness. Epidemiologic and antimicrobial prophylactic efforts have failed as preventive measures.

**Adenoviruses.** Adenovirus Types 4 and 7 caused sharp, localized, winter epidemics among military personnel over a 4-year period. The antibody titer for adenovirus rose in several victims of respiratory tract infection and acute thyroiditis suggesting that the virus was the cause of both. Pharyngitis, cough and fever often accompany epidemics of keratoconjunctivitis caused by Type 8 virus each summer in Taiwan.

Apprehension was raised lest contamination with an oncogenic hybrid offspring of a mating between adenovirus Type 7 and SV40 virus used in vaccine may occur. This raises the further question whether vaccination against usually mild infections is desirable or necessary. The distribution of adenovirus 7 vaccine has been stopped for the time being.

**RS Virus.** Respiratory syncytial virus caused two winter epidemics in a nursery for premature infants. Coryza usually lasted one to eight days before respiratory distress began. Pneumonias occurred in 9 of 14 sick infants. RS Virus caused 60% of pneumonias among infants and children in Newcastle. Antibody against the virus was present in 66% of 329 persons, chiefly in adults. Neutralizing antibody was found in 25% of persons of all ages, and after four seasons, the percentage rose to 83. RS virus is related to measles virus and may cause an exanthem.

Reovirus caused hepatitis, encephalitis, myocarditis and pneumonia in children. In one victim, virus was recovered from the brain and feces.

**ECHO virus Type 25** is an enterovirus, and a strain isolated from feces caused febrile respiratory tract infections in intranasally inoculated adult volunteers.

**Influenza.** A commercially prepared polyvalent vaccine that contained antigens to the current viruses failed to prevent infection among 90 children against influenza A as compared with 90 control subjects. Antibody induced in the blood in titer higher than 1:64 was not protective. Oil-adjuvant vaccine was shown to evoke antibody that persisted as long as 16 months, but in accordance with the preceding sentence, the protective value of measurable antibody in the blood is of little significance. In another institution, an outbreak of influenza A2 affected children who had been vaccinated with a polyvalent vaccine five months before. The number of illnesses among the vaccinees was slightly less than in non-immunized children. Encephalopathy appeared 12 hours after a child had received a polyvalent vaccine.

U.S. Public Health Service officials predicted no widespread epidemics of influenza this year. From past experience, one wonders how trustworthy such predictions are. Influenza A2 was rampant in the United States and in Europe in the winter of 1964-1965.

By a specific immunofluorescent technique, influenza virus was detected in bronchial epithelium 8 hours after the inoculation of mice, mostly in the cytoplasm and occasionally intranuclearly. Virus reached a maximum amount in tissue in two to three days and progressively invaded the bronchi, bronchioles, alveolar ducts and alveoli. Fluorescence vanished after seven days.

A parainfluenza virus liberated a pyrogen from granulocytes in the blood that caused the fever of infection. A lysozymic or antibody-like microbic-inhibiting substance was demonstrated in mucosal secretion years ago by Fleming. Recent studies of nasal secretion disclosed that its viral neutralizing activity correlated with the presence of specific antibody to each of several viruses tested. During respiratory tract infection, antiviral substance was chiefly in the gamma 2-globulins.

From 210 students with acute respiratory tract infections, only two kinds of viruses were recovered. In 122, serologic evidence of influenza B was present in 16 and of respiratory syncytial virus in five. To account for the large percentage of unidentified infections, either the technique used was faulty, immune bodies failed to appear, or unknown microbes awaited discovery.

Study of 300 other students with acute pharyngitis-tonsillitis disclosed hemolytic streptococci to be the cause in about 25%, as recorded in previous surveys. Viruses were causal in 38%, and 36% were of undetermined cause.
origin. Surprisingly, the virus of herpes simplex was implicated in 13%. Coxsackie, influenza, parainfluenza and adenoviruses accounted for three to five per cent of infections. Twenty-three of 86 patients, regarded as having a viral infection also harbored hemolytic streptococci. Specific diagnosis of the six different infections mentioned seldom could be made clinically because of many features in common. A few points of differentiation were helpful: Exudate, cervical adenitis and leukocytosis were present in 26% of streptococcal infections and in 14% of the others. General aching was present in 3.4% of patients with streptococcosis, as compared with 23% during viral infections. Penicillin therapy failed to shorten the course of any of the infections and broad spectrum agents seemed to prolong illness. Penicillin is indicated: (1) if the patient has had rheumatic fever, glomerulonephritis or repeated attacks of streptococcal sore throat, (2) in the presence of exudate, severe inflammation, otitis media or leukocytosis higher than 13,000/u. mm., (3) for severe sore throat in the absence of rhinorrhea, hoarseness or cough, and (4) if other chronic disease exists. Cultures of the exudate and other tests to identify the cause should be made in any event.

Pneumonias. Specific pneumonia occurs in one-third of victims of varicella, but in less than 3% of those with herpes zoster. Twenty-two cases of the latter were reviewed. Mycoplasma Pneumoniae. Two reports emphasize the frequency of respiratory tract infections caused by Myco. pneumoniae, with and without pneumonia. One paper perpetuates the outmoded term "primary atypical pneumonia" that should not have been coined in the first place. Myco. pneumoniae infections are nonseasonal, but they accompanied a winter epidemic of adenoviral pneumonia. These are circumstances that I described in 1938 before either agent was known. An agent was recovered that in retrospect probably was Myco. pneumoniae. The historic aspects of these earliest observations were recited.

Cold agglutination occurred in eight patients who had meningoencephalitis and mild upper respiratory symptom without pneumonia. Two had mucocutaneous fever (Stevens-Johnson syndrome). In 1944, I reported severe nonpneumonic disease in a patient whose cold-agglutination titer rose to 1:20,000. During the course of infection, Myco. pneumoniae causes cold-agglutination of erythrocytes by altering the I antigen that evokes erythrocytic auto-antibody.

A hemagglutination test for the detection of antibody for Mycoplasma pneumoniae is simpler to perform than the immunofluorescent procedure. Antibody against the microbe was demonstrated in titer of 1:256 or higher in five victims of mucocutaneous fever (Stevens-Johnson syndrome), a disease often characterized by a viral-like pneumonia. Because Mycoplasma (PPLO) has no rigid cell wall, it is pleomorphic and hard to see microscopically. Question was raised if it is a virus, a fungus, or a bacterium that has lost its wall and therefore is not an independent microbe. A newly recognized Mycoplasma caused fatal septicemic disease in puppies.

Psittacosis caused 24 cases of pneumonia in Scotland from 1950 to 1963. Several victims contracted the infection from pigeons or budgerigars. In 1963, 54% of pigeons in Glasgow were found to be infected, but apparently they were not a source of disease in man. Antimicrobics added to food for parakeets and other birds was said to minimize the risk of spreading psittacosis.

A peculiar form of pneumonia occurred in six patients who had renal transplants and were treated with azathioprine and prednisone as immunosuppressants. Cold agglutination of erythrocytes occurred in five. The disease, uninfluenced by antimicrobics, lasted 12 to 34 days. Necropsy in one disclosed Pneumocystis carinii and cytomegalic inclusion disease. Others may have been caused by Mycoplasma.

Cytomegalovirus was recovered post mortem from the lungs of four recipients of renal homografts. The disorders represent maladies induced by iatrogenically impaired resistance. The virus was found in 1% of 200 well children. Among 20 symptomless virus-positive children, 14 had hepatomegaly, and five had splenomegaly. The virus was isolated from nine of 23 children with chronic hepatic disease.

Other Viral Infections

Rubella. Rubella, absent for 22 years, caused a large epidemic in Alaska as described in two papers in the J.A.M.A. of February 22nd, 1965. Virus was recovered 13 days before the rash appeared and for 6 days afterward. Inapparent and mild infections were common, and 40% of patients had no rash. Rubella virus isolated from seven patients during an epidemic in Texas was pleomorphic by electronmicroscopy. Some victims had classic rubella, others had severe arthritis. Clinical differentiation from ECHO virus infection may be impossible and the name rubeco virus disease was applied to an outbreak in Africa. Nine months later more
than 30 infants were born with congenital defects. Rubella virus was isolated up to 41 weeks after birth from three malformed infants whose mothers had been infected in first trimester. Virus survived in uterus in mothers for at least 36 weeks. Four nurses contracted rubella by handling congenitally infected infants some of whom shed virus for months after birth. During an epidemic, the injection of gammaglobulin seemed to prevent rubella as compared with control persons. In other studies, gammaglobulin failed to prevent rubella in mothers and in experimentally infected children. For the present, it may be wise not to rely on gammaglobulin as a protective agent. About 17% of pregnant women have no demonstrable antibody for rubella. The salivary gland virus caused 1% to 3% of birth defects. Unfortunately, the infection usually is inapparent in adults and is undetectable without special investigation.

Measles. In a region of Alaska where measles had not occurred since 1942, 164 persons received live measles vaccine and gammaglobulin. About 7% of them reacted with fever and 6% had a rash. The failure of antibody to increase in titer in seroimmune persons indicated that durable immunity had followed a natural attack of the disease. The immunity evoked by one injection of an improved vaccine persisted for 30 months. Reactions thereto occurred in 5% of vaccinated children.

At a symposium on virology in Florida, Smorodintzev reported success in vaccination against mumps with live attenuated virus applied transnasally. The vaccine can be administered with antimeasles vaccine, but not with gammaglobulin which neutralizes mumps virus.

Contrary to previous opinion, the incubation period of infectious mononucleosis instead of being four to 15 days was 34 to 39 days in seven patients. At a recent meeting of the American Association for the Advancement of Science, Schneider described evidence that a virus caused the disease. The agent was said to have been isolated in tissue cultures from the blood and from the liver of patients. A benign infection resembling infectious mononucleosis, presumably viral in origin, was transmitted to nine patients by the transfusion of blood after open cardiac surgery. Symptoms appeared after three or four weeks.

Herpes Simplex. Constitutional symptoms and dermal lesions among five wrestlers posed a diagnostic problem, until it was shown that close contact and dermal abrasions favored infection with herpes simplex virus as "Herpes gladiatorum".

Fatal herpes simplex necrotizing pneumonia of an infant was acquired during passage through the birth canal of the mother with primary herpetic vulvovaginitis. Gammaglobulin injected into the mother before delivery had no effect. Herpes simplex cervicitis was caused by sexual contact with recurrent herpetic genital lesions. Herpes viral pneumonia and toxoplasmic encephalitis were fatal in a patient with Hodgkin's disease treated with prednimson, alkylating agents and roentgen rays. Herpes virus is an occasional unsuspected cause of viral pneumonia. Herpes simplex in a 9-year-old boy was said to have caused 17 episodes of psychosis during three years, coincident with vesicles on the oral mucosa and encephalitis.

Viral Hepatitis. Among 737 military men exposed to hepatitis after eating food contaminated by an infected food-handler, 96 were investigated. In most of these, hepatic functional tests gave abnormal results and biopsy of the liver of 68 showed histologic evidence of hepatitis in 51. Only three were icteric. Thirty cases of inapparent hepatitis discovered by laboratory tests during a routine study of Koreans also portrayed symptomless infection.

By using sensitive procedures for detecting hepatitis, infection by transfusion occurred oftener than believed. Among 56 patients who had received blood, 10 had evidence of inapparent infection, but none was icteric. In two, evidence of hepatitis appeared within six weeks, and in two others hepatic disturbance persisted 10 months. The rate of inapparent to overt infection was estimated as 1:100. The three articles just referred to have examples of transient inapparent infections that account for undetected carriers who serve as sources of infection. The number of cases of hepatitis in the United States reached a peak in 1960-61, but has declined. The next 7-year cyclic peak may occur in 1968.

Viral hepatitis affects other tissues besides the liver. Inflammation and granulomas were detected in specimens of gastric and intestinal mucosa and of the kidneys. Mild anemia and hemolytic anemia occasionally were observed. Since 1961, 87 cases of hepatitis occurred in persons in close contact with chimpanzees of other primates. The mode of infection suggested airborne transmission which seems possible, but thus far is unproved.

There are three or more serotypes of the
causal hemovirus. Inoculation with tissue-cell cultures caused hepatitis in four of 15 volunteers. Hepatitis has a spectrum of severity ranging from inapparent infection to fatal jaundice. Hemoviruses are prevalent in healthy persons without their having had known hepatitis. If epidemic hepatitis and serum hepatitis are caused by the same viruses, but differ clinically according to the portal of entry, one wonders why gammaglobulin protects against one and not the other.

Strain WW-55 virus caused mild hepatitis in inoculated West African monkeys, the first time that this has been accomplished. Treatment of plasma with propiolactone and ultraviolet radiation was said to eliminate the danger of transmission of the virus. Several authorities do not believe that the viruses of hepatitis have been isolated.

As in the case of viral hepatitis just mentioned, there has been a tendency to regard many viruses as specifically unitropic, but evidence accredits that other tissues also are affected. The myocardium, the gastrointestinal and neural system may be invaded by enterorespiratory and varicella viruses; herpes zoster may be disseminated especially in victims of lymphoma and in those treated with corticosteroids; and various tissues are involved in mice inoculated with the virus of lymphocytic choriomeningitis. Disturbed renal function and viruria occurred in victims of mumps. The virus may cause renal lesions and induce occasional transitory nephritis. To see if the kidneys were the site of viral multiplication, and to account for viruria, attempts were made to recover viruses from the kidneys of children at necropsy. From 158 specimens, 84 yielded viruses, but the number decreased with increasing age of the subject. Cytomegalovirus, adenovirus, measles, varicella and Coxsackie viruses were recovered. In five instances, the isolated virus probably was related to the disease of the child. The others probably were commensals.

Recently, when antismallpox vaccination was widespread in England and Wales, 185 persons had eczema vaccinatum. More than half of them were accidentally inoculated and 6% died. Vaccination may be hazardous in hypersensitive people. Acute genital arthritis occurred 12 days after vaccination against smallpox. The virus of vaccinia was present in the synovial fluid. Doubt has been cast on the need for routine general vaccination in the United States.

Enteroviral Infection. Apprehension was raised by the occurrence of 87 reported cases of poliomyelitis-like illness associated with or caused by orally administered antipolio vaccines. It was not possible always to determine if vaccines caused infection. Fifty-seven suspected cases, mostly in adults, occurred 4 to 28 days after vaccination. For that reason a suggestion was made, but with dissent, not to vaccinate persons more than 18 years of age, except under circumstances of unusual risk. The danger of vaccine causing serious infection is minimal, considering the millions of persons so treated. Concurrent enteroviral infections interfere with the action of polio vaccine.

In a study of the cause of sudden unexpected death of infants, ECHO viruses Types 7 and 22 were isolated from 7 of 10 babies. Whether or not the viruses were pathogenic was uncertain. Enteroviruses were "typed" successfully by complement-fixation. The technic was reliable and correlated with neutralization tests. The clinical aspects of enteroviral infections in general were reviewed by Altman.

Viral Dysentery. Bacteria were the chief causes of diarrhea among 214 Puerto Rican children. Coxsackie and ECHO viruses were isolated from 22% and specific immune bodies appeared in the blood of most. Mixed viral, bacterial and parasitic flora were present in 23%. "Epidemic collapse" affected 404 pupils in three schools in Coventry in 1964. The features were frontal headache, nausea, vertigo, collapse abdominalgia, sore throat, cough and vomiting. Diarrhea occurred in only 11%. A virus was suspected as the cause. This infection also is called epidemic nausea and vomiting and seems to be similar to epidemic viral dysentery except for the infrequency of diarrhea.

Meningoencephalitis. St. Louis encephalitis virus exists in human serum, in domestic pigeons, mice and in mosquitoes of South and Central America, the West Indies and Florida as reported on in seven papers in the May, 1964, issue of the American Journal of Tropical Medicine. An epidemic of St. Louis encephalitis occurred for the first time in Pennsylvania and New Jersey. Forty-four cases and five deaths were reported, but many more mild cases, no doubt, were undiagnosed and uncounted.

Reoviruses were recovered from the stools of three children with encephalitis and hepatitis. The viruses could not be proved to be the cause except for the presence of virus Type 1 in the stools and in the brain in one fatal case with myocarditis and interstitial pneumonia. Herpes simplex virus was recovered from the brain of a child with encephalitis.
Two adults had three or four attacks, and two children had two attacks of meningoencephalitis at intervals of four months to eight years. Coxsackie B5 and B2, and ECHO 1 and 7 apparently were the causes. The same virus or different ones may cause successive infections.

Road building in Liberia favored the spread of the tsetse fly from endemic areas of Gambian encephalitis. The flies now are a dangerous roadside hazard.

Eight of 520 bats in New England had evidence of infection with rabies virus, but only 3 seemed sick at the time of study. The authors were apprehensive of the spread of infection to other forms of wild-life. It is more likely, however, that rabies was always endemic in the region and is not apt to "spread" anew. Rodents rarely transmit rabies to man. Among 50,000 rabid animals only 199 (0.42%) were rodents; 82 were squirrels. Attempts are underway to collect serum from vaccinated veterinarians as a substitute for hyperimmunized horse serum that causes serious reactions. Apparently many persons receive antirabic vaccine unnecessarily. An estimated 30,000 people were so treated annually. In August a bite by a skunk caused the first reported case in the United States in 1964. Immediate vaccination failed to prevent death. In Brazil improperly prepared vaccine caused fatal post-vaccinal encephalomyelitis in 18 of 66 persons. One wonders if more persons die from vaccination than from rabies. Inapparent attacks and mild rabies never have been observed in man. Nevertheless, according to Bell's experiments, recovery is possible since 33% of his mice survived after inoculation.

Russian scientists believe that a variant of rabies virus may cause multiple sclerosis and acute disseminated encephalomyelitis. Another virus suspected to cause amytrophic lateral sclerosis is being investigated in the U.S.A.

Hemorrhagic Fevers. The hemorrhagic fevers of Asia seem to be caused by one or more viruses possibly related to dengue virus. Dengue viruses were isolated from victims of hemorrhagic fever in Singapore, where the disease generally was mild except in young children. A similar disease called Machupo observed in South America was caused by a virus similar to Junin virus and probably is transmitted by a wild rodent. One wonders if this is a "new" disease or one that has come to attention. Hammon warned that A. aegypti mosquitoes may spread infection to the southern United States and elsewhere. To account for the disease, he suggests that dengue virus acquired unusual pathogenicity by genetic transformation. If the Junin and Machupo viruses are similar to the Asian viruses, and if all are members of the dengue group, it is likely that they are antigenically related, but not necessarily mutant forms.

An accidental infection in a laboratory worker with the virus of louping-ill had features similar to Kyasanur Forest disease and Omsk hemorrhagic fever. Thrombocytopenia and bleeding are common to each, but also to dengue and other viral diseases.

In a flurry of papers, thrombocytopenia and purpura were described as peculiar to dengue, mumps, rubella, and infectious mononucleosis. A diminution of circulating platelets during pneumococcal pneumonia and compensatory thrombocytosis shortly after were described 40 years ago, and during typhus in 1929. Similar changes induced in inoculated animals resulted in purpura. Thrombocytopenia apparently is a common occurrence during infectious diseases.

Newly Recognized and Unusual Viral Diseases. Knowledge of epidemic neuromyasthenia of unknown cause was reviewed. A "new" or hitherto undescribed dermatitis was characterized by fever, leukocytosis and painful dermal plaques with dense infiltration of neutrophil cells. Tetracycline had no therapeutic effect but cortisone caused rapid improvement. A peculiar epidemic infection with a papulo-vesicular rash on the hands and feet, called "Summer-term blains" affected 90 of 488 school-girls in England. A virus was suspected as the cause but none was isolated.

Chargers virus was isolated from persons in Panama. A man exposed to epizootic bovine abortion died from pneumonia caused by an agent of the bedsonia group similar to the cause of the bovine disease.

Mink disease of probable viral or mycoplasmal origin caused hypergammaglobulinaemia like that of multiple myeloma. A virus of mouse lymphosarcoma caused hypergammaglobulinaemia, plasma cell infiltration and amyloidosis. Amyloid nephrosis occurred in the late stage of lymphocytic choriomeningitis.

A virus that seemed to be the cause of human warts was cultivated in vitro. The virus of Venezuelan equine encephalomyelitis was isolated from the mawor late in the disease when it was not found elsewhere in the body. The procedure may be applied successfully for the diagnosis of other viral infections.

Miscellaneous Viral Studies. "Hospital
infections” caused by staphylococci and salmonellas are of serious import, but other microbes also are blamed. Chief among these are the viruses of hepatitis, smallpox, poliomyelitis, Coxsackie and ECHO disease, herpes simplex, vaccinia and respiratory tract infections. Viruses may be transmitted by contaminated enema tubing. Although viruses were present only in the central neural system in seven of 48 dead infants, they have not been proved to be the causes of unexplained sudden deaths as mentioned previously.

More knowledge of “slow acting” viral infections of animals may shed light on the cause of some obscure human maladies. Ovine diseases such as scrapie, maedi and visna, and perhaps mink disease, are examples. They have characteristics resembling lupus erythematosus, rheumatoid arthritis, myeloma, polyarthritis, multiple sclerosis, pneumonia and encephalitis.

An interferon-like substance produced by herpes simplex virus suppressed the activities of vaccinia, herpes and influenza viruses. Because antibody to herpes simplex seems to have no effect on the infection or in preventing it, interferon may regulate the host-virus equilibrium. Interferon in the crusts of vaccinal lesions may be a nonfunctional response to viral growth or may suppress viral growth until an immune mechanism evolves. It also may modify the clinical course of smallpox.

Antiviral Agents. The antiviral activity of IDU (5-iodo-2’ deoxyuridine) may depend upon the short intermolecular distance between the iodine and oxygen of a carbonyl group. The agent not only inhibited the multiplication of Rous sarcoma virus in vitro, but suppressed the transformation of cells into malignant ones. A combination of 5-bromo-deoxyuridine and N-methyl-isatinthiosemicarbazone eradicated vaccinia virus from cultured cells.

Views on the efficacy of IDU to cure vaccinal and herpic ketritis and dernal herpes are at variance. In experimental studies, infected rabbits that were treated improved temporarily, but infection persisted. Similar disappointing results ensued in patients. In one study, treatment with IDU delayed healing. Another drug, tri-fluorothymidine may be of value in therapy. IDU failed in the treatment of herpes zoster, cutaneous herpes simplex and trachoma and 5-fluorodeoxyuridine had no effect on rubella virus in cell-cultures.

Amantadine inhibited the growth of influenza virus in vitro. Therapeutically, the agent had antiviral activity in mice inoculated with the virus if given within 72 hours of infection. It also inhibited the growth of rubella virus. Viractin (actidione) from Strepzymes griseus had doubtful value for respiratory tract infections. Sulfamethoxypyridazine was said to cure trachoma, and a vaccine seemed to be effective for prevention. Other antiviral agents under study are: halogenated pyrimidine nucleosides for herpes viruses, hydroxybenzylbenzimidazole and guanidine for picorna viruses, and pteridines and cyclopin for others.

Improvements in the diagnosis and treatment of cutaneous viral infections were reviewed.

A thiosemicarbazone (methisazone) said to be of value as a prophylactic agent against smallpox in India, gave disappointing results in South Africa. It has no therapeutic value.

Viruses and Neoplasia. Because of evidence relating viruses to the cause of leukemia, the Congress of the United States authorized ten million dollars to support further research for these reasons: Virus-like particles were found in 30% of children with acute leukemia; the particles were structurally the same in human and animal leukemias; virus-like particles were transmitted in mouse milk to infant mice; and a hope that vaccines to prevent leukemia may be developed.

Electronmicroscopy disclosed discrete virus-like particles in human embryonic tissue infected with material from the bone marrow of patients with leukemia, but similar particles occasionally were seen in control cultures. Microbes isolated from leukemic children either were viruses or mycoplasmas that caused leukemia-like disease in inoculated mice. They were not found in normal or leukemic adults. Confusingly, similar microbes were isolated from children with sarcomas and with lupus erythematosus. The usual question of the presence of commensals activated by impaired host-resistance pertains. Viral and mycoplasmal particles obtained from human leukemic tissue appeared in the viscera of marmosets inoculated therewith. A relation between the particles and leukemia was not established, but similar ones have been found in leukemic mice, not in normal ones according to Domchowski’s report at a recent meeting. On the other hand, neither Girardi nor Phillips and their co-workers were able to isolate viral agents from children with acute leukemia or with infectious mononucleosis. Epidemiologic research so far has not revealed convincing evidence of a virus-like spread of leukemia in man.

In an attempt to “interfere” with the
presumed virus of leukemia, a variety of viral vaccines was injected into a patient with acute leukemia. Periods of temporary clinical improvement occurred. Injection of gamma-globulin with antimicrobics had no beneficial effect on febrile infections during acute leukemia.

A Reo virus was isolated from a patient with Burkitt's lymphoma that seems to be endemic in Africa. Virus-like inclusions were present in marrow cells of three patients with multiple myeloma, but not in 15 other victims.

The prospects for establishing a causal role of viruses in human malignancy were outlined by Hilleman and Enders. Suspected that some cancers in man either may be caused by viruses or that viruses like other irritants serve as incitants.

Inoculated SV40 virus disappeared rapidly from infant hamsters but reappeared in tumors. Virus was not always present and seemed not to be essential to the retention of oncogenicity. Neutralizing antibody appeared in some animals, but was unrelated to the subsequent appearance of tumors. Cells infected with SV40 virus synthesized viral antigen and also the specific antigen of induced tumors. DNA inhibits the formation of the viral antigen and serves to differentiate the two. An X-irradiated SV40 transplant as a vaccine prevented tumor formation in newborn hamsters inoculated with SV40 virus. Tumor cells produced by SV40 virus in hamsters did not yield the virus on culture, but when seeded onto sensitive indicator cells, characteristic viral lesions appeared. The tumor cells evidently harbored persistent viral subinfection called the "virogenic state." Tumor cells induced by adenovirus Type 12 and polyoma virus failed to show viral subinfection. Evidently, basic differences occur in cells transformed by different viruses.

Adenoviral particles recovered from tumors induced by virus Type 12 were similar to the inoculated ones, but were "incomplete" suggesting why the living, infectious virus could not be isolated despite serologic evidence of its activity. Among a variety of viruses including adenoviruses, influenza, RS, mumps, measles, rhino-, polio, varicella and others, only adenoviruses 12, 18 and especially Type 7 caused tumors in inoculated newborn hamsters. Tumors appeared after long latent periods and were free of detectable viruses. Adenovirus Type 12 transformed hamster cells in vitro to morphologically altered cells, but whether the changed cells were malignant was not determined. The oncogenicity of adenovirus Type 12 in hamsters was inhibited or prevented by the later administration of large amounts of the virus. The larger the quantity of virus inoculated initially, the fewer tumor-free animals.

Because adenovirus 12 induces sarcomas in newborn hamsters, persons who have been infected with the virus should be observed for years. Antibody studies indicated that about 25% of children and 48% of adults have had such infection, often inapparently. In one laboratory, Type 12 virus comprised only 3% of all adenoviruses isolated from 7,000 patients in four years.

According to several investigators, "there is no definitive information at present to relate any known virus to neoplasia in man." Perhaps only a genetic portion of a virus is responsible or a virus may act as an accelerator to chemical or hormonal induced neoplasias which would develop anyway. The problem is summarized in Chapters 15 to 19 of a recently published book.

Bacillary Infections

Tuberculosis. Although a number of sanatoriums for tuberculosis have been closed or used for other purposes, the incidence of tuberculosis has risen in the United States in recent years. Some authorities feel that since anti-polio vaccine has been so successful, had BCG vaccination been widely practiced, a similar decline in tuberculosis might have ensued. Other observers recommend BCG vaccination only for special groups likely to be infected. Its value in protecting against late postprimary tuberculosis is doubtful. Vaccination destroys the value of the tuberculin test to locate sources of infection and for diagnosis. According to Dubos, BCG vaccine evokes strong and lasting immunity only if the nature and quantity of a standard strain of bacilli used are correct, and if the vaccinees are able to produce antibody. At best, acquired immunity does not prevent the primary establishment of lesions nor does it result in the immediate eradication of super-infecting bacilli. Unfortunately, vaccination may prove to have limited usefulness even in unhygienic social environments. Thus the controversy continues.

The hope for the eradication of tuberculosis is dim for several reasons: (a) failure to detect and report cases, (2) failure of victims to accept therapeutic management, and (3) failure to prevent inactive disease from reactivating.

Deaths from tuberculous meningitis have de-
clined after modern therapy, but serious sequels are common among survivors. Among 65 of them, intracranial calcifications ensued in 21, auditory disturbance in 26, and abnormal electroencephalograms in 47. Normal education was possible in only 35\textsuperscript{189}.

Continued surveillance of previously untreated patients has not disclosed an increasing resistance of \textit{Mycobacterium tuberculosis} to antimicrobics. Less than 2\% of strains resisted streptomycin and isoniazid and 2.2\% resisted paraaminosalicylic acid\textsuperscript{187}.

\textit{"Atypical" Tubercle Bacilli.} These bacilli cause pulmonic disease, lymphadenopathy, generalized infection, and destructive polyarthritis\textsuperscript{188} indistinguishable from classic tuberculosis. Skin testing with various tuberculins also suggests the existence of inapparent infections. Both cross-reactions to various antigens and multiple infections probably occur\textsuperscript{189}. The skin reactivity of 947 white infants and children indicated a higher incidence of infection with nonchromogenic atypical tubercle bacilli than with \textit{Mycobacterium tuberculosis} and skotochromogens. Among coloured patients, the relative incidence was reversed\textsuperscript{190}.

Uncertainty persists in regard to the origin of mycobacteria that are regarded as atypical, anonymous or unclassified. Some authorities believe them to be separate, distinct strains; and others, that they are variant forms of \textit{M. tuberculosis}. Perhaps both views are valid. In my own experiments, culture of a strain of standard \textit{H37Rv} for months or years on solid or in liquid media evoked several variant forms that had many, most, or all of the features of "atypical" strains\textsuperscript{191}.

\textbf{Leprosy.} Immigrants from Indonesia increased the number of lepers in Holland to 250. Within months after arrival, supposedly cured patients had exacerbations\textsuperscript{192}. Two patients who failed to improve after therapy with a sulfone compound (Dapone) were infected with bacilli resistant to the drug\textsuperscript{193}. Capreomycin was used successfully to control infection with \textit{Mycobacterium leprae} in the foot-pads of mice. It may have value in treating human victims\textsuperscript{194}.

\textbf{Tetanus.} In a 10-year period, 2,130 cases of tetanus were admitted to hospitals in Bombay. Eleven patients (0.5\%) had had tetanus before; one of them three times. The intervals between attacks varied from three months to five years. All except one recovered. Six of the eleven were hypersensitive to antitetanus serum given for the initial attack. Recurrences may be due to the persistence and reactivation of the original infection or to a new exogenous infection, indicating the need for active immunization in such persons. Apparently little or no active immunity ensues as the result of an attack of tetanus\textsuperscript{195} in some cases.

Active immunization against tetanus with toxoid is the method of choice. Unimmunized persons who need protection should be given human tetanus immune globulin for quick action. Tetanus antitoxin is not reliable and there is danger of reaction to equine or bovine serums\textsuperscript{196}. The use of homologous antitetanus serum that has half-life 10 times longer than serum from other species would eliminate the danger\textsuperscript{197}. Penicillin protected mice against tetanus only when given within four hours after infection, but spores persisted unharmed\textsuperscript{198}.

Nine patients with tetanus were said to be cured promptly by hyperbaric oxygenation therapy\textsuperscript{199}. If \textit{Cl. tetani} were active and were suppressed by oxygen, such treatment conceivably may be effective. But the toxin presumably is bound to neural tissue and the symptoms appear long after bacilli have ceased to grow or have disappeared. If oxygen therapy is curative, its mode of action is obscure.

While tracheostomy occasionally is life-saving when less traumatic measures fail, serious sequels may follow. Among 29 patients so treated, 23 lived more than three days and of these, 18 wounds became infected, eleven by staphylococci and five by \textit{Pseudomonas}\textsuperscript{200}. In another report, complications followed tracheostomy in 33\% of 212 patients, 6 of whom died\textsuperscript{201}. Tracheostomy is greatly overdone.

Parenteral injection of medicaments caused infection with \textit{Cl. welchii} in five patients, three of whom died\textsuperscript{202}. When the buttocks are the site of injection, it is surprising that such incidents are so rare. For this infection, hyperbaric oxygen therapy has a logical base for use against actively growing anaerobes. Some noncytopathogenic viruses caused cytopathic effects in tissue cultures when subjected to 95\% oxygen under pressure, but not in air\textsuperscript{203}.

\textbf{Salmonella.} An epidemic of 23 cases of infection with \textit{Salmonella infantis} probably came from eggs contaminated by a carrier. The disease generally was mild, and in one patient it was clinically inapparent. Despite the indication that the bacilli were sensitive by the tube-dilution test, both tetracycline and chloramphenicol failed in treatment\textsuperscript{204}. No one knows why all salmonellas except \textit{S. typhosa} resist chloramphenicol.

In a 3-month period, 745 cases of \textit{S. newport} infection occurred. These were acquired from
baker products in Upsala. About 66 per cent of victims were inapparently infected; the rest were sick in varying degrees of severity; and one died. Sal. typhosa phage Type A infected 26 persons in Harlow, England. The source probably was contaminated corned beef. One patient had fever but no symptoms, and a child had neither fever nor symptoms yet typhoid bacilli were present in the blood of both.

Salmonella paratyphi B caused an epidemic in Scotland, affecting 188 persons in May, 1964. The source probably was a confection prepared with artificial cream, imported eggs or canned meat. Forty patients were symptomless with inapparent infection. Four victims who had other chronic disease died.

Ampicillin (Penbritin) was said to have controlled typhoid in seven of eight patients and was credited in ridding the bacilli from seven of eight carriers.

Hodgkin disease renders patients particularly susceptible to infection with M. tuberculosis and Salmonella. Three patients infected with Salmonella were observed, two of whom died. Salmonella also may invade victims of hepatitis and others whose resistance is impaired. Pet chicks, dogs and turtles are sources of infection.

Shigella. A cell-free vaccine will be ready soon for clinical trial. One wonders if its immunizing effect will be as poor as that from cholera and typhoid vaccines.

Esch. coli. During an epidemic of enteritis among infants, Es. coli was present in the oropharynx of many symptomless carriers. The carrier rate was 33 per cent in households of neighboring families and 0 per cent in more remote places. Airborne transmission seemed likely to have occurred. The percentage of strains of Escherichia coli resistant to neomycin increased from none in 1957-58 to 80 per cent in 1961-62.

Pseudomonas, unlike pathogenic staphylococci and salmonellas, seldom caused widespread "hospital" epidemics. Yet, during a 42-month period, 73 premature, congenitally defective, leukemic and otherwise debilitated children were infected with Pseudomonas in Wales. Hygienic surroundings, the use of sterile instruments and parenteral medicaments or fluids are the best measures for prevention. Polymyxin was used therapeutically but without decisive effect.

Among 100 patients with bacteremia caused by gram negative bacilli, the urinary tract was the source of infection in 65 per cent, the skin in 14 per cent. Fifty-five died. The commonest pathogens were Esch. coli and Klebsiella. Such serologic diversity that specific identification was impossible. Thirty-five of 45 patients who had vasomotor failure died.

An unexpected observation concerned a factor in the serum of some patients with chronic bacterial infection that specifically favors an increased growth rate of the pathogen. Serum from a patient infected with Pseudomonas allowed their rapid growth, but inhibited the growth of Esch. coli. and Proteus.

Anthrax. Anthrax as an occupational disease affected 57 patients in a 10-year period in Massachusetts, and undiagnosed infections no doubt occurred. Infection does not confer immunity yet prophylactic vaccination was recommended. Antimicrobics were said to have been effective in therapy. Anthrax was fatal in a pipe-fitter who handled goat-hair insulation felt. Diagnosis was made when bacteremia was discovered postmortem. Several persons were infected during an epidemic among bis in Canada. Anthrax still is prevalent in southwestern Iran where 25 victims were observed in a hospital and of these four died. Many more cases no doubt occur for which medical aid is not sought or is not available.

Cholera. Extensive physiologic studies, previously lacking, were made. Dehydration was caused by a depletion of extracellular fluid. There is a normal, or greater than normal, flow of protein-free plasma through the normal appearing enteric membrane that is not resorbed. One patient required the intravenous injection of more than 60 liters (15 gallons) of fluid in five days. Experiments also showed that water and electrolytes can be restored orally when possible. The suggestion that the loss of fluid was the result of disturbed permeability not caused by local inflammation of the enteric mucosa, the use of the copper sulfate dilution method to measure plasma viscosity, the design of the "cholera cot", a trial of streptomycin, and a low death-rate of 5%, mentioned in the paper had all been described 20 years ago after the 1945 epidemic of cholera in Chungking in a report to which no reference was made.

Unusual manifestations of brucellosis may cause diagnostic perplexity. Debono observed 18 patients whose symptoms and signs were mistaken for poliomyelitis. Chronic suppuration of the liver or spleen occurs.

Plague occurred as usual in India. An American soldier contracted bubonic meningitis in Viet-nam. Lymphogranulomatosis first was suspected. Diagnosis was made after


P. pestis was recovered from a guinea pig inoculated with spinal fluid. The cause of "endotoxin shock" still is vague. Shock cannot be prevented by antimicrobial prophylaxis and its treatment is unsatisfactory. It is probable in some instances that antimicrobics, if given, may liberate endotoxin by destroying enteric bacteria. Early diagnosis and therapy was said to have reduced the death-rate from 70 per cent to 30 per cent in a hospital.

Although the fluorescent antibody technique does not replace cultural and other diagnostic procedures, it was successful for making rapid diagnosis in epidemics of pertussis and of Ech. coli infections in a remote area.

Coccal Infections

Streptococci. Monthly injections of repository penicillin to serve as both prophylaxis and therapy were superior to intermittent injections in reducing the attack rates of streptococcal infections and rheumatic recurrences. Penicillin G or phenicillin given orally are the drugs of choice for the treatment of acute hemolytic streptococcal infection in children. Recurrences happen, but some of them may be from exogenous reinfection, not from failure of therapy. Recovery occurred promptly in most patients so treated, and in 80 per cent of those given tetracycline. Treatment with tetracyclines did not result in quick cure. Treatment had to be changed for victims of scarlet fever because streptococci were not eliminated. The failure of penicillin to eradicate streptococci from the throat in some instances may owe to the presence there of penicillinase-producing staphylococci.

The problem persists of differentiating viral pharyngitis, the commoner infection which needs no treatment, from hemolytic streptococcal sore throat which does. Methods of accurate diagnosis were outlined by Stollerman. The recommended treatment is 600,000 units or more of benzathine penicillin G. Penicillin may be given orally in doses of 200,000 to 250,000 units four times daily for ten days. Erythromycin is substituted for patients sensitive to penicillin.

Three patients thought to have poststreptococcal glomerulonephritis instead had widespread inflammatory and necrotizing vascular lesions. Streptococci seemed also to cause polyvasculitis, but the drugs used for therapy may have been responsible. A follow-up study was made 10 years after a unique epidemic caused by streptococci-induced poststreptococcal glomerulitis in 62 persons. No evidence of chronic renal disease was detected. Previous studies had shown that permanent harm rarely ensued. Group B beta-hemolytic streptococci (Str. agalactae) were the commonest causes of neonatal sepsis, accounting for 25% of infections.

L-form colonies of Group A streptococci can be identified with their parent cocci because both contain a specific M protein detectable by an immunofluorescent procedure. L-form of Streptococcus fæcalis caused fatal septicemia in two patients.

Rheumatic Fever. Unless infection with Group A hemolytic streptococci is treated with penicillin within 24 hours of its onset, rheumatic fever can ensue. The fluorescent antibody technique serves to identify streptococcal infection in that early period and obviates treatment of other infections not influenced by antimicrobics. Unfortunately, streptococcal infections may be symptomless and undetected. Previously, evidence accrued that too early treatment of streptococcosis impairs the development of immunity.

A review of 4,500 cases of rheumatic fever over a 40-year period disclosed that its incidence has decreased somewhat and the mortality rate has decreased to a greater extent. A Russian investigator described the pattern of changes in lesions of the myocardium.

In another co-operative study, a recent report of the beneficial effect of therapy with cortisone was not confirmed. Prednisone did not terminate the course of rheumatic activity any better than aspirin, but was helpful in controlling the exudative phase of severe acute myocarditis in critically sick patients. Prednisone therapy therefore is not needed for treating acute rheumatic polyarthritis with or without mild or questionable carditis.

Staphylococci. Airborne transmission of staphylococci, though it occurs, is not a common mode of spread, nor does beding appear to be a major source. Important means are the transfer of cocci from the nose to the hands of attendants and to the patient, and from infected patients to the hands of other hospital personnel to the next person and so on. Results of studies also minimize the importance of environmental reservoirs of Group A streptococci. Transfer was limited to intimate contact with carriers. Staphylococcal infections are more difficult to control with penicillin than those caused by streptococci. Tetracycline given to a carrier of staphylococci increased their number in his nose and in the
surrounding air, and their spread to other persons246.

During a year, 213 patients with staphylococcal sepsis were admitted to a 17-bed isolation unit. Only 14 died from that infection, but 14 other deaths were caused by superinvasive gram negative bacilli. About half were infected with untypable staphylococci resistant to penicillin, tetracycline and chloramphenicol. The types of staphylococci present in the noses of patients were not the same as those of their infections. Nursing personnel did not become carriers of patients' strains, nor did the carrier rate increase among them. The present mortality-rate (31%) is about the same as it was in the patients during 1945 (28%), before staphylococci became antimicrobial-resistant247.

In a survey, 14 per cent of patients were infected after admission to a hospital. Staphylococcus aureus was the chief cause in 34% of these and gram negative bacilli in 22 per cent. Twenty-six per cent of the patients were receiving antimicrobics at the time248. Twenty-one of 25 patients with fulminating staphylococcal infections recovered after treatment with a combination of a semisynthetic penicillin and Fucidin249.

Further evidence was added to show that deliberate nasal colonization of harmless staphylococci prevented the invasion of heterologous virulent ones250. A staphylolytic substance was isolated from a species of Pseudomonas250a.

With the addition of new phages to the standard ones, more of the currently untypable staphylococci can be classified. Type UC-18, for example, caused 10% of infections in a hospital and resisted penicillin, tetracycline and streptomycin. The strain was absent in persons not in hospitals251.

Pneumococcal Pneumonia. Between 1952 and 1963, 2,000 cases of pneumococcal pneumonia and 529 instances of bacteremia were observed in a hospital, indicating the continued prevalence of that infection. Pneumococcus Types 1, 7, 8, 4, 3, 12, 14, 19, 6 and 2 in that order were the chief causes. Type 1 infection was associated with bacteremia in 66 per cent of cases. Type 3 gave the highest mortality, 51 per cent of 35 cases. The average death-rate without complications was 20 per cent; with complications, 53 per cent and with meningitis, 63 per cent. In adequately treated patients the death-rate in general was 12 per cent. antimicrobial treatment was not always successful. It had little or no effect on the outcome among those destined at the onset of illness to die, even when treatment began on the first or second days. These studies reemphasize the need to revive the procedure of type determination that is helpful in diagnosis, prognosis, therapy and epidemiology. The authors recommend specific vaccines for prophylaxis252. Considering the relative rarity of lobar pneumococcal pneumonia, and the multitude of vaccines available against other infections, the procedure is impracticable excepting for small epidemics of pneumococcosis in closed populations.

Purulent meningitis in adults usually was caused by pneumococci or meningococci in the Detroit hospital between 1943 and 1963 and there has been no increase in the incidence of other gram positive or gram negative bacterial infections. Despite modern therapy, the mortality-rate of pneumococcal meningitis was 68 per cent253. The death-rate of Klebsiella pneumoniae meningitis was reduced from 99 per cent to 50 per cent. The infection occurred chiefly in debilitated patients among the 153 cases on record254.

For therapy, attempts often are made to secure large amounts of an antimicrobial in the spinal fluid255, as if the bacteria floating therein are harmful. Intravenous injection to achieve high concentration of the agent in the meninges and tissue at the site of infection is more logical.

Serious outbreaks of meningococcal meningitis afflicted recruits in military centres and elsewhere in the western United States. Apparently antimicrobial prophylaxis failed and other methods were applied to stop the disease. In one area, 15 of 105 victims died256. Meningococcus Type 2, Group B, became resistant to sulfonamides. A high carrier-rate persisted among persons treated orally with sulfadiazine or penicillin257.

Venereal Diseases
Modern aspects of syphilis and other treponemoses, gonorrhea, lymphogranuloma venereum, granuloma inguinale and nonvenereal genital diseases were discussed in several articles in the Medical Clinics of North America of June, 1964. A few points of interest are that about 65 per cent of untreated victims of syphilis have little inconvenience therefrom and that both syphilis and gonorrhea have increased in incidence. Indiscriminate penicillin therapy probably has inadvertently cured patients with either infection. At present, most syphilitic patients are treated by private physicians and perhaps 90 per cent of cases are not reported to health officers. The modern treatment of syphilis was outlined.
The standard serologic diagnostic tests for syphilis sometimes fail. In one study, negative reactions were obtained in 24 proved infections. The faulty result in 16 of them was caused by a positive prozone reaction. Among 66,000 Austrian soldiers who donated blood to a blood bank, the VDRL test gave a positive reaction in 49. Thirty-nine of these had syphilis. If the test is not wholly reliable, one wonders how many cases were missed or misdiagnosed.

Not long ago, suggestion was made that syphilis gradually evolved from the prototypes of yaws and bejel. A more recent view casts doubt on the separateness of the treponemes of venereal syphilis, endemic syphilis, bejel, yaws and pinta. Perhaps the same microbe causes each disease and the different clinical responses may depend upon epidemiologic factors, the mode of transmission, the site of entry and the resistance of the human hosts. The incidence of atypical forms of infection may depend upon the frequency of febrile malaria in some areas of the world. Treponemes do not survive at temperatures higher than 40°C.

Improved methods of treatment have had no effect on the spread of gonococcal infection. Infections have increased in incidence worldwide and "the time has come for an entirely new attitude to this major source of human illness and unhappiness." After exposure to infected partners, 26 of 98 men had asymptomatic gonorrhea that was diagnosed by the fluorescent antibody procedure. Falsely positive results may occur in tests of carriers of meningococcus that share an antigen with the gonococcus. Among 203 men with urethritis, Gonococcus was the cause in 139. The only microbe recovered from the rest was the T-strain of Mycoplasma. It resisted penicillin, but was sensitive to tetracycline. The infection probably represents the "sixth" venereal disease but may be asymptomatic at times. No viruses or evidence of their presence was discovered in 45 patients with nongonococcal urethritis. Immunofluorescent staining for the identification of Tr. pallidum and N. gonorrhoeae directly from smears of lesions can be done in about a minute. The test also gave positive results in 7 of 42 patients with Reiter's syndrome and negative results in urethritis of other cause. Spectinomycin was said to be as effective as other antimicrobics for the treatment of acute gonorrheal urethritis.

Mycotic Infections

Histoplasmosis. In 706 routine necropsy studies, evidence of histoplasmosis previously undiagnosed or as an inapparent infection, was discovered in 85% of instances in the midwestern United States and in 12% elsewhere. A medical student contracted histoplasmosis in a laboratory. Studies then disclosed that 26 of 62 exposed classmates were sensitive to the histoplasmin, and nine had pulmonary infiltration. Direct staining of sputum is a reliable method of diagnosis. Soil polluted by bird droppings and sprayed with 36 gallons per 100 square feet of a 3% solution of formaldehyde was said to have reduced the incidence of histoplasmosis in an epidemic area.

According to Furlow, attempts to control environmental exposure, sterilization of infected foci, and vaccines have not been successful in the eradication of histoplasmosis. Amphotericin B is the drug of choice for the treatment of chronic histoplasmosis, but it must be used cautiously.

Histoplasmosis was discovered for the first time in Cyprus in two persons who were infected in a cave that harbored bats. In Colombia, H. capsulatum was present in a bat's liver. The disease had been known for years in Italy and the microbe was isolated from the soil near Bologna. Since 1963, 31 cases were recognised in Montreal. Many Puerto Ricans reacted positively to the histoplasmin skin test. In Japan, some agent other than H. capsulatum probably accounts for the rare reactors to the test. H. duboisii differs from H. capsulatum; in Africa lesions of the disease were in the skin, bone and abdominal viscera, not in the lungs or central nervous system. The epidemiology of the infection there is unknown.

Coccidioidomycosis in the American Southwest was discussed by three essayists at the October 9 meeting of the American College of Physicians. The irregular distribution of the disease in endemic areas may be explained by differences in local soils and the temperature that either do or do not favor the existence of the fungus. The infection is clinically inapparent in 60 per cent of infected persons. Disease ranges in severity from mild respiratory tract discomfort to severe pneumonia and death. A chronic form occurs: Amphotericin-B is effective if therapy is prolonged, but as mentioned elsewhere in this review, it may be nephrotoxic.

The hazard of contracting coccidioidomycosis in the endemic area of the St. Joaquin Valley, 1963-64, was less than that reported previously. During the first year of residence,
infection was evident in only 1.58% of persons in the susceptible population. Suppression of dust was a factor in reducing the incidence. Among 1,895 persons who served in a laboratory where *Coccidioides immitis* was under study during 18 years, about 10 per cent gave evidence of having been accidentally infected. One third of those whose skin reacted to coccidioidin were asymptomatic. The rest had had dermal lesions or respiratory tract illness.

Among 22 patients with aspergillosis, 16 were leukemic and four had cancer. Of these, 20 had received corticosteroids, antimicrobics or antineoplastic drugs that impaired their resistance. Growth of *Candida albicans* was inhibited by the intact conjunctiva and extracts thereof. The inhibition was not ascribed to an antimitabolic action and was not caused by lysozyme.

*Cryptococcus neoformans* usually is regarded as an opportunistic invader in patients whose resistance is impaired. A case was described, however, in a previously healthy youth who apparently contracted the infection from pigeon droppings. He had severe hepatitis, pneumonia, splenomegaly and lymphadenitis. In retrospect, a transitory attack of pleurisy and pulmonic invasion, suspected as tuberculous 19 months previously probably was cryptococcal in origin. Spontaneous remission then was followed by systemic dissemination. Subsequent therapy with amphotericin B was successful.

**Protozoal and Metazoal Infections**

In 1936, 148 confirmed and presumptive cases of malaria were reported in the United States. *P. vivax* accounted for 78 cases and *P. falciparum* for 36. On a ship from Africa recently 40 persons had malaria. Twelve infections were caused by *P. falciparum* of which eight were overt and four were inapparent. Five other cases originated in the United States. Of these, two were caused iatrogenically, a third infection had been acquired years ago, and in two the origin was unknown. The fluorescent antibody test gave positive results in malarial infections.

Diaprime (pyrimethamine) was used successfully in the prevention of infection in a hyperendemic region of Gambia. None of the protected children developed detectable antibody in contrast with untreated ones. Frequent reinfection also maintains specific antibody at a high level. According to other investigators, Camolar (cycloguanil pamoate) also afforded long-term protection after a single intramuscular injection.

Despite control programs, malaria is the most serious insect-borne disease in Central America. Mosquitoes have acquired resistance to synthetic antimalarial drugs. Malaria occurred among troops in Vietnam who received chloroquine and primaquine, and among Cambodians who were given amodiaquine. Evidently, the disappointing results are a serious setback in the control of the disease. Perhaps a return to the use of quinine is imminent. There is evidence that *P. falciparum* may resist quinine.

It still is uncertain if different species of Leishmanias account for the different clinical manifestations of infection as oriental sore (*L. tropica*), mucocutaneous disease (*L. braziliensis*) and kala azar (*L. donovani*) or if the microbe is the same in each and host resistance designs the form of the disease takes. In the Sudan, six infected Americans were observed. Four of these had dermal ulcers only, and two had classic kala azar as if they were less resistant to the same microbe. Chloroquine had been used as an antimalarial agent in those who had dermal lesions, but not in those severely ill, as if the drug had a suppressive action on leishmaniasis. Six persons who were not sick and without lesions reacted positively to the dermal leishmanin test, indicating that they, having a higher degree of resistance, had been inapparently infected.

Cutaneous leishmaniasis is widely distributed in forested regions of Central and South America. Treatment with pyrimethamine was said to be effective on therapy, but is toxic.

Chagas disease caused by *Trypanosoma cruzi*, endemic in Central and South America, is transmitted by several species of triatominae bugs. About 22% of Panamanians had serologic evidence of infection.

Schistosomiasis affects about 5 per cent of the world population. *S. japonica* causes the most serious infections. With increased travel in and from endemic regions, the infection is becoming more prevalent elsewhere.

More than 600 cases of leptospirosis were recorded in the United States since 1953. Rats are not the only source of infection. Farmers, veterinarians, packing-house employees and meat inspectors are at risk. In the general population, 2.6 per cent of sera from persons gave positive results to serologic tests. *E. coli* and *C. multilocularis* infected foxes and cows in midwest United States, Alaska and Canada.

Trichinosis among 11 diners was treated with thiabendazole. The drug induced defervescence.
of the disease and a sense of well-being in four victims. It failed to kill the larvae, caused dermatitis and central neural disturbance and did not alter the eosinophilia. The fluorescent antibody procedure was said to have greater diagnostic value than the precipitin test and the complement fixation test. It gave a positive reaction within two weeks of the onset of disease.

Another antihelminthic drug, dithizone iodide (Delvex) caused serious gastroenteric and other disturbances. Eight treated patients died. It should be used only for severe infection caused by Trichuris or Strongyloides.

Miscellaneous

Urinary Tract Infection.—Urinary tract and other infections caused by gram-positive bacteria have declined more than 50 per cent. in 12 years only to be replaced by infections with Klebsiella, Aerobacter and Proteus. The change in the flora probably was brought about by antimicrobial therapy. The problem of infection acquired in hospitals, particularly of the urinary tract was reviewed by Sanford.

The lining of the urinary bladder is naturally able to destroy bacteria. Cystitis often heals and the urine becomes sterile. The introduction of a retention catheter may not cause infection in a normal bladder. Measurement of specific agglutinins in the blood was said to be helpful in the diagnosis of overt or inapparent pyelonephritis.

Infections occurred in 26 of 30 patients in whom renal homotransplantation was done, and contributed to the cause of death in 10. Staphylococci, Pseudomonas and other gram-negative bacilli were the chief causes. Infections often followed immunosuppressive therapy that impaired the patients' defensive mechanism.

Protoplasts, as bacteria without cell walls, persist in renal tissue after apparent cure of pyelonephritis and may account for a relapse of infection. Erythromycin killed protoplasts, but was ineffective against intact bacteria. Protoplasts and L forms were subjects of a symposium, the summary of which appeared in Science magazine of 5 February, 1965. Their possible causal relation to subacute bacterial endocarditis, rheumatic fever, Reiter's syndrome and other diseases was suggested.

Other Studies. The value of ultraviolet radiation in reducing the number of bacteria in surgical operating rooms was studied cooperatively in five hospitals. Differences in the number of surviving air-borne bacteria varied according to the nature of the infected wounds. Irradiation reduced the risk of postoperative infection of clean wounds by 25 per cent. The net effect in all instances, however, was negligible, that is, infection occurred in 7.4 per cent of wounds in irradiated rooms and in 7.5 per cent of those in control areas. Infection rates varied from 3 to 11.7 per cent among the five institutions indicating that many other factors play a role in the incidence of postoperative infection.

An account of contagious diseases among the English pilgrims on ship-board and after their arrival in America in the 1620's also describes the ravages of smallpox among the native Amerinds. They, not having been exposed to smallpox before, had no immunity. The decimation of hostile tribes was an important factor in the success of the immune or partially immune pilgrims in establishing permanent colonies. Similar circumstances, no doubt, pertained in Polynesia after measles was introduced by early explorers.

The thymus gland was said to play a key role in the maturation of immunologic capabilities by means of a humoral mechanism. Electronmicroscopy of microbes is advancing rapidly as shown by many articles in a symposium.

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