ANNUAL REVIEW

Infectious diseases:
Annual review of significant publications

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Introduction

Hepatitis, rubella, rubeola, respiratory tract infections, smallpox, and vaccination against them dominated interest in 1971. The possible viral cause of vascular and pancreatic injury was considered. The relation of viruses to cancer, and of herpes and EB virus to various diseases remains unsettled. Venereal infections continue to increase. More instances of amoebic meningitis were reported. No striking improvements of antimicrobial therapy accrued, but ensuing iatrogenic and nosocomial troubles arising therefrom and from immunosuppressive procedures were of serious concern.

Respiratory tract infections

According to a compilation, in a year about 3000 physicians visited 118,924 patients for acute respiratory tract infections (1130 for lobar pneumonia). For cardiac disease, 76,883; diabetes, 28,792; and for arthritis, 25,885.1

Family members excreted respiro-viruses in faeces for weeks, but from the oropharynx often less than a week. Re-infections with the same viruses were common. Preschool children often were the source.2

As usual, respiratory syncytial viruses caused severe disease in infants. In one hospital, RS virus caused 40%; rhinoviruses, 6%; adenoviruses, 4%; parainfluenza viruses, 2%; enteroviruses, 2%, and influenza viruses 1% of cases.3

According to three papers in the September American Journal of Epidemiology, extensive epidemiologic study affirmed the complex nature of the problem. Two or more pathogens often are present simultaneously; at times all of them at once. Rhinoviruses were present most of the time. Mycoplasma was absent in a community for 3 years. Children between ages 5 and 9 had the highest incidence of infections.

Self-limited mild infections need no medication. The use of 'cough mixtures' except for a single antitussant (codeine) is as antiquated as are 'elixirs', 'expectorants' and 'antihistamines'4 as I stated 26 years ago.5 The use and abuse of antimicrobial therapy for colds was discussed in 1971 in the British Medical Journal, 3, 101.

Influenza

Among college students in January, 1969, 45% had evidence of influenza A2. The ratio of overt to inapparent infections was 1 : 4.6 A strain of virus was similar antigenically to A2/68 virus. Volunteers were easily infected. Two other strains were dissimilar. Swine are a source of infection7 as first shown by Shope. Fatal influenza in a mother infected the foetus transplacentally.8

Eickhoff discussed in detail the problems and recommendations for vaccination and chemoprophylaxis. The value of influenza vaccine remains controversial. Although inhaled aerosol vaccine failed to give protection, injected A2 vaccine protected company employees probably by inducing nasal as well as systemic immunity. The antibody response was transient. The total respiratory infection rate was not reduced.9 Vaccination, according to other studies, reduced infection-rates by 75% and serologically confirmed illness by 82%.10, 10a Amantadine for treatment reduced fever averaging from 75 to 47 hr during influenza A2 without influencing other symptoms. Direct antipyresis was not considered to be the effect.11

Four cases of severe influenza viral pneumonia with two deaths during the 1968–69 pandemic were described.11 Staphylococcal pneumonia complicated 30% of 128 patients, or three times oftener than in prior years.12

A2 influenza virus caused an epizootic in thirty-six gibbons. Four died, three with pneumonia. The disease closely resembled that in man.14 Poly I.C. given to baboons infected with influenza A2 virus delayed or suppressed antibody formation and did not prevent persistent virus excretion.15
Adenoviruses
In an epidemic, virus 7A infected 84% of children, but only 40% were sick. The disease resembled streptococcosis. Pneumonia was not recorded. Adenovirus 7 caused severe pneumonia in twenty-nine Finnish infants and children. Three died. Encephalitis, hepatomegaly, cardiac failure and bleeding occurred. Virus type 21 caused fatal myocarditis and pneumonia in an infant. Adenoviruses may be one of several causes of acute haemorrhagic cystitis. Live types 4 and 7 viruses given orally as vaccine reduced the severity of disease among military recruits without unwanted reactions.

Respiratory syncytial virus
Respiratory syncytial virus, as usual, mostly affected children and aside from the high incidence of involvement of the bronchi and lungs (38%), illness was the same as that caused by Parainfluenza type 3 and Adenovirus type 1. Prompt etiologic diagnosis obviates unnecessary antimicrobial treatment. Coronavirus probably caused 19% of infections in children.

Serum (SH) (MS-2) hepatitis
During 1970, 6400 cases of serum hepatitis and 53,000 cases of infectious hepatitis were reported in the U.S.A., far fewer than actually occur. The mortality-rate presumably is 0-4/100,000 population. Because of required reporting and perhaps for other reasons, the incidence of hepatitis appears to be 10–40 times greater in eastern European countries. Case fatality rates generally are lower because of statistical inclusion of mild cases. SH causes disease mostly in adults; IH chiefly affects children and in point-source epidemics.

The presence of AU (HAA) antibody was related to the number of transfusions received in eleven patients. The incidence of antibody in 23,000 units of donor blood was 0-2%. A specific response followed in thirteen of 100 recipients of blood containing HAA antigen. Curiously, none of forty-two patients convalescent from acute antigen-positive hepatitis had detectable antibody. Anti-HAA present in 14–22% of blood donors and in persons with no history of hepatitis or having received injections suggests that serum hepatitis is endemic and may be transmitted by non-parenteral routes. An estimated 10,000 carriers of HAA will be detected annually in the U.S.A. Post-transfusion hepatitis probably is caused by more than one agent. Laboratory-acquired hepatitis affected twenty-seven of fifty-six persons. The ecology was discussed editorially. Bed-rest is unnecessary except for existing symptoms.

Hepatic injury seemed to be the result of an immune response to the antigen rather than to the amount of virus present. HAA antigen detected in an infant with giant-cell hepatitis led to the discovery of the antigen in three asymptomatic family members in whom biopsy disclosed acute or chronic hepatitis which would have been undetected otherwise. Absence of interferon during serum hepatitis may be a cause of prolonged or chronic disease.

For the first time, specific immunization was successful. Injection of B immune serum globulin prevented or modified type B (MS-2) serum hepatitis. Small amounts of specially prepared gammaglobulin added to blood for transfusion may modify the virus. Specific gamma-globulin may protect workers in blood banks and others at risk.

The HAA probably provides a genetic basis for chronic hepatic disease and hepaticomas. Responses of different tissues to infection may depend upon host peculiarities. Circulating immune complexes may explain the concurrence of arthritis and of urticaria. Arthralgia occurred in three patients. In one instance, it preceded evidence of hepatitis by 6 weeks. Antigen–antibody complex present in the glomerular basement membrane probably caused glomerulonephritis. The HAA antigen has an outer coat and an inner body resembling a rhinovirus. Among thirty necropsies, haemorrhagic myocardial lesions were present in twenty with lymphocytic invasion and fatty changes. They result either from a coagulation defect or viral invasion. Changes in the brain, kidneys, pancreas and intestine indicate the systemic nature of viral hepatitis. A review appeared in 1971 in the Journal of Pediatrics 78, 887.

Infectious (IH) (MS-1) hepatitis
A virus morphologically resembling HAA but unrelated to it appeared in patients. It was absent in ninety-seven victims of epidemic IH. Gamma-globulin-protected soldiers had less chills, fever and jaundice than control subjects, but with no other significant benefit. The incidence of infection was diminished. Eleven papers about hepatitis appeared in 1971 in the Postgraduate Medical Journal, 47, 462. Krugman summarized knowledge.

Q fever hepatitis without pulmonic involvement affected one patient; two others had hepatitis and patchy pulmonic infiltrate.

Measles
Among 650 vaccinated children, 34% had fever of 38.5° or more and 14% had mild illness 9–11 days afterward. Authors discussing measles and tuberculosis are in agreement with my pessimism of eradicating either disease in the foreseeable future.

Forty-three patients with multiple sclerosis had immunoglobulin M specific for measles and mumps viruses. Viral antibody titres during multiple sclerosis were higher for measles than in control
subjects. However, similar titres were present in siblings probably as a familial trait, casting doubt on the causal relation of the viruses. If measles virus were implicated in the cause of multiple sclerosis, it may be there in a latent, masked or defective condition. Antibody appeared in only one-fourth of 119 patients. Suppressed measles virus was isolated from lymph nodes of two of five patients with subacute sclerosing panencephalitis.

Laboratory tests verified a diagnosis of mumps in 86% of cases. Involvement of the parotid glands, meningoencephalitis, cervical adenitis, orchitis, atypical mumps, oophoritis and thyroiditis in that order portrayed the polytropism of the virus.

**Herpes hominis**

Herpes virus discovered serologically and post-mortem caused fifteen instances of bronchitis and pneumonia. The virus infected digits of eight patients, five of whom were medical and dental personnel. Immunologic defects favoured chronicity of cutaneous infection in four patients. Interferon therapy seemed to cause temporary improvement in a fatal case of herpes simplex encephalitis. The rapidity of cerebral necrosis and formation of a mass during herpetic encephalitis can be detected by scanning, by angiograms and proved by biopsy and isolation of the virus. The adjective 'simplex' is inappropriate.

Genital infection with *Herpes hominis* type 2 virus in monkeys provides an experimental model for studying the relationship of the virus to neurologic diseases and cancer. Acute lymphocytic leukaemia developed in owl monkeys and marmosets inoculated with a herpes virus indigenous to squirrel monkeys. The virus is a suspected oncogenic agent. Considering the ubiquity of herpetic infections, the problem is difficult.

**EB virus**

Evans discussed the unsettled relation of EBV to infectious mononucleosis, pharyngitis, Burkitt’s lymphoma, nasopharyngeal cancer, Hodgkin’s disease, sarcoidosis and lupus erythematosus. Acute diseases may represent a host response in immunologically competent persons; chronic diseases in incompetent ones. It is difficult to believe that the wide array of conditions associated with high titres of antibody to EBV could all reflect a causal relationship. Infectious mononucleosis occasionally complicating leukaemia does not indicate that the EBV causes both diseases. Demonstration of antibody to EBV aids in identifying susceptibility to and immunity against infectious mononucleosis. Among 175 students whose blood contained no antibody, twenty-three later samples did. Of these, all had proved or presumptive mononucleosis. False spot tests for mononucleosis occasionally occurred in leukaemia, lymphoma, viral hepatitis and pancreatic carcinoma.

Dengue virus isolated from patients in Nigeria indicated its existence in Africa. The great variety of newly discovered viruses of haemorrhagic fevers was discussed editorially. *Emmonsia crescens* may be a cause. Marburg virus disease was the subject of a symposium.

**Vaccines**

Combined measles–rubella–mumps vaccine induced antibodies without significant side-reactions and is being prepared for general use. Rubella–mumps vaccine satisfactorily immunized children without significant side-effects. Perennial control of measles by vaccination may be difficult. Communal protection lasts less than a year. According to two papers in the 24 May *Journal of the American Medical Association*, herd immunity of vaccinees failed to prevent epidemics of measles. The disease occurred in 18–29% of previously vaccinated children. Some failures may be attributed to faulty vaccine. Transient cerebral changes detected by electroencephalography appeared in six of eight children after measles vaccination. Vaccination of a dysgammaglobulinemic infant caused fatal disseminated measles.

Studies are underway to develop antimalaria vaccine.

**Rubella vaccine**

Five articles about rubella appeared in the 25 January, 1971, issue of the *Journal of the American Medical Association*. During an outbreak, infection occurred in twenty-two of thirty-three susceptible persons. None of twenty-two previously vaccinated persons or of sixty-six naturally immune ones were ill. Inapparent infections occurred in five vaccinees and in an 'immune' child. The duration of vaccine-induced resistance is unknown but may last 4 years. Inadvertent inoculation of pregnant women is dangerous. None of them received rubella vaccine. Two were infected and virus was isolated from conceptuses 69 and 28 days later. Apparently, there is some danger of spread of virus by vaccinees. Two instances were observed.

History of actual or probable rubella does not guarantee immunity. Ninety-two per cent of women who had been infected had antibody. More than 50% who had no history of having had rubella, and 85% of doubtful ones also had antibody. Measurement of antibody is the only certain method of detection. Induced immunity is brief and protection against the natural infection is incomplete. Epidemics persisted in populations in which 80–90% of persons were 'immune'.


Arthralgia followed vaccination in 39% of susceptible subjects, in 12% of immune ones, and in 10% (!) of placebo recipients. In one instance, arthralgia recurred after a year.84 Pain may be severe enough to enforce a crouching position for months.85 Rubella virus grew in cultured synovial cells which is what probably occurs during rubella.86 Disappointing effects of rubella and polio vaccines were encountered in Syracuse.87 A second ‘booster’ dose of vaccine failed to induce a significant rise of demonstrable antibody and may be useless in enhancing resistance to infection.88 A biologic change in the virus may account for the present unusual prevalence of disease and higher rate of foetal malformations.89 Stokes outlined the practical approach for using vaccine.90 Two authors summarized problems of control.91, 92

Smallpox

A symposium of eight papers about smallpox vaccination appeared in the April American Journal of Epidemiology. Some observers favour discontinuance of routine vaccination, except for persons at risk. Some have alternative plans, and others favour continued routine vaccination in children despite the occasional harmful effects. Airborne contagion was emphasized. Persons with record of vaccination may not have been immunized. Excepting for persons at risk and those entering from endemic areas, routine vaccination was stopped in Britain.93

Mack’s study of 1040 cases of smallpox disclosed a wide spectrum of severity from inapparent infection to severe disease among the unvaccinated.94 Serologic study disclosed a secondary attack rate of 14% of 143 households after an epidemic of smallpox. At least 27% were inapparently infected, and others were ill but had no eruption. Both groups were sources of infection.95 In a child, encephalitis ended fatally 7 days after revaccination.96

Thirty years before the introduction of Jennerian vaccination in 1800, Dr Zabdiel Boylston inoculated 247 persons with smallpox pus. Six died representing 2.4% compared with 14% of fatalities among the unvaccinated.97

Miscellaneous viral infections

Chang summarized information about recurrence of latent viral infections after a first attack and exogenous re-infections. These often are inapparent clinically and diagnosed only by serologic evidence. Each vaccination represents a re-infection. Successive attacks of inapparent illness may account for belief in permanent immunity after a primary attack.88

Knowledge of cytomegaloviruses gained since their first isolation 15 years ago was summarized in the 22 and 29 July, 1971, issues of the New England Journal of Medicine. Electron microscopy visualized viral vibrations of varicella-zoster in the axons of unmyelinated nerves and the destruction of cutaneous nerves.98

Intranuclear bodies appeared in epidermal cells of milkers’ nodules.100 Virus-like particles were in the glomerular endothelium of Goodpasture’s syndrome.101 Virus-like renal endothelial inclusions in thirty-three biopsy specimens had diagnostic import in lupus erythematosus and were present in only 4% of other renal diseases. They had no relation to the clinical behaviour.102

Monkey-pox contracted in the tropics differs from tanapoxosis.103 The arenavirus group includes those of lymphocytic choriomeningitis, Lassa fever, the Tacaribe complex, Pichinde virus and others.

Mice fed a protein-deficient diet resisted viral infections better than well-fed ones supporting old observations that underfeeding is better than overfeeding.

A symposium of eleven papers on viruses and autoimmunity appeared in the September, 1971, issue of the American Journal of Clinical Pathology. The ‘germ-war-laboratory’ at Fort Detrick was said to be consigned to the study of cancer viruses at a projected cost of $15–20 million annually.108

Viruses and cancer

Although a viral cause of mammary cancer is unproved,107 virus-like particles, like those in mouse cancer, were present in a woman who shared a tendency to familial mammary carcinoma.108 A new but similar agent, unrelated to EB virus appeared in a nasopharyngeal cancer.109 Further study supported the ‘association’ of EB virus with nasopharyngeal carcinoma and Burkitt’s lymphoma.110 A brain tumour contained papova-like particles.111 Particles of a new papovavirus were in cells lining the ureter of a patient after renal transplantation.112 Another papova-like virus was present in the brain of a patient with Hodgkin’s disease.112a A relationship of ESP-1 virus to cancer is unproved.113

Immunosuppressive therapy in animals favours the development of neoplasms caused by polyoma, adenovirus 12, sarcoma and leukaemia viruses. In one hospital, neoplasms followed therapy in 6% of treated patients as compared with a general incidence of 0.6%.114 BCG inoculation caused regression of dermal tumours and prevented metastasis,115 but was ineffective for leukaemia.116 Difficulties involved in antiviral chemotherapy were reviewed.105a

According to one theory, ‘promine’ and ‘retine’, not viruses, incite cancer.111 Ninety percent of neoplasms may be due to chemicals118 which appear to be most involved in the etiology.119

Viruses and endocrinopathy

Evidence of viral polytopism increases. Besides
involving the heart and kidneys, coxsackievirus B4 caused endothelial degeneration and vascular intimal necrosis in mice. Similar infection may initiate vascular disease and atherosclerosis in man. The virus also injured the pancreas of mice. Among fifty young adults with congenital rubella, active or latent diabetes was detected in nine (20%), suggesting a causal relation. Previous studies had disclosed acute pancreatitis during infectious hepatitis and diabetes in mice caused by encephalomyocarditis virus. Possible overt and inapparent viral infections as causes of diseases of the thyroid, adrenal, pituitary, gonadal, parathyroid, pineal, thymus glands and the pancreas were reviewed.

Interferon
An interferon stimulator decreased the mortality of mice even when injected on the fifth day after inoculation with Simliki forest virus. The substance increased the severity of T. cruzi infection in mice. Tilerone hydrochloride, toxic for man, stimulated interferon production in animals.

Bacillary infections
Waterborne salmonellosis in California affected more than 16,000 persons of whom 70% were severely ill and three died. Chlorination of water stopped the epidemic. A patient who had had typhoid at age 13, developed typhoid cholecystitis at age 80 probably after harbouring the bacilli for 7 decades. Providence bacilli (paracolon bacteria) often cause urinary tract infections and systemic disease. Esch. coli and pneumococcus caused most instances of peritonitis in seventy patients with hepatic cirrhosis. Less than 5% of victims survived. The infection may be overlooked. In samples of raw milk, Esch. coli resistant to antimicrobics transmitted resistance to other bacilli which may infect man.

Brucellosis in the U.S.A. now is chiefly an occupational disease. Fifty-three cases were discovered in an abattoir. Only 19% of patients had lymphadenopathy and 11% had splenomegaly.

An epidemic of 676 cases of tularemia in Sweden seemed to be related to an increased population of voles. These animals infested hay and inhalation of airborne-contaminated dust resulted in systemic illness. The dermal test for tularemia becomes positive promptly and remains so longer than the agglutination test. It may persist 40 years. In San Antonio during 1970, diphtheria attacked 201 persons of whom three unimmunized ones died. Parenterally injected penicillin or erythromycin was therapeutically effective and corrected the carrier state. Antitoxin is the prime treatment.

Bordetella parapertussis alternates with B. pertussis causing epidemics at 4-year intervals. Inapparent infection is far more common with the former.

Since 1900, 1696 reported cases of botulism and 959 deaths occurred in the U.S.A. caused by types A, B, and C bacilli. The incidence decreased after 1940. Two severe and two mild cases followed ingestion of potato salad. Edrophonium chloride and guanidine hydrochloride were helpful in treatment. The production of toxin by C. butolinum may be due to a converting bacteriophage, as in the case of the diphtheria bacillus. The diagnosis and treatment were outlined.

Anthrax bacilli propagate in soil and infect livestock. The ecology of the disease in the U.S.A. was outlined. The prevention and treatment of gas gangrene was described. In one hospital, the yearly incidence was 1-8 cases. Sero- or antimicrobial prophylaxis was ineffective. Two patients had pseudomonal septic arthritis. Surgical drainage and therapy with gentamicin cured one of them.

The danger of not recognizing melioidosis in persons returning from South-east Asia was re-emphasized. A long latent period may precede disease. Eleven such instances were observed. A fatal neonatal infection resisted antimicrobial therapy. The parents had not been ill, but the father was a Vietnam returnee. Variable manifestations render diagnosis difficult.

Pasteurella (Yersinia)
After plague occurred in Denver, an epizootic was discovered in urban tree squirrels in the vicinity, the first time that these animals were incriminated. All but four of nineteen cases in 1969-70 occurred in New Mexico. The decline of epidemics during hot weather may be due to the non-survival of P. pestis in fleas at temperature higher than 27.5° C.

Infection with P. pseudotuberculosis occurs in Europe, but only three cases were observed in California resulting from intestinal invasion. Septicaemia, appendicitis and mesenteric adenitis occur. The bacillus is easily mistaken for banal enterobacteria and is sensitive to several antimicrobial drugs. P. multocida sepsis from maternal chorioamnionitis killed a premature infant.

Tuberculosis
Morbidity from tuberculosis increased in proportion to people’s height and decreased with bodily weight. It was more than three times greater for underweight persons although the frequency of infection was the same as for normal persons. A familial trait may be responsible. After exposure to tuberculosis, inapparent bacillemia carried bacilli to a traumatized area on the chest wall resulting in a localized tuberculous lesion. Silent bacillemia is well-known to account for miliary and metastatic tuberculosis.

Myers, discussing a report on an outbreak of
tuberculosis spread by an infected person in a school, re-emphasized the value of the tuberculin test in discovering reactors in a community.  

The cost of routine administration of isoniazid to prevent infection of one exposed person usually is justified except for healthy tuberculin-positive persons with normal pulmonic roentgenograms. Isoniazid therapy induced hepatic disease in a few patients especially during prolonged therapy. Rifampin-isoniazid therapy for tuberculosis was as effective and caused less toxicity than the best regimen previously used. Unfortunately, rifampin caused potentially serious side-effects. Combined therapy is of especial value for treating drug-resistant disease.  

**BCG.** Dermal sensitivity to tuberculin persisted for 15 years in 16% of BCG-vaccinated sailors. BCG pulmonary tuberculosis developed 4 years after vaccination of a defectively immune child. Vaccination of infants with granulomatous disease resulted months later in fatal disseminated 'BCG-osis'. Vaccine injected into dermal tumours of guinea-pigs caused tumour regression and prevented metastases. Growth was inhibited by a delayed hypersensitivity reaction provoked by an antigen unrelated to the tumours. Evidence failed to corroborate the therapeutic value of BCG vaccination against leukaemia. 

In contrast to *M. tuberculosis* which is restricted to mammalian tissue, 'atypical' mycobacteria are widely distributed and free living. *M. bovis* infected six of 2086 tuberculous patients. *M. fortuitum* caused dermal abscesses in five patients and meningitis in another. Spontaneous recovery is common. *M. kansasii* infected the urinary tract of two patients. Dermal infection with *M. marinum* was acquired from a tropical-fish tank. 

**Dysenteries**

Shigellar enteritis probably derived from ingested shrimp affected 288 students during 5 days. Coexistent streptococcal pharyngitis represented a dual epidemic. I described a similar circumstance involving viral dysentery and *S. sonne*. All *S. shigella* strains obtained during the large outbreak in Central America resisted many antimicrobial drugs. All were capable of transferring the resistance (R) factor to *Esch. coli*. The infection was carried to Florida and probably elsewhere. In another outbreak from food, eighteen persons were ill and two died. *Salmonella enteritidis* was causal, but *Clostridia* and *Str. fecalis* in the food probably participated. The pathogenesis of bacterial diarrhea was reviewed in the *New England Journal of Medicine* of 7 October, p. 831 and 14, p. 891. 

*Giardia lamblia* seemed to cause an outbreak of disease in tourists. It began later than 'travellers' diarrhea' and persisted for weeks. Possibly some other agent was the primary cause and giardia were enabled to flourish. Iodochlorhydroxyquin (Enteroxioform), often wrongly used to prevent travellers' diarrhea, caused neuropathies in thirty-eight of 110 patients. In further confirmation of my experiments in 1945, viral dysentery was transmitted to volunteers by the ingestion of bacteria-free stool filtrates from victims. Precaution was taken against inadvertent transmission of hepatitis and poliomyelitis, a hazard unknown in 1945. 

**Cholera**

A Tunisian visitor carried cholera to Spain. Isolated cases appeared in France, Sweden and Portugal caused by biotype el Tor, serotype Ogawa. It would seem unnecessary to urge West Germany to stock large depots of vaccine in case of an emergency. A vaccinated physician dealing with victims contracted a severe attack. Cholera vaccine is of little use in preventing the spread of the disease. The only effective method is environmental sanitation, and avoiding ingestion of contaminated food and drink. Because immunity after infection is brief, fourteen persons had second attacks. Ordinary immunization procedures have little or no value and give a false sense of security. Antitoxic immunity, as induced in dogs, would be more logical. Cholera differs from other enteric diseases and resembles the effect of a hydroscopic purgative. The enterotoxin rapidly affects transport of fluid by direct action on mucosal cells in which adenylyclease may be the intracellular mediator. Knowledge of the enterotoxin was summarized editorially. A WHO book outlines methods for control. 

As in cholera, enterotoxic *Esch. coli* disturb mucosal permeability without evidence of invasion. The induced disease was identical to cholera. One wonders if proposed vaccine can be any more effective than that for cholera? *Esch. coli* toxin is as potent as cholera toxin, but the antibody response in rabbits was poor and vaccine failed to immunize. The same question may apply to oral vaccine now under trial for shigellosis. Some types of *Esch. coli* penetrate the enteric mucosa to cause shigella-like disease.  

**Streptococci, rheumatic fever, endocarditis, nephritis**

The incidence of first attacks of rheumatic fever declined by only 30% since 1930. About 100,000 new cases occur annually. In 1968, 16,000 deaths ensued during the acute attack or from resulting cardiac disease. The estimated cost of physicians' visits in 1969 was $28 million. Methods of diagnosis, management and prevention were described by a study group.
Nonhemolytic Group A Type 18 streptococci caused an epidemic of pharyngitis among soldiers with six cases of acute rheumatic fever. A new type of haemolytic streptococcus, M29-T 28, appeared in Chicago associated with four cases of rheumatic fever. No rheumatic fever occurred among 14,000 children during 4 years in a community where special study and treatment were performed. The carrier rate for streptococci was 1.8% compared to 15% to 30% elsewhere. In Sweden, the incidence of acute rheumatic fever caused by Pasteurella (Yersinia) pseudotuberculosis was said to equal that of streptococcal origin.

Rheumatic fever recurrence is uncommon in summer even when prophylaxis is stopped. Rheumatogenous streptococci cause more illness in late autumn in contrast to acute nephritis when, during summer, pyoderma is common from nephritogenic strains. Nephritis may result from a reaction between the streptococcal and glomerular basement membranes. Evidence does not support a view that penicillin therapy of streptococcosis prevents acute nephritis. The changing nature of endocarditis was reviewed. The incidence declined only slightly during 30 years, and an older age group is involved. Rheumatic fever still accounts for most valvul cardios. Viruses, fungi and other microbes have increased as causes. Bedsonial infection was fatal in two patients.

Two papers in the Lancet of 12 June condemn dental extraction to prevent endocarditis, as expressed 32 years ago. The routine use of prophylactic antimicrobics to "cover" patients undergoing cardiac surgery does more harm than good. The drugs should be applied when there is clinical and bacteriologic evidence of infection. "Defective", mutant streptococci persistent in cardiac valves or the blood require the addition of thioles for growth in media. They are difficult to isolate and are less sensitive to antimicrobics than the usual strains.

Staphylococcosis
Bacteria rarely infect muscles. After trauma, staphylococci caused myositis of muscles of a patient's back. Vaccine failed to prevent staphylococcal infections in neonates, because of the peculiar surface of the coccus. Fibrinogen, its derivatives, and a substance in neutrophil cells clumped staphylococci. It was shown in 1931 how increased viscosity of plasma by plasma proteins or gum acacia enhanced the clumping ability of specific immune serum.

Meningitis
Among thirty-two patients convalescent from meningococcal meningitis, six had pericarditis, four also had arthritis. Penicillin, heparin and dextran controlled purpura and coagulopathy during fulminant infections. However, the effectiveness of heparin to prevent deaths from intravascular clotting during infections was questioned. In one report, recovery from meningococcemia occurred without heparin therapy. Group Z meningococci caused infection in five patients.

The incidence of carriers in a non-epidemic time was 5-10%. Carriage persisted about 10 months. The carrier-rate for meningococci among Norwegian soldiers exposed to patients varied from 11 to 26%, chiefly with type B. The usual antimicrobics, excepting rifampin, failed to eliminate the cocci. Rifampin effectively reduced the carrier-rate in 95% of students and among soldiers. Prophylactic application rapidly induced resistance to the drug precluding its continuous use.

Meningococci, easily confused with gonococci, caused vaginitis in a child. Groups B and C cocci can be separated into subclasses by their sensitivity to specific bacterocins.

Clostridium welchii caused meningitis in a patient 4 months after surgery for perforated duodenal ulcer followed by protracted illness and recovery. Twenty-five cases of Listeria meningitis were observed. Ampicillin may be the therapeutic agent of choice.

Meningoencephalitis
Amoebic meningoencephalitis, contracted in swimming pools or lakes, killed sixteen persons in a small area of Virginia. It is believed to be fatal, but unrecognized mild cases probably occur. Some amoebas contained a virus-like agent able to infect tissue-culture cells. It may have some bearing on human infection. The "old swimmin' hole" also is a source of poliomyelitis, hepatitis, typhoid, schistosomiasis, conjunctivitis, leptospirosis and others.

Eastern equine encephalitis reappeared in Massachusetts after 14 years. Venezuelan equine encephalitis killed many horses and caused mild febrile disease in man in Texas. An attempt was made to control the epidemic with specific vaccination against official recommendation.

Fifty-seven U.S. soldiers contracted Japanese B encephalitis in Vietnam during the summer of 1969. One died and fifteen had severe sensorial disturbances. Inapparent infections probably occurred in 10,000 soldiers. Gsell summarized information about the problems of newly recognized encephalitic entities. Postinfectious encephalomyelitis occurred after infectious mononucleosis. Encephalitis is the commonest neurologic manifestation of cat-scratch disease. Recovery usually is complete.

Rabies
Further data support a report of the first case of
recovery from rabies mentioned in last year's review. Questions arose as to whether encephalitis was of rabies after a rabid bat bite, or the result of injected duck-embryo vaccine, or if vaccine meliorated rabies. By letter, Doctor Hattwick stated that mononuclear vascular lesions but no Negri bodies were seen in biopsied tissue. It is probable that other unreported or unrecognized recoveries occur with or without vaccination. Duck-embryo vaccine caused transient myelitis in another patient. Some rabies vaccines cause temporary electroencephalographic changes. The obscure pathogenesis of rabies and the uncertain value of vaccines were discussed. Nevertheless, when indicated, both vaccination and injection of antiserum were recommended. Human rabies-immune-globulin, if available, may be preferable. Its dosage must not counteract vaccine-induced immunity. The failure of antirabies vaccine to protect against disease may lie in the prolonged IgM response to current procedures. The antibody may not reach the tissues involved soon enough. The circumstances and difficulties in deciding whether or not to vaccinate were outlined. Poly I : C effectively protected rabbits inoculated with rabies virus. Raccoons have become a major host of infection in southern U.S.A.

Knowledge of chronic 'slow' viral infections of the central nervous sytem was summarized.

Polioymyelitis

Antibody for poliomyelitis persisted 10 years after vaccination in almost all of 565 vaccinees. No antibody appeared in 142 unvaccinated persons. Paralytic poliomyelitis was acquired by an immunized woman apparently after contact with a child who received type II vaccine orally. In children after tonsillectomy, nasopharyngeal antibody diminished or disappeared for 7 months. Vaccination of control children gave 2-4 times as much antibody.

Before the work of Enders and his group, Flexner and Noguchi in 1913 discovered and cultivated the virus. Their so-called globoid bodies probably were viral aggregates but were disregarded by most authorities.

Gonorrhea

Alarm continues about pandemic gonorrhea and the increased incidence of syphilis. Physicians fail to register 90% of cases. Among 231 women examined for gonorrhea, six were infected, but only one recalled known exposure. Diagnostic cultures were recommended especially for patients less than 30 years old who have acute vaginitis. Almost all of forty-two patients with disseminated infection were women most of whom were pregnant or menstruating. Arthritis, myo-, endo- and pericarditis, septicaemia, exanthems, hepatitis and meningitis occurred. The misdiagnosis of gonococcal arthritis in 25% of cases resulted in delayed therapy. It is the commonest form of acute infectious arthritis, especially in women. A Gram-stained smear of the exudate is best for diagnosis. Gonococci in one patient caused meningitis and in another, meningococci caused endocarditis. The incidence of gonorrheal conjunctivitis is increasing. Septic dermal lesions and arthritis accompanied gonorrhea in twenty-three patients (3% of women, 0-7% of men). Fiumara outlined the value and pitfalls of tests for venereal diseases. Report of a laboratory test is not a diagnosis, it merely confirms clinical judgment. Large doses of penicillin (2-4 or 4-8 million units) for the treatment of gonorrhea effectively aborted incubating syphilis in patients also exposed to syphilis. Gonococcal urethritis was established in chimpanzees and one had conjunctivitis.

Pneumonia

Routine sputum cultures for etiologic diagnosis failed in 50% of tests. Pathogens other than pneumococci were present in about 25%. A stained smear of sputum and the capsule swelling test are more reliable for diagnosing pneumococcal pneumonia and bacteraemia is conclusive for any bacteria. Bacteraemia, predominantly of type 14, was associated with otitis media in 71% and extranasopharyngeal infections in 96% of 111 infants and children. Four died.

As apprehended, penicillin-resistant pneumococci appeared among New Guineans who had received penicillin prophylactically for 10 years. Fifteen strains, all of type 4, remained resistant after subculture.

H. influenzae pneumonia may be increasing in adults due to the widespread use of antimicrobial drugs. Seven non-fatal bacteremic cases were observed.

Intranuclear inclusions present in 'desquamative interstitial pneumonia' are not specific. They are not viral particles, are present in other conditions, probably resulting from cellular degeneration.

Gram-negative bacillary pneumonias were discussed editorially and in more detail in my 1971 compend. Alveolar necrosis or necrotizing pneumonia is not specific for any pneumonia. Mumps virus probably caused pneumonia in five children.

Mycoplasmosis

Mycoplasma pneumoniae infection, endemic in Seattle, caused an epidemic in 1967. Children were the chief spreaders, but usually were mildly sick. Although most of them had lower respiratory tract symptoms, only 13% were diagnosed as having pneumonia. One patient had two attacks of
pneumonia within 5 years. If different types of M. pneumoniae are heterologous, immunity to one specific infection does not protect against another, or immunity is brief. Mycoplasmas were present in synovial tissue during rheumatoid arthritis and osteoarthrosis without serologic evidence of invasion. M. hominis probably was a colonizer in facial wounds.

Mycoplasma hominis resists phagocytosis and impairs phagocytic action of granulocytes. By electron microscopy, mycoplasmas in tracheal organ cultures appeared among cilia and entered intercellular spaces, without evidence of localization.

Rickettsioses

Rocky Mountain spotted fever, better named 'tick-borne typhus', to avoid geographic restriction, rose in incidence in Virginia. Population increase and land-use changes may be reasons therefore. An attenuated live typhus vaccine was said to be effective. No antirickettsial vaccines as yet are licensed in the U.S.A.

Mycoses

Candidosis. Colonization is harmless in contrast to invasion. Therapy of infection consists of withdrawing inserted catheters, and stopping antimycotic, corticosteroid and immunosuppressive therapy. The procedures just mentioned, and glucose in saliva, enhance growth of Candida especially in diabetic patients. Candidal sepsis occurred in twenty-seven other patients and nineteen died. Pulmonary candidiasis occurs in infants. Reconstitution of defective cellular immunity may control chronic mucocutaneous infection. 5-Fluorocytosine caused improvement in five cases of cryptococcal meningitis and candidal endocarditis after treatment for 22–820 days. Relapse occurred in two. Drug-resistance may develop.

Torulopsis glabrata caused fatal endocarditis. All of twenty-one patients with pulmonary aspergillosis had other underlying disease. In some instances, the pulmonic reaction was allergic without evidence of invasion. Infection of the lungs occurred in 28% of cardiac transplant patients. Antibody appeared during non-invasive pulmonary aspergillosis, but not in fourteen patients with widespread invasive disease. Lymphocutaneous sporotrichosis affected nine children exposed to baled prairie hay. Ten children were infected in Oklahoma. Pneumonia in a patient was attributed to an actinomycete aerosolized by a furnace humidifier.

Histoplasmal pneumonia recurred 20 months after the primary attack. The diverse behaviour of histoplasmosis was reviewed. Hematogenous dissemination follows in about 70% of asymptomatic patients. Among fifty-four cases of disseminated histoplasmosis between 1947 and 1969, only two of thirty untreated patients have survived. All but three of twenty-four patients treated with amphotericin lived 8 months and nine are still alive. Fatal adrenal insufficiency occurred in half the patients regardless of treatment. Recognition of histoplasmosis in a school teacher led to the discovery of an epidemic involving 31% of 949 students and faculty sick enough to stay home. Another eighty-nine remained ambulatory. Leucocytes surround yeast cells too large to be phagocytosed. Pseudopods then penetrate the yeast capsule and destroy the cells with lysosomal enzymes. A book describes the pathologic anatomy of mycoses.

Metazoal and protozoal diseases

Schistosomiasis once rampant in China is being controlled by destroying snails, proper disposal of human excrement and chemotherapy. Seven other papers about the subject appeared in the same journal issue. Schistosomiasis is said to be spreading because of new dams which provide still water suitable for snails. Marsh flies feed on certain snails and may be useful in controlling infection of livestock in Hawaii and Australia and in man elsewhere. An estimated 200 million persons are afflicted. As occurs in other diseases, salmonellar bacteremia persisted for months in eleven patients.

Hydatidosis is most prevalent in sheep-raising areas of the Americas. Expansion of the livestock industry increased its incidence in South America where it is of great importance. In California, sixty-nine cases, mostly in foreign-born persons, occurred in 10 years.

Thiabendazole had no effect in the treatment of pulmonic strongyloidosis possibly because a corticosteroid drug had been given.


Plasmodium berghei fed to rodents probably penetrated the esophagus to induce parasitemia, a new idea in the pathogenesis of malaria.

Bedbugs rarely, if ever, have been incriminated as vectors of disease, yet a South American variety transmits Trypanosoma cruzi of Chagas disease. Amoebomas as sequels of acute amoebiasis often are unrecognized.

Antimicrobial drugs

Carbenicillin controlled fifty-four of fifty-nine pseudomonal infections, but relapse ensued in six. Superinfections occurred in ten and seven strains became resistant. Acidosis and seizures occurred
during renal impairment.

A great decrease of gentamicin-resistant *Pseudomonas* and *Klebsiella* in hospitals followed the cessation of topical application of it. The drug combined with carbenicillin cured nine of twelve pseudomonal urinary tract infections, but only one of five infections at other sites. Seven of nine endocardial infections resisted surgical and antimicrobial therapy. The combined drugs are not synergistic when bacteria resist either one. One drug may inactivate the other when mixed in vitro. No convincing evidence of the value of any drug for pseudomonal disease has appeared. Gentamicin controlled fourteen of sixteen staphylococcal infections and six of *Staph. albus*.

Enthusiasm for the value of ampicillin was dampened editorially. It is not a superpenicillin. Ampicillin apparently rid *S. typhosa* from nine of ten carriers. Because injected hetacillin becomes ampicillin, its use was disapproved. For treating childhood streptococcal pharyngitis, lincomycin somewhat exceeded the value of penicillin. Erythromycin was said to be equally efficacious.

As if another study were needed to emphasize misuse, antimicrobics had no effect on upper respiratory tract infections. Because none of thirty-two children had bacteremia after dental procedures, routine antimicrobial prophylaxis is considered needless. The choice and dangers of therapy during renal failure were summarized editorially. Lorian reviewed the action of antimicrobics on Gram-negative bacilli. New antimicrobial drugs include clindamycin, cephalaxin and trimethoprim.

Electron microscopy showed the normal morphology of bacteria and mycoplasma and the changes induced by antimicrobics. Failure of drugs to penetrate intact neutrophil cells to kill ingested bacteria probably accounts for microscopic survival in abscesses.

**Unwanted effects of antimicrobial therapy**

About 100 instances of anaphylactoid shock and five deaths after ingestion of penicillin are recorded. In many there was no indication for therapy. Twenty million units of penicillin given intravenously daily caused encephalopathy. Therapy induced chronic laterial meningitis. Penicillin or ampicillin caused haemolysis and thrombocytopenia. Ampicillin wrongly given for respiratory tract infection induced necrotizing angiitis and renal failure especially in previously treated patients. Haematuria followed methicillin therapy.

Chloramphenicol and cephalothin caused haemolysis, and carbenicillin induced excessive bleeding. Inhaled aerosol polymixin failed to influence pseudomonal infection, but caused respiratory acidosis and distress, flushing and nausea. The value of aerosol-applied antimicrobial drugs is unproved. Tetracycline therapy preceded the development of neisserial endocarditis. It also induced transient multiple drug-resistance of faecal *Esch. coli*. Antimicrobial therapy predisposes to overgrowth of resistant *Klebsiella* favouring nosocomial epidemics.

Rifampin in combination with other drugs given to forty-nine tuberculous patients caused fever in eight, thrombocytopenia in three and renal failure in one. Naladixic acid caused neuropathy. Griseofulvin and lincomycin may impair the taste sensation. From 3 to 9% of patients treated with sulfisoxazole, sulfamethoxazole and nitrofurantoin had adverse reactions especially during prolonged therapy. Wound infections by *Phycomycetes* and *Aspergillus* after burns increased ten-fold since 1964, probably as a result of previous topical application of antimicrobics. Gangrene and amputation of an arm followed accidental intra-arterial injection of dicloxacillin.

**Iatrogenic and nosocomial infections**

Infections continue as the major cause of illness and death after cardiac surgery and organ transplants. Among twenty patients, twelve were infected and five died. Immunosuppressive therapy was the chief causal factor of multiple infections by bacteria, fungi, viruses and protozoa. Cytomegalovirus affected twenty-one of fifty-five patients, seven mildly. None with pre-existing immune bodies higher than 1 : 128 in titre were infected. ‘Third-day surgery fever’ in fifty-four patients resulted from intravenous devices contaminated by *Serratia, Klebsiella, Bacteroides* or *Staphylococcus*. The death rate from sepsis and thrombophlebitis was 30%. Similar microbes caused death after thirty-nine renal allograft operations. Among fifty-one patients, severe pneumonia followed renal transplantation and immunosuppressive therapy in seven. Pneumococcus type 3, also participated. A transvenous cardiac pacemaker instigated fatal coccal endocarditis. *Serratia marcescens* caused thirty-five episodes of bacteremia, mostly in burned patients and after antimicrobial therapy, intravenous catheters, tracheostomy or other debilitation. *Serratia* caused sixteen cases of bacteremia mostly in patients with underlying disease treated with antimicrobics. *Bacteroides* bacteremia occurred in 250 patients with a mortality rate of 32%. In another report, seven of thirty-seven adults died.

Serious infections by *Proteus* species increased from 2% of bacteremic infections between 1935 and 1941 to more than 10% between 1947 and 1957.
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