ANNUAL REVIEW

Infectious Diseases:
Annual review of significant publications

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Introduction
Prophylactic and therapeutic measures, better hygiene and other factors reduced the importance of many infections, but have increased concern with others. Review of 'significant' publications appearing in 1969 therefore uses about as many words as did the first of these consecutive annual reviews 34 years ago.

Interest in antimicrobial drugs continues but gives rise to a statement that their use 'has become so thoroughly ingrained that even the suspicion of an infection or fever evokes the prescription of an antimicrobial drug almost as a reflexive response'.

Reports of harmful effects of antimicrobial prophylaxis and therapy, of vaccination and of nosocomial infections grow in number. Evidence of a possible cause of hepatitis stimulated much investigation. Viral respiratory tract infections, viral neural diseases, the herpes group of viruses, rubella and vaccines commanded much attention. The relation of viruses to cancer in man remains unproved.

New antimicrobial drugs
Lincosamycin was superior to penicillin but not to erythromycin for the treatment of recurrent haemolytic streptococcal infections in children. It should be prescribed only if there is intolerance to erythromycin or if the bacteria resist it. Clinacyclic exceeded the action of lincosamycin against staphylococci and pneumococci. Neither affected N. gonorrhoea, H. influenza or other Gram-negative bacilli. Ampicillin gave a cure-rate of 95% of gonorrhoea in military personnel. Gentamicin controlled pseudomonal and Proteus infections especially in combination with carbenicillin. While strains of Pseudomonas acquired slight resistance to polymyxin and to gentamicin, resistance to carbenicillin increased greatly. Resistant strains rapidly displaced others in a hospital ward. Gentamicin effectively controlled acute enteritis caused by E. coli. Because kanamycin is ineffective against Pseudomonas, Serratia marcescens, staphylococci and recently has induced resistance of other Gram-negative bacilli, gentamicin will replace it. Gentamicin rarely induces respiratory paralysis, nephro- and oto-toxicity.

Carbenicillin, a semisynthetic penicillin, cured several pseudomonal infections. Treatment failed in ten of thirteen other patients with incurable underlying disease. It was useful against urinary tract infections, but less so in pulmonary infections. Klebsiella overgrowth followed occasionally. Phosphonamycin, a broad spectrum agent given orally or intravenously, kills bacteria by inhibiting cell-wall synthesis.

The only advantage of doxycycline (Vibramycin) over tetracycline is the smaller and less frequently needed dosage. Cephalexin and cephaloglycin as analogues of cephalosporin affected streptococci, pneumococci, meningococci and staphylococci in vitro but not Gram-negative bacilli. Oral therapy controlled E. coli, Proteus and klebsiella urinary tract infections. Rifampicin exceeded other antimicrobial drugs in the elimination of meningococci from carriers thereof. Will the cocci become resistant to the drug? Rifampicin in high concentration inhibits growth in vitro of vaccinia and adenoviruses.

Besides the new antimicrobial drugs mentioned, cindamycin, bluensomycin, kanendomycin, biniramycin and others appeared. Effort could be devoted better to determine the proper use of agents now available, obviating the need for new ones unless they prove to be exceptional.

The Food and Drug Administration of the U.S.A. acted to prohibit commercial preparation of fixed antimicrobial combinations. Crofton outlined the principles of antimicrobial therapy and its different actions on bacteria in the April 12 and 26
issues of the *British Medical Journal*, which provide a useful guide to physicians. The complex problem of bacterial resistance to antimicrobics was summarized. For trustworthy information, sensitivity tests must be done by trained technicians to avoid many sources of error. Cooperation with the clinician assures better interpretation of the results.

**Unwanted effects**

Huge amounts of penicillin caused fatal encephalopathy in eighteen of twenty-eight patients. Purpura, myalgia, arthralgia, anemia, cerebral edema and vasculitis as delayed reactions to penicillin lasted five weeks in a child. A systemic reaction followed a dermal test with penicilloyl-polysine. Fatal anaphylaxis ensued from a skin-test with penicillin. Traces of penicillin in ingested milk and by inadvertent inhalation caused allergic reactions in a healthy woman. Topical application of bacitracin caused anaphylactic shock in a victim of atopic dermatitis. A patient who had received tetracycline previously had a severe shock 20 min after an unnecessary oral dose for a viral infection. Four times the recommended dose of colistimethate caused palsy and fatal renal failure in a child. Among 149 antimicrobial-treated bacterial pneumonias, twenty-four were superinvaded by Gram-negative bacilli or staphylococci.

Tetracycline-resistant pneumococci resided in 12 of 252 persons. A case of acne form eruption attributed to tetracycline, recalls the homeopathic dictum 'similia similibus curantur' since antimicrobics often are used to cure acne. Sulfaguanidine caused agranulocytosis. Deafness followed local application of neomycin in granulating tissue. It also caused pyoderma from resistant staphylococci and *Candida*.

Chloramphenicol is the most important and preventable cause of aplastic anemia. Its use should be restricted to typhoid and severe Gram-negative bacillary infections for which no other agent is suitable. Penicillin, tetracycline, streptomycin, griseofulvin, sulfonamides and aminosalicylic acid have been implicated as causes of sytemic lupus erythematosus.

Bacteria with genetically acquired antimicrobial resistance present in the environment infect patients more often than those acquiring the R (resistance) factor in the body. Transferred resistance of *E. coli* in the human intestine involved few bacilli and was transient. Resistant bacteria were absent in patients admitted to a hospital but later appeared in 25% of them. Antimicrobial therapy is the main factor inducing bacterial drug-resistance heritable or otherwise. Indiscriminate antimicrobial prophylaxis therefore may be regarded as public health malpractice.

Antimicrobial treatment of salmonella enteritis except typhoid is useless and is harmful by inducing drug-resistant bacilli and increasing the chances for person-to-person spread by prolonging the excretion of the bacilli. Antimicrobial therapy has no effect on the clinical course of illness. Antimicrobial therapy of *E. coli* and *Shigella* enteric infections also failed to shorten the duration of excretion of the bacilli.

Three patients with 'pseudosepticemia' were wrongly treated with hazardous antimicrobics. *E. coli* grew in blood cultures but the bacilli had contaminated penicillinase in the culture media.

**Viral respiratory tract infections**

**Influenza**

According to serologic evidence in persons older than 60 years, A5 virus or one like it caused outbreaks in 1890. Seras tested in 1957 often had antibody against A5 1968 virus. Perhaps a limited number of strains exist and replace each other from time to time. It is also possible that infection with A5 virus occurred any time after 1890. Persons on a remote Pacific island apparently had influenza in 1924 which had not occurred before or since. This unusual circumstance, according to serologic study on persons born before 1918, supported a view that the pandemic of 1918–19 was caused by an A virus closely related to type A strains current in the 1930s. Viraemia was present in a person 12 hr before illness began. A5 influenza virus infected inoculated baboons and spread to animals in neighbouring cages. Perhaps baboons carry infection naturally. Equine influenza virus caused illness in inoculated volunteers.

Persons who received A5 vaccine in 1964 and 1966 had 90% fewer febrile illnesses than control subjects. Monovalent adjuvant vaccine was equally effective. On the other hand, a weak vaccine failed to protect aged persons for whom vaccination is especially recommended. A combination of adjuvants '5s' (mannide monooleate) and complex polynucleotides acted synergistically to enhance greatly the immunizing action of influenza vaccine. Pyrogenicity and reactions were said to be reduced by the use of another new vaccine. Intranasal immunization with inactivated anti-influenza vaccine, resulted in higher titres and longer duration of antibody in respiratory tract secretion than did subcutaneous injection. The predominant immunoglobulin in nasal secretion is an 11S IgA dimer different from serum IgA.

Amantadine and rimantadine in a controlled study were said to be therapeutically effective for influenza A5. An isoquinoline compound (UK 2054) also was said to suppress B virus infection when given orally or intranasally before inoculation of volunteers.

**Rhinoviral infections** exceeded respiratory syncytial viral infections in children causing more illness than
other viruses combined. Some types of the virus spread widely, others did not. \textsuperscript{52} Rhinoviruses heretofore associated only with mild colds apparently caused sixteen instances of pneumonia in soldiers. \textsuperscript{53} Intranasally applied vaccine protected against deliberate infection. \textsuperscript{54} Common colds were caused by inoculating volunteers with parainfluenza 2 and 4 viruses. \textsuperscript{55} Respiratory syncytial (RS) viruses were the agents isolated most often from sick Scottish children. Rhinoviruses accounted for 9\% of infections with diarrhea in addition. Viral pneumonia occurred in 29\% of the children. \textsuperscript{56}

Rhinoviruses, RS viruses and mycoplasma caused 64\% of exacerbations of chronic pulmonic disease. \textsuperscript{57} Evidently, continuous prophylactic antibacterial therapy will not be effective in most patients.

Adenoviral infection demonstrated in fifteen of fifty-seven infants with intussusception suggested a casual relationship of the virus. \textsuperscript{58} Severe viral pneumonia in twenty-five Polynesian infants ended in two deaths; others had residual pulmonic injury after adenovirus 21 infection. \textsuperscript{59} Several types of the virus were susceptible to the action of interferon. Perhaps the agent could be substituted for vaccine to avoid the risk of ontogenicity. \textsuperscript{60}

Interferon appears transiently on the mucosal surface during influenza, Coxsackie and rhinoviral infections, but not enough to play a role in therapy. \textsuperscript{61} RS, parainfluenza and adenoviruses can be demonstrated by electron microscopy within an hour for early diagnosis. \textsuperscript{62} Newly named coronaviruses, carried by birds and animals are similar to murine hepatitis and avian bronchitis viruses known to cause epidemics of colds in man. \textsuperscript{63,64}

As if further warning were needed, another of many papers emphasizes the ineffectiveness of antimicrobial therapy for viral respiratory tract infections. \textsuperscript{65} Knowledge about the epidemiology, clinical behaviour, serology, diagnosis and their control was summarized in a WHO report. \textsuperscript{66}

**Herpes viral infections**

Of six patients with *herpes hominis* encephalitis treated with idoxuridine two died. Three of four who recovered had been comatose. All were neurologically intact afterward. Four untreated comatose patients died, four survived but with neurologic defects. \textsuperscript{67} When IDU fails for treating keratoconjunctivitis within 6 days, corneal freezing was recommended. \textsuperscript{68} *Herpes hominis* virus present in a normal maternal genital tract invaded the infant who died of disseminated disease. \textsuperscript{69} After renal transplantation, four patients had fatal herpetic infections. \textsuperscript{70} IDU had no effect on the vesicular stage of labial herpes. \textsuperscript{71} Two antigenic types of herpes virus have different biologic and epidemiologic features. \textsuperscript{72}

Evidence of infection with herpes-like (EBV) viruses could not be detected in monkeys inoculated with the blood of patients with infectious mononucleosis. \textsuperscript{73} Nor was the virus isolated from the throats of eleven patients. Causal relationship is unproved. \textsuperscript{74} Herpes-like viruses, probably commensal, had previously been isolated from healthy chimpanzees. \textsuperscript{75} EB virus invades children sooner and oftener than *Herpes hominis* and cytomegaloviruses. Between ages 4 to 7 years, 70\% to 90\% of children had specific antibody without clinical evidence of disease. Question remains whether the virus might cause infectious mononucleosis later or if the positive result of the test were an anamnestic one. \textsuperscript{76} EB viral antibody appeared in four of five patients after cardiac surgery. Two were sick. \textsuperscript{77} EB virus and cytomegalovirus persist long in circulating lymphocytes and one or the other may account for post-transfusion mononucleosis especially after cardiac surgery. \textsuperscript{78} The viruses either enter in transfused blood or are related to the operation.

**Meningoencephalitis**

ECHO 9 viral meningoencephalitis affected 196 children mildly in the summers of 1967 and 1968, but one died. \textsuperscript{79} An epidemic of grippe-like illness without meningitis caused by lymphocytic choriomeningitis virus involved eleven laboratory workers in contact with infected hamsters. Two patients similarly exposed elsewhere had characteristic meningitis. Serologic diagnosis can be missed if weak antigens are used. \textsuperscript{80} Two Swiss patients had Central European encephalitis. Complement-fixing antibodies in healthy persons suggested endemicity of the virus. \textsuperscript{81}

Eight patients in a small area had subacute sclerosing panencephalitis. Antibody for measles virus in the blood and spinal fluid, and cellular inclusions in cerebral tissue suggested a causal relation of the virus. \textsuperscript{82} Measles virus grew in cultures from the brain of two other patients. \textsuperscript{83} Administration of 5-bromo-2-deoxyuridine may have halted the progression of the disease. \textsuperscript{84} More than fifty papers on the subject have already been published. Question arises if inoculated measles vaccine itself may cause the disease long afterward.

Fatal spongiiform encephalopathy occurred a year after inoculating chimpanzees with tissue from patients. Infection then was transmitted from animal to animal. A viral origin is likely as in kuru, scrapie and mink encephalopathy. \textsuperscript{85} Seven papers on viral infections of the neural system appeared in the July issue of the *Postgraduate Medical Journal*.

**Diseases of probable viral origin**

**Hepatitis**

*Australia (AU) Antigen.* The cause of viral hepatitis at last may have been discovered. If so, a vaccine eventually may be made. Leading articles in the
Lancet, and elsewhere summarize the problem. The so-called Australia (AU) antigen when activated by an impaired immune mechanism, may be the response to the infectious agent of hepatitis in some patients and of leukemia in others. It was present in forty-six of sixty-two hepatitis patients and persisted longer than 10 months in four. Electron microscopy disclosed virus-like particles in the blood of patients and of healthy apes. The antigen may be the actual virus causing both serum (SH) and infectious (IH) hepatitis. On the other hand, the antigen existed in 98% of 130 patients with SH, but was present less often or not at all during infectious hepatitis. Its demonstration aided in diagnosis and in detecting blood donors who carry the agent. The antigen appeared in three of thirty-one patients with chronic active hepatic disease and cirrhosis. A virus in some instances may cause chronic disease, or the AU antigen may be a non-specific reflection of hepatic injury.

Somewhat different findings also were reported. The antigen was present in five of seventeen patients with acute hepatitis, in three of seven with prolonged hepatitis, but not in any during drug hepatitis, active chronic hepatitis or primary biliary cirrhosis. The persistence of the antigen was said to be an unlikely important cause of chronic hepatic disease. Because of the present uncertainty, the term hepatitis-associated antigen was preferred. SH and AU antigen probably are the same.

Demonstrating the SH antigen on viral particles in SH and its absence in IH served to differentiate the two. The antigen was present during SH without prior blood-transfusion or other injections. In a year all nine patients in a hemodialysis unit and six of fifteen personnel acquired hepatitis. The attendant had acute disease, but probably because of impaired resistance or for other reasons, the patients had inapparent chronic infection. The AU antigen developed in most subjects and its demonstration provided diagnosis. In another study, after multiple transfusions, antibody appeared in two of thirty-two patients with hepatitis and in four of thirty-two without hepatitis. AU antigen was present in four patients of the thirty-two with hepatitis, but not in those without. Antigen and antibody did not coexist. Prior presence of antibody failed to prevent hepatitis. The possible concurrence of hepatitis and cytomegalovirus would obscure the problem. The problem indeed is unsettled and awaits resolution.

Another antigen said to be specific for both SH and IH appeared and disappeared within a month. Its relation to the AU antigen is unknown. A greater amount of IgM during IH may serve to distinguish it from SH, as may measurement of serum guanase which perhaps is more specific than changes in transaminases. Diagnostic tests now included in the 'liver profile' indeed are redundant and un-specific.

Hepatitis was suggested to be a primary enteric infection, but tissue from the small-bowel obtained by biopsy showed no lesions. Serum hepatitis induced a 22-month remission of lymphosarcoma. Clams were probably the source of an epidemic in 123 victims. Ear-lobe piercing may transmit the infection. Hepatic lesions often found in narcotic addicts may have been caused by drugs. Hepatitis appeared in marmosets about a month after inoculation with plasma from three patients in the early stage of hepatitis. Evidence indicated that the disease in the animals represented transmission of the human infection rather than activation of latent marmoset hepatitis.

Prevention and therapy

One injection of immunoglobulin failed to prevent infectious hepatitis in overseas employees. The same substance also failed to reduce the incidence of hepatitis among military personnel in Asia. On the other hand, semi-annual injections in Peace Corps volunteers lowered the incidence as compared with unprotected personnel. Ninety-three immunized persons developed hepatitis within a year or more, mostly between 18th and 34th weeks. Gamma globulin did not prevent post-transfusion (SH) hepatitis. Corticosteroid therapy failed to influence laboratory evidence of hepatitis, but seemed to render the symptoms milder as compared with control subjects. Steroid therapy was abandoned as useless in Swiss hospitals. According to Sherlock, the value of corticosteroids and exchange transfusion is unproved. Therapy consists of bed rest and adequate convalescent care.

Small particles in the blood and faeces during IH resembled an unidentified virus or adenovirus type 3. Adenoviruses occasionally isolated may have been commensal. Specific serologic tests were positive as often in normal persons as during hepatitis. Herpes hominis virus, apparently the cause of hepatitis in a pregnant patient, was present in her mouth and liver.

Viral dysentery

Two large epidemics of mild dysentery occurred, one from sewage polluted water in a camp, the other, after a picnic involving 454 persons with an attack-rate of 69%. From both, infection was carried to homes, but the agent was not discovered. A virus was suspected. Viruses probably account for 90% of diarrhoeal disease in Americans in Vietnam.

Twenty-eight percent of 600 participants of the September, 1968, Congress on Tropical Medicine in Teheran had mild dysentery during a separate
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epidemic of influenza affecting others. Only 8% of those from regions of endemic diarrhoeas were sick as compared with 41% from elsewhere where such disorders are less common.120 Probably a virus was extant.

An epidemic of diarrhoeal disease affected 123 skiers in a winter resort. Of fifty-nine stool samples tested, twenty-five contained *Giardia lamblia* incriminated as the cause and probably spread by a faulty water-supply.121 It still is uncertain whether the protozoan is pathogenic or commensal or if a virus was the primary cause.

Miscellaneous viral infections

Healthy persons occasionally have cytomegalovirus. Seventeen adult patients in Finland had prolonged fever, hepatic involvement and blood changes resembling those in infectious mononucleosis, but without pharyngitis, lymphadenopathy or a positive heterophile test. New names were proposed—cytomegaloviral mononucleosis and cytomegaloviral hepatitis. Chronic disease may ensue.122 Perfusion transmitted infection to four patients. Virus also was recovered from one of four donors of blood.123 In another study, the urine of six of 185 pregnant women contained the virus, but all delivered normal infants.124 Mental retardation attributed to cytomegalovirus in 10% of cases and to rubella and toxoplasmosis 2–3%.125

Maternal rubella after the first trimester resulted in fifteen probably abnormal and seven normal offspring.126 Many papers about rubella appeared in the July and August issues of the *American Journal of Disease of Children*. Measles was fatal in a nephrotic child treated with cyclophosphamide.127 Mumps oophoritis may harm the reproductive function.128 Herpes zoster immune globulin, but not unspecific globulin, given within 72 hr of exposure prevented childhood varicella.129

During cat-scratch disease in 152 patients, only 30% had fever but all had adenopathy and in 6% the site of entry was visible. All but two instances were associated with cats. As in other infectious diseases, thrombocytopenia and purpura occasionally occur.130 Electron microscopy showed herpes-like viral particles in biopsy specimens of lymph nodes.131 Five papers on dengue and chikungunya viral infections in Thailand appeared in the November, 1969, issue of the *American Journal of Tropical Medicine and Hygiene*. Virus-like particles resembling those of parainfluenza virus appeared in tissues from patients with lupus erythematosus.132 Methisazone given to 2610 persons exposed to smallpox resulted in only eighteen infections as compared with 113 cases among 2710 untreated persons. Vaccination after exposure failed.133 Negri bodies detected by immunofluorescence are specific for rabies.134 Viral particles were seen in dermal lesions of molluscum contagiosum.135 Crystals of poliovirus were visualized by electron microscopy in the endoplasmic reticulum of endothelial cells and in inflammatory mononuclear cells in the spinal cord of a sick monkey.136 Any virus able to grow in cell cultures can be identified in infected tissue within hours by electron microscopy.137 Three papers about St. Louis encephalitis in the October *Annals of Internal Medicine* described clinical and laboratory features, pathophysiology and the general absence of detectable interferon.

Summary of knowledge about therapy with antiviral drugs raised questions of possible interference with the natural development of immunity from the infection itself.138 According to a book review, the importance of interferon as an antiviral agent is speculative.140

Vaccines

Live vaccine prevented overt rubella in 93% of vaccinees, but whether it is preventive or only suppressive is uncertain. The duration of induced immunity is unknown.141 Antibody appeared in thirty-five vaccinated women, but twenty got mild rubella. Virus entered the genual synovial fluid in one of them.142 Among twenty-one other persons, all but one developed antibody. Rubella virus was recovered from seventeen and viraemia occurred in one; none was ill.143 Mumps vaccine affords immunity as durable as the infection itself. Protection lasted for 19–32 months in children even when exposed to the infection.144 Combined mumps, rubella and measles vaccines evoked persistent antibodies against each.145 A new method provides an antirabies vaccine free from nonviral material but with high immunogenicity. A "soluble antigen" may produce a better vaccine.146 Vaccines against pseudomonal infection147 and shigellosis are in preparation, but what can be hoped for when even the value of vaccines against typhoid, cholera and plague is uncertain?

‘Vaccine’ composed of polysaccharide antigens to prevent groups A and C meningococcal infection is under study.148 Like the pneumococcal polysaccharide preparations, it is not really a vaccine. If effective, these will be the first able to prevent cocal infections.

Discussion of controversial ‘infectious’ asthma revived the use of mixed ‘stock’ vaccine containing eight kinds of bacteria commonly found in the respiratory tract. ‘Significant statistical benefit’ from hyposensitization followed as compared with the effects of a placebo.149 One wonders if the effects were specific. If statistics were needed for support, the benefit may be dubious. Similar question may apply to a vaccine prepared from condylomatous tissue and said to prevent warts.150
Exception may be taken to statements in the introduction to a symposium of sixteen papers on vaccines and immunization in the British Medical Bulletin 25:119–212, 1969. It is not generally agreed that typhoid, pertussis and BCG vaccines 'are highly effective'. Vaccines, antitoxins and globulin for preventing infections are discussed with more optimism than others feel. According to Hilleman, who summarized the problems of prevention, human immune globulin has little usefulness. 181

Hazards of vaccination

Vaccines and antitoxins for immunization against thirty-two diseases are available or experimental and eleven of them are licensed in the U.S.A. Questions arise as to if, when, where and how to apply them, and of possible harm from repeated vaccination. Amyloidosis in a patient ensued after forty-one injections during 22 months of antistreptococcal vaccine182 and amyloidosis appears in horses repeatedly vaccinated for the production of antitoxins. The matter of multiple vaccines was discussed by Smith. 183 A book describes the hazards accompanying immunization. Physicians should know the dangers inherent and the need for constant vigilance. 184

According to four reports in the April issue of the American Journal of Epidemiology, vaccination against respiratory syncytial virus infection not only failed to prevent the disease, but induced an exaggerated clinical response to the natural infection 9 months later. Vaccines against measles, mumps, myxoviroses, 185 and mycoplasmosis also may sensitise vaccines to both microbial and other material. 156 More respiratory tract infections happened in children vaccinated with parainfluenza viruses than among those vaccinated against rubella. 187 Question arose as to the possible danger to the foetus of maternal rubella vaccination. The virus may replicate for 3 months in vaccines. Probably 15?30% of women never had rubella. 188 Complications followed smallpox vaccination in 500 of 14 million vaccines. Nine died, four from encephalitis. 159 Controversy about the need for routine immunization continues. 160 Minimal estimates indicate that seventy-four complications and one death per million occur after primary vaccination, and among infants 112 complications and five deaths. The benefits of routine vaccination no longer outweigh its risks. 161 Immunization with streptococcal M protein preceded infection with a different type of streptococcus in eighteen of twenty-one siblings from families with rheumatic fever. Rheumatic fever ensued in three as if incited by the procedure. 162 There is as yet little evidence of successful vaccination against any cocal disease.

Virus and cancer

A herpes-type virus present in a nasopharyngeal cancer and evidence of a virus in Bowman's dermal cancer, raised question as to their causal relation. 183 According to Burkitt, Burkitt’s lymphoma may be induced by an interaction of some virus or viruses with a reticuloendothelial system injured by malaria or by other parasites. 164 The virus present in lymphoma may be the cause of infectious mononucleosis, but the relationship remains obscure. A review of the role of viruses in carcinogenesis reveals the difficulties involved. It is unlikely that viruses are the sole incitants of cancer. 165

Virus-like particles in cultured human liposarcoma cells resembled those of avian and murine sarcoma viruses. Antibodies in the patient’s serum reacted with cytoplasmic antigen in the original cells and in the cultured ones, but the potentially defective viral genome was not recovered. 166 In cultures, hamster embryonic cells became sarcoma-producing ones after exposure to benzo[a]pyrene without the agency of a virus. 167 Simian virus 40 DNA in tissue culture can transform human fibroblasts permanently into cells oncogenic for animals. 188 Dermal fibroblasts are three—fifty times more sensitive to transformation in culture by SV 40 virus when derived from persons with a high risk for cancer and from mongoloid persons or those with aplastic anemia. 189 Virologists report the transmission of lymphoma to monkeys by inoculating herpes saimii virus which is latent in some of these animals. 170 Virus-like bodies similar to those found in murine leukemias and other particles were present in lymphoid germinal centres of normal guinea pigs. 171 Cytoplasmic invaginations as found in many tissues especially of the liver, adrenal, cortex and kidney may be mistaken for viral nuclear inclusions. 172 Crystals and other micro-particles often are deposited in cancerous tissues. A cat tumour virus induced fibrosarcomas in dogs, rabbits and monkeys. 173 Russians report the production of leukemia-like disease by inoculating baboons with material from human leukemic patients. Ten baboons in contact with the infected ones also became ill. 173

Statolon, a penicillium derivative, stimulated the production of interferon, inhibited the growth of murine leukaemia viruses and prevented the cellular transformation induced by murine sarcoma viruses. 174

Bacillary infections

Tuberculosis

During 7 years, among 6000 tuberculous Danes, 522 had relapses which was fifty times more than the incidence of primary infections. Isoniazid therapy halved the relapse-rate, but the death-rate was 43% greater than in normal persons. 175 The
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disease will be discussed extensively in a forthcoming monograph by J. A. Myers who studied the problem for 50 years.176

The reactor-rate to the tuberculin test in Philadelphia school children declined from previous 25% at age 6 and 53%, at age 16, to 0-4% and 1-4% respectively.177 In Saigon 85% of adults react positively. Edwards reviewed the use and value of the tuberculin test for both typical and atypical tuberculosis.178

Vaccination with BCG protected 74% of persons in Africa from Buruli ulcer, but only 18% in a highly endemic region.179 Among thirty infants vaccinated soon after birth from tuberculous mothers, none was infected in the succeeding 11 years. Without vaccination, thirty-eight of seventy-five became tuberculous and six died.180 Both reports are subject to question. Vaccination has caused twelve deaths from BCG tuberculosis among children with sex-linked immunologic deficiency. BCG vaccination against leprosy was criticized because its value even for tuberculosis is controversial.181

Rifampicin effectively controls tuberculosis.182 It is also active in vitro against M. kansasii, M. fortuitum and Battey strains. Few resistant forms emerged.183 Ethambutol hydrochloride combined with other drugs is effective but may cause visual disturbance.184

Detailed advice about the indications for prophylaxis and therapy with isoniazid is available.185 In chemoprophylactic attempts among 9000 persons in a slum area, 45% of tuberculin-reactors took only half the amount of isoniazid prescribed.186

Avian-Battey type bacilli caused eighty-nine infections in Britain. One-half were pulmonary and often fatal. Most others were of cervical adenitis.187 The presence of M. kansasii in family members with pulmonary disease suggested possible intrafamilial spread of the infection as appeared to happen on shipboard previously. A scheme for clarifying the nomenclature of 'atypical' mycobacteria was outlined.188

Salmonellosis as a major public health problem affects 2 million persons a year in the U.S.A. Fewer than one of 100 cases are reported officially.190 An epidemic spread by food vendors involved more than 500 persons in Austria. Oral vaccination seemed to stop the epidemic, but the title of the author's paper as a question implies scepticism. Newly recognized Edwardsiella tarda of the Enterobacteriaceae group causes a variety of infections as Salmonella does. Hepatic abscess, septicemia, mild diarrhoea and wound infections occur.191 Perhaps the bacillus often is commensal.

In Britain, and probably elsewhere, most typhoid patients were infected during travel in endemic regions. It is doubtful as stated that vaccination offers 70% protection.193 Mild typhoid affected thirty-one students in a fraternity house in California.194 Intestinal perforation occurred in 22 of 121 typhoid patients in Ghana. Even with early repair and drainage the mortality rate was 30%.195 Severe bleeding and coagulation defects accompanied typhoid in a patient. These incidents also occur in many infectious diseases and represent a 'consumption coagulopathy'.196 This and thrombocytopenia cause bleeding. Chloramphenicol remains superior to ampicillin for treating the typhoids.197

Shigellas were thought not to enter the blood, but two instances of shigellemia with dermal lesions in an infant with sickle cell disease were observed.198 Antimicrobial resistant strains of resident E. coli appeared in the human bowel by transfer of the R factor from resistant exogenous strains ingested orally.199

The treatment of bactereemic shock was described in detail.200

Tetanus

The mortality-rate from tetanus in the U.S.A. (1965–66) was 68% among 507 victims and highest in the south eastern States. Few had been immunized before and eight apparently within 10 years. Five others had received an additional booster injection and among these the death-rate was 38%.201 A properly immunized child needs no booster dose before entering a school or a camp lest a reaction to toxoid occur. Human antitetanus globulin injected on the day of injury in an unimmunized patient failed to prevent tetanus. Antitoxin given on the 6th day when symptoms appeared, failed to prevent death.202 The treatment of tetanus as outlined in a paper, resulted in the recovery of forty-six of fifty-nine (75%) patients. Paraldehyde was the sedative of choice.203

Tularemia

In a sheep-ranching region among 365 tested persons 6-6% reacted to the tularemia skin-test. Only four had been sick so that most infections had been inapparent or undiagnosed.204 Forty-seven Vermont residents contracted tularemia from musk rats during 1 month. Dermal ulcers appeared in twenty-nine. The nature of the disease ranged from inapparent to severe. Tetracycline or streptomycin was curative.205 Among twenty-nine instances of pleuropulmonary involvement, none was contracted by inhalation. Roentgenographic changes were unspecific. Except one victim treated with penicillin, all recovered when treated with streptomycin.206

Miscellaneous bacillary infections

Brucellosis, probably acquired from Italian cheese, affected seven persons in London.207 Newly
encountered *Br. canis* caused widespread epidemics of chronic illness among beagles. Live vaccine occasionally infected healthy dogs. Five persons contracted the disease.\(^{207a}\) *H. influenzae* septicemia accompanied arthritis, osteomyelitis, cutaneous abscesses and respiratory tract involvement in several patients but with fever alone in eight children. Only three had meningitis.\(^{208}\) Bone-meal was the source of cutaneous anthrax in two patients\(^{209}\) and another died after inhaling the germ during goat-hair processing.\(^{210}\) Type E *botulism* from canned fish affected three persons. Uncharacteristic symptoms mistaken for intestinal obstruction and myocardial infarction delayed diagnosis and specific therapy. One victim died.\(^{211}\) Rattlesnake fangs usually harbor clostridia, cocci and Gram-negative bacilli as potential agents of infection from bites.\(^{212}\) House sparrows carry salmonellas.\(^{213}\)

*Melioidosis* has affected 136 military persons in south-east Asia and seventeen died. Pulmonary invasion, empyema and thin-walled cysts were observed. The infection may stay quiescent for years before becoming overt. Tetracycline is preferred for treatment.\(^{214}\) As in the case of histoplasmosis and coccidioidomycosis once thought to be fatal infections, melioidosis now also is regarded as a common infection in south-east Asia, where previously only the severe and fatal cases had been recognized. Specific antibody was detected in 16% of a population in Malaysia, especially in rice-growing areas where *P. pseudomallei* exists in soil and water. The problem was discussed in three papers in the September 1969, *American Journal of Tropical Medicine and Hygiene*.

**Cholera.** A few recovered patients who harbour vibrios in their gall bladder and upper enteric tract serve as perpetual carriers.\(^{215}\) Cholera toxin was thought to disturb vascular permeability locally, but its neutralization failed to modify the symptoms.\(^{216}\) Perhaps the toxin acts on the local or central neural system without demonstrable lesions. Senna, a cathartic, for example, injures the neural tissue without obvious lesion, possibly by irritating the myenteric plexus.\(^{217}\) Chinchillas are suitable for experimental studies.\(^{218}\) *Vibrio parahaemolyticus*, a cause of food poisoning in Japan, is present in blue crabs as a potential danger in the Chesapeake Bay.\(^{219}\)

Opinion is changing about cholera. It is a unique infection resembling the toxic effects of a powerful hydrogogue as suggested in 1946.\(^{220}\) In a recent paper, cholera now is 'considered an intoxication'. In addition to the endotoxin, exotoxins cause similar disease in inoculated animals. The choleragenic and permeability factor of type 2 toxins are different.\(^{221}\) It is unknown if the permeability factor acts directly on the mucosa or in the central nervous system.

In a Pakistani community where cholera is endemic, the infection-rate was 27·4 per 1000, but no overt cases occurred. There are many mild and inapparent infections for every clinically recognizable one,\(^{222}\) as also suggested in 1946.\(^{220}\) Elsewhere, stillborn infants were delivered from eighteen of thirty-six mothers who had cholera late in pregnancy.\(^{223}\)

*Diphtheria* bacilli still are prevalent. Most were isolated from healthy children probably because they were immune.\(^{224}\) During 14 months, dermal diphtheria affected thirty otherwise well persons. Six of eight children had classic diphtheria and three were asymptomatic. In eighteen, the bacilli were in the respiratory tract. Dermal infection resulted in healthy carriers in the vicinity oftener than did pharyngeal involvement.\(^{225}\) Diphtheroid bacilli, like other commensals, are pathogenic only when resistance is impaired. Nine infections were described. Single antimicrobics, not combinations should be used therapeutically.\(^{226}\)

**Coccal infections**

During 10 years, the prevalence of important types of staphylococci declined in Denmark and elsewhere only to be replaced by strains resistant to antimicrobial drugs. Extensive antimicrobial therapy favours an exchange of genetic factors in massive staphylococcal populations in hospitals. Lipase production in 'new' strains increased the severity of bacteremia.\(^{227}\) Replacement of pathogenic staphylococci by avirulent ones by interference reportedly cured furunculosis in twelve patients.\(^{228}\) Conversely, implanting avirulent cocci on infants to prevent invasion of pathogenic ones, probably caused pustules in seventeen of fifty infants.\(^{229}\) Six cases of epidermal necrolysis probably caused by type 71 were observed in a 10-month period.\(^{230}\) Each of fifty-eight infections with methicillin-resistant staphylococci was acquired in a hospital. Vancomycin was the only effective therapeutic agent.\(^{231}\) Staphylococci rapidly became resistant to lincomycin, clindamycin and erythromycin.\(^{232}\)

**Streptococci**

A review emphasized the importance of pathogenic streptococci besides those of group A or D. Many strains still are untypable.\(^{233}\) Group G streptococci, probably in contaminated food, caused 155 cases of acute pharyngitis among 502 students. Therapy with penicillin, erythromycin or lincomycin failed in 34%.\(^{234}\) Fluorescein-labelled immunoglobulin G fractions from sera of patients with acute glomerulonephritis and from many normal persons stained the glomerular basement membrane and mesangium during early post-streptococcal glomeru-
lonephritis, but not tissue injured by other disease.\textsuperscript{335} Cerebrovascular involvement caused the main complaint of one-third of 385 patients with infective endocarditis.\textsuperscript{336} Because only three instances of bacteremia or endocarditis followed 12,367 cardiac catheterizations, antimicrobial prophylaxis is needless for that procedure \textsuperscript{337} and for the transvenous insertion of pace-makers unless there is specific indication.\textsuperscript{338}

**Meningococci**

Acute myocarditis more often caused by groups B and C strains than by A strains accompanied meningococcosis in 174 of 200 fatal cases in adults.\textsuperscript{339} Corticosteroid therapy had no beneficial effect in the treatment of meningitis. Thirty-one percent of children had sequels.\textsuperscript{340} Intravascular consumption coagulopathy probably is an important cause of death in meningococemia. Therapy with heparin may be helpful.\textsuperscript{341}

**Gonococci**

According to a survey, the number of reported cases of gonorrhoea in the U.S.A. increased 35\%, but the incidence of syphilis decreased 29\% since 1962.\textsuperscript{342} Three papers about gonorrhoea appeared in the October *Journal of the American Medical Association*. In one report, seventy-two infections were discovered by routine examination of 875 female patients in a gynecologic clinic, a rate of 8\%. Negative cultures occurred in about 7\% of patients with gonorrhoea. In one study, no *N. gonorrhoea* were found among 505 asymptomatic military men and women. By contrast in a separate report, gonococci were cultivated from 57\% of all routine samples from persons even from those without evidence of gonorrhoea.\textsuperscript{344} Much depends on proper collection and examination of specimens and from whom they are obtained.

**Pneumonias**

Among 193 cases of pneumonia, pneumococci probably were causal in 106, *Klebsiella* in twelve and other microbes in the rest. Etiologic diagnosis was spoiled by prior antimicrobial therapy. No close relation between respiroviral infections and bacterial pneumonia was evident\textsuperscript{345} which is unusual. Twenty-three percent of pneumococci isolated from patients in Liverpool resisted tetracycline.\textsuperscript{346} Among eight cancerous patients treated with drugs, fatal lobar consolidation was caused by *Aspergillus* usually discovered post mortem. Amphotericin was weakly effective.\textsuperscript{347} *Pneumocystis carinii* pneumonia occurred in 107 isolated instances in the United States. Elsewhere it probably is endemic, occasionally epidemic.\textsuperscript{348} The infection was controlled in two lymphomatous patients with pentamidine isethionate, but with temporary impairment of renal function.\textsuperscript{349} Several incidents suggest that *Pn. carinii* pneumonia can be contagious.\textsuperscript{350} Lung puncture abandoned as hazardous for years was revived as an aid in diagnosis. On thirty-two occasions in infants, pneumococci and staphylococci each were yielded in four instances. Pneumothorax occurred three times, hemoptysis once.\textsuperscript{351}

**Nosocomial infections**

About 2\% of hospital patients had nosocomial infections chiefly of operative wounds, less so of the urinary tract, lungs and other areas. *E. coli*, *Staphylococcus* and *Proteus* invaded 80\% of them; *Klebsiella*, *Enterococcus*, *Pseudomonas*, *Pneumococcus* and *Streptococcus* the rest.\textsuperscript{352} Among 860 other patients with Gram-negative bacillary infections, the death-rate increased from 37\% in 1958 to 57\% in 1966. Eighty-one percent were infected in the hospital. Sepsis with the *klebsiella*-enterobacter-serratia group exceeded that with *E. coli*. The death-rate was 23\% in previously healthy patients and 88\% when resistance was impaired. Bacteremic shock occurred in 42\%.\textsuperscript{353} In another study, shock in 60\% of instances followed Gram-negative bacterial infections. *Pseudomonas* was causal in 20\% with a death-rate of 85\%.\textsuperscript{354} Shock also complicated fungemia\textsuperscript{355} and may do so in any bacterial or viral disease.

*Serratia marcescens* heretofore regarded as harmless now is an occasional invader when resistance is impaired. Endocarditis followed cardiac surgery\textsuperscript{356} and was fatal in five of seven other patients despite multiple antimicrobial therapy.\textsuperscript{357} *Serratia* septicemia in forty-two instances followed thrombophlebitis treated with antimicrobics.\textsuperscript{358} Unsterile nebulizers accounted for forty-nine infections.\textsuperscript{359}

*Cl. septicum* also a commensal caused septicemia in twenty-three cancerous patients. Antimicrobial therapy was successful in thirteen of fifteen patients, while eleven of twelve untreated ones died.\textsuperscript{360} *Bacteroides* and other anaerobes appeared in the stomach only in achlorhydric patients.\textsuperscript{361} Experimental ingestion of hydrogen-fixing *H. eutropha* irritated the enteric tract wherein digestion probably released an endotoxin.\textsuperscript{362}

Three defects among others account for recurrent infection: a defective bactericidal process by phagocytes, lack of a humoral phagocyte-promoting factor identified as the fifth component of the complement system and a defect of the chemotactic function of neutrophils.\textsuperscript{363} Aspirin was said to be 'antidifensive' by blocking reactions of the body to noxious agents.\textsuperscript{364} The assertion needs confirmation.

**Mycoses**

Fatal histoplasmosis followed renal transplantation.
Blood smears contained fungal bodies which by electron microscopy appeared in phagosomes. Bats carry H. capsulatum. Coccidiodomycosis relapsed fatally in a diabetic patient 10 years after apparently successful amphotericin therapy. Para-coccidiodomycosis (South American blastomycosis) affected several patients in the U.S.A. Candida albicans fed to a volunteer invaded the enteric mucosa, entered the blood and urine after 3 hr and caused transient illness. Pulmonic and dermal aspergillosis in a child apparently cleared at least temporarily after inhalation of aerosolized nystatin. The drug, surprisingly, entered the blood after inhalation but not after ingestion. The observations require proof. A mysterious 'new' disease, appeared in Sweden, mycosis ventriculi, characterized by clumps of fungal growth in the stomach.

**Malaria**

In Britain since 1954 more than 2000 cases of malaria, mostly falciparum, were contracted in Africa. About 100 cases are reported annually but many are undetected. Among 671 American military returnees from Vietnam, 70% failed to complete the prescribed prophylactic regimen. Sixteen developed malaria. Of 2610 patients with malaria in the U.S.A. and Puerto Rico in 1968 only twelve had indigenous infections. The majority had been in Vietnam. Pl. vivax accounted for 81% and Pl. falciparum for 13%. Pl. malariae was transmitted by mosquito bite from monkeys to 'human' (what other kind are there?) volunteers.

Progress in the control of malaria was summarized in six papers in the January 1969 issue of the *Annals of Internal Medicine* and elsewhere. Despite recent optimism about its eradication the goal is far from reached and cannot be without better methods.

**Miscellaneous items**

Acute toxoplasmosis diagnosed by laboratory tests affected five persons after eating partly cooked hamburger (beef) sandwiches. Headache, myalgia and lymphadenopathy persisted for more than a month. Antibody also appeared in 33% of 3000 pregnant women. Foetal infection is a danger. Because the symptoms and histopathologic changes resemble those of lymphomatoses, diagnosis is essential for proper treatment. The two diseases may occur together. Knowledge of myocardial and pericardial involvement was summarized.

Meyer reviewed the subject of psittacosis-ornithosis. Control of infection in psittacine birds apparently reduced the incidence of human infection. Control involving poultry and feral birds is more difficult. Chlamydia also infects cats, cattle, sheep, goats, hogs, guinea pigs and many wild animals but rarely attacks man in contrast to avian strains. Chlamydia were suspected as a cause of Reiter's disease and acute follicular keratoconjunctivitis. Acute follicular keratoconjunctivitis of Bedsonial origin (feline pneumonia) was contracted from a similarly affected cat. A cat in another household carried the agent. Cat-eye disease (?) not cat-scratch fever. Mycoplasma seemed to be the cause of amnionitis during puerperal sepsis. The delivered infant soon died from interstitial pneumonia of undetermined cause. Mycoplasma also was implicated in the Guillain-Barré syndrome.

A resident of Boston contracted borreliosis during a visit in western U.S.A. Eleven of forty-two campers in the state of Washington contracted relapsing fever uninfluenced by penicillin or tetracycline. Borrelia infected an infant transplacentally. Listeria caused meningitis in fifteen French patients of whom six died. Therapy with penicillin and streptomycin gave fair results. The recognition of trench fever and infection of volunteers by inoculating R. quintana was described in two papers in the September 1969 *American Journal of Tropical Medicine*. Tick paralysis with ascending lower motor neuron involvement caused 300 cases and thirty deaths in British Columbia in the past 68 years.

In Britain, four cowherdsmen had leptospirosis caused by *L. hebdomadis*. Two had meningoencephalitis. Leptospira have tubular structures similar to those of the Marburg agent and of the vesicular stomatitis-rabies group of viruses. Laboratory technicians contracted rat-bite fever from infected rats. Available now in city and state laboratories and the National Communicable Disease Center in Atlanta are serologic tests to aid in diagnosing amebiasis, toxoplasmosis, trichinosis, echinococcosis and Chagas' disease.

Tissue from joints of patients with rheumatoid arthritis caused lesions in the joints, small bones and phalangeal shafts when injected into mice. Transmission through generations of mice complicated a causal agent. Another 'slow virus'? Sarcoïd-like changes induced in immunologically deficient mice months after injection of sarcoid tissue from patients also suggested the activity of a transmissible pathogen.

A round worm, *Capillaria philippinensis*, caused an epidemic of 1000 cases of severe, often fatal diarrhoea in the Philippine Islands. Thiabendazole was effective in therapy. Five papers about thiabendazole therapy of helminthic infections appeared in the October issue of *Texas Reports on Biology and Medicine*. A supplement to the November 1969 *American Journal of Tropical Medicine and Hygiene* contains a report of leishmaniasis in the Sudan.

When hypertonic salt or sucrose containing media were used after routine methods failed, aberrant
micr"omic forms appeared. On reversion to the parent strain, two grew as corynebacteria, two as hemolytic streptococci and one as Cryptococcus neoformans. Mutation may explain occasional therapeutic failure. Therapy directed against the stem form benefited one patient. Knowledge of spherocytes, spheroplasts or L-forms was summarized.

Further evidence accrued that fever may serve as a protective factor in combating some infections. Hyperthermia delayed disease, made it inapparent or prevented death of mice inoculated with dengue virus.

The possibility of spreading smallpox, cholera, yellow fever, plague and other exotic infections by the increasing number of airplane travellers in endemic areas was discussed. Undetectable healthy carriers import diseases and impede eradication. Smallpox, influenza, tuberculosis and measles allegedly were spread purposely to reduce the native Indian population in Brazil. A description of infectious diseases of military personnel in World War II appeared in book form.

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