THE YEAR BOOK *of* MEDICINE

(1962-1963 YEAR BOOK *Series)*

EDITED BY

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YEAR BOOK MEDICAL PUBLISHERS

INCORPORATED

35 EAST WACKER DRIVE

CHICAGO 1

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DEPARTMENTS *of the* YEAR BOOK *of* MEDICINE

Infections

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The Digestive System

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INFECTIONS

PAUL B. BEESON, M.D.

PART I

INFECTIONS

PATHOGENESIS OF INFECTIONS

Factors Contributing to Recovery from Viral Diseases. Frank L. Horsfall, Jr.[1] (Sloan-Kettering Inst.) believes that although recovery from virus diseases is considered natural, little is known about the factors that contribute to it.

Spontaneous recovery is the most probable outcome of human virus disease. Most persons have recovered fully from several childhood exanthems, particularly measles, rubella and varicella, and have also recovered repeatedly from various acute respiratory diseases, especially the common cold, adenovirus infection and influenza. Moreover, most human beings have recovered from herpetic stomatitis and mumps. Except for rabies, no virus disease of man seems to be uniformly fatal.

In man and animals, viruses are recognized as containing antigens unlike those of the host. Infection with them leads to production of antibodies specifically oriented to react with the protein coat of the virus particle. In some instances, though by no means all, signs and symptoms of virus disease tend to become less striking, and recovery may begin about the time that production of circulating antivirus substances becomes significant. This occasional association in time has led to the assumption of a causal relation that holds that in man and animals, at least, the antibody response to virus infection may be important in recovery.

Unlike animals, plants appear unable to produce antibodies, so when recovery from virus disease occurs in such species, specific antibodies against the virus can hardly be invoked as contributory. Animal embryos and fetuses also are thought not to be capable of producing antibodies. Many virus diseases can be induced in such embryos with agents

(1) Canad. M. A. J. 84:1221-1226, June 3, 1961.

derived from man. In some instances, particularly with influenza or mumps virus, recovery may occur, and on hatching, the chick appears to be wholly normal. This provides further evidence that recovery does not necessarily depend on production of antibodies against the infecting virus.

Nature has provided one of the most telling arguments against the antibody hypothesis in man himself. Patients with agammaglobulinemia appear not to possess antibodies and seem to be incapable of producing them. Yet such patients, although constantly in jeopardy of recurring bacterial diseases, appear to react as do normal persons to various virus diseases. Further injection of immune serum containing specific antibodies does not affect the course of virus diseases after definite signs and symptoms have appeared. Regardless of the amount of antibody given after the disease has become manifest, the outcome is not altered, and the time of recovery appears not to be advanced.

In view of current concepts on the mechanism of virus reproduction and the associated damage that may be induced in cells, it would, in fact, be surprising if antibodies were able to affect either process. The mechanism by which viruses are reproduced appears to be unique, for it seems to involve disintegration of the infecting virus particle and the separate synthesis within the host cell of the specific precursor materials needed to produce new virus particles.

Unlike the multiplication of cells, be they animal, plant or bacterial, wherein new cells arise from growth and division of older cells, viruses seem to have no continuity as formed elements and are reduced to their molecular components during each reproductive cycle. Because reproduction is wholly intracellular, both specific precursor materials and new virus particles are protected from any contact with antibodies, for these substances appear to be unable to enter the living host cell. However, when mature virus particles escape from infected host cells and are temporarily free in intercellular fluid or blood, they are readily affected by specific antibody, which inhibits them from infecting other cells. Although this process may prevent systemic spread of the agent and certainly is important in subsequent immunity to reinfection, it seems to have little relevance to the process of recovery from disease.

It has been discovered recently that virus nucleic acid can

itself initiate infection, even when it is not contained in an intact virus particle. Thus, virus reproduction depends on the stimulus and the information provided to the cell by the genetic material, the nucleic acid, of the infecting particle. Most important, free nucleic acid is not affected by antibodies produced against the intact virus particle and retains full infectivity in the presence of these substances. This self-replicating material, the virus nucleic acid, appears to carry in molecular code all the genetic information needed for production of new virus particles in the cell. Among substances classically associated with immunity, none yet appears to be identified that would be expected to interfere with serial infection of cells in successive cycles by virus nucleic acid.

Reproduction of certain animal viruses may lead to self-inhibition. This situation is comparable to a feedback mechanism, which results in the production of fewer and fewer mature infective particles as more and more immature or noninfective particles are assembled. If this reaches the point that, on the average, less than one infective particle is produced per cell, it seems obvious that the infectious process cannot maintain itself and must diminish. Under these circumstances, certain virus infections appear, as it were, to drown in their own juice.

The most recently discovered factors that may contribute to recovery are virus inhibitory substances that appear to be produced by the affected cells themselves. These substances, of which there may be several, seem to be proteins and are not related to the viruses that induce their production. One designated "interferon" was found after cells had been exposed to inactivated influenza virus. Another, found in fluids from infected tissue cultures, develops during multiplication of poliovirus. These substances inhibit reproduction of a number of viruses, including poliovirus, measles virus, vaccinia virus and several myxoviruses. They also inhibit the spread of virus particles from cell to cell. Should the production of these currently mysterious inhibitory substances be found to occur commonly during virus diseases, it would seem necessary to consider them as factors that might favor recovery. Another factor that may contribute is exhaustion or elimination of susceptible cells. Once cells are infected with a particular virus they promptly become resist-

ant to reinfection with the same agent. They need not be damaged to become resistant; they merely need be infected in the sense that they are actively supporting virus multiplication.

It is doubtful that any one of these contributing factors provides an adequate and generally applicable explanation for the recovery phenomenon. Together, however, they constitute a series of hypotheses which, if reasonable, can be used as guides for further study.

► [Horsfall presents here a lucid discussion which helps to orient us in regard to host defense mechanisms in virus infection. His case that antibody plays little part in recovery is impressive, because there has always been a tendency to conceive of host defense mechanisms largely in terms of antibody and phagocyte, neither of which seems to play much part in eliminating viruses from the host animal.—Ed.]

Cellular Aspects of Immunology as Manifested in Simonsen Reaction are discussed by F. M. Burnet[2] (Walter and Eliza Hall Inst. Med. Res., Melbourne). Five sets of findings have given support to the concept of cellular participation in immunologic phenomena. (1) In a child with congenital agammaglobulinemia who cannot produce any type of conventional serum antibody, measles infection runs a normal course and is followed by specific immunity against reinfection. (2) Algire has produced evidence that homograft immunity is mediated by cells, not antibody. (3) Coons and associates, White, and others have produced evidence that the cells responsible for antibody production are plasmacytes (immature or mature) present in clonelike accumulations. (In most instances, at least, they produce antibody against one antigen only.) (4) A wide range of immunologic capacities can be transferred by cells but not by serum from an actively immunized animal to a normal recipient. (These include the capacities to show delayed hypersensitivity, produce antibody on secondary challenge and protect animals whose resistance has been destroyed by irradiation.) (5) The phenomena of autoimmune disease point strongly to the interpretation that tissue damage is due to pathogenic cells and not to the direct or indirect action of antibody.

A major present-day need is to find ways of recognizing immunologically competent cells according to their specific reactivity—in a manner analogous to that by which a solu-

(2) Yale J. Biol. & Med. 34:207-218, Dec.-Feb., 1961-62.