THE YEAR BOOK *of* MEDICINE

(1962-1963 YEAR BOOK *Series)*

EDITED BY
PAUL B. BEESON, M.D.
CARL MUSCHENHEIM, M.D.
WILLIAM B. CASTLE, M.D.
TINSLEY R. HARRISON, M.D.
FRANZ J. INGELFINGER, M.D.
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35 EAST WACKER DRIVE
CHICAGO 1

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DEPARTMENTS *of the* YEAR BOOK *of* MEDICINE

Infections

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The Chest

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The Blood and Blood-Forming Organs

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George Richards Minot Professor of Medicine, Harvard University; Director Thorndike Memorial Laboratory; Director, Second and Fourth Medical Services, Boston City Hospital

The Heart and Blood Vessels and the Kidney

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The Digestive System

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Metabolism

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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.

tion of gamma globulin can be identified as an immune agglutinin, etc.

The Simonsen phenomenon is characterized by the production of lesions in chick embryos after inoculation of mature blood or spleen cells from the same species. These lesions average about 0.5-1 mm. in diameter and are easily counted with the naked eye. They are composed of embryonic host cells, most of which in the early stages result from local proliferation but later include many cells from the blood. The pathogenesis of the lesion is interpreted as follows: An immunologically competent cell from the adult chicken blood reacts with the foreign antigenic determinant present in the embryonic tissues to release pharmocologically active material which can stimulate adjacent host cells—epithelial and vascular endothelial—to proliferate irregularly.

The Simonsen phenomenon provides a model system which permits an assessment of the immunologic potentiality of single cells. It is a typical example of a graft-versus-host reaction, and its interpretation must follow the pattern for similar mammalian phenomena. Several theories have been set forth for its interpretations.

The clonal selection theory suggests that a population of immunologically significant cells from a normal animal can be divided into subpopulations which differ in their specific immunologic reactivity. The instructive or subcellular forms of the clonal selective theory all assume that a potentially competent cell may, by appropriate contact with antigen, take on any one of an unlimited number of immunologic patterns and that all such cells are immunologically equivalent.

The population of cells put on the membrane in one way or another carries the information permitting it to distinguish whether the chorioallantoic membrane contains only antigens with which the organism has been in contact during embryonic life or whether a foreign antigenic determinant is present.

The phenomenon of recognition demonstrated in experiments with inbred chickens is immunologically based and demands that in the cells responsible for the initiation of foci there are preadapted patterns complementary to the histocompatibility antigens by which the host chorioallantoic

membrane differs from that of the donor. In all discussions of clonal selection theory it has been emphasized that the special virtue of the simple form of the theory is that it can be experimentally disproved. Although it might be possible to devise ad hoc explanations to overcome the difficulties encountered in fitting the Simonsen phenomenon into the pattern, the over-all picture indicates that a straightforward clonal selection theory is not an acceptable interpretation of the phenomenon.

To account for the relatively small number of large lymphocytes per specific focus would demand the postulation of a nonrandom distribution of patterns among the cell population. There is no clear increase in the number of foci on embryos differing by several antigenic factors as compared with the number on embryos differing from the donor by only one factor. Some rather special pleading is needed if this fact is to be explained on the assumption that a subpopulation of competent cells is available for each antigenic determinant.

The problem of the recognition of "being foreign" by the normal lymphoid cells of the vertebrate organism remains the major difficulty of immunologic theory. The clonal selection theory was devised mainly in an attempt to resolve the difficulty, but the results of the Simonsen reaction studies show that if the theory is to account for primary immune responses it must be reformulated in some more sophisticated form.

► [Last year I led off with a long abstract of an article by Burnet on his "clonal selection" hypothesis, and commented, "Burnet, who recently was awarded a Nobel prize for contributions in this field, freely acknowledges that he is offering only hypothesis, which must be revised continually as new knowledge develops." True to form he now reports that last year's hypothesis won't fit this year's facts.—Ed.]

Malaria in African Children with Deficient Erythrocyte Glucose-6-Phosphate Dehydrogenase was studied by A. C. Allison and D. F. Clyde.[3] It has been recognized for 20 years that some subjects—particularly among populations of African, Asian or Mediterranean origin—are apt to show hemolysis when given therapeutic doses of the antimalarial 8-aminoquinolines (primaquine, pamaquin, etc.), sulfonamides and certain other drugs. Sensitivity to primaquine is due to an intrinsic erythrocyte defect, a striking feature of

(3) Brit. M. J. 1:1346-1349, May 13, 1961.

which is diminished activity of the enzyme glucose-6-phosphate dehydrogenase (G6PD), which catalyzes the first and rate-controlling step in the hexose monophosphate shunt metabolic pathway (Carson *et al.*, 1956). Although the G6PD deficiency trait is not usually associated with hemolysis, it is potentially harmful. In Mediterranean countries, subjects with the trait get favism after ingestion of broad beans, and evidence is accumulating that they have hemolysis when exposed to virus infections. The distribution of the enzyme deficiency trait parallels that of Plasmodium falciparum malaria until its recent eradication. The question therefore arises whether the trait has become common in malarious regions because carriers are protected to some extent against P. falciparum malaria, as is the case with the sickle cell gene. The authors tested this hypothesis directly by measuring parasite rates and densities in 532 susceptible African children aged 4 months to 4 years, with and without enzyme deficiency, living in a holoendemic area.

In both sexes the parasite rates were lower in enzyme-deficient subjects. In males the difference was statistically significant, but it was not so for females. Parasite densities showed evidence of protection by enzyme deficiency, since the proportions of subjects with high parasite densities were lower in both males and females with G6PD deficiency than in the corresponding groups with normal enzymes.

It appears that G6PD deficiency in young African children affords considerable protection against P. falciparum malaria. Poor growth of malaria parasites in G6PD-deficient cells would be expected. Plasmodia require reduced glutathione for growth in vitro and about half the glutathione of the red cell contributes to the cysteine requirement of the parasites. Enzyme-deficient cells have a subnormal concentration of glutathione. Moreover, there is evidence that malaria parasites use the hexose monophosphate shunt in red cells, and the rate of metabolism by this pathway is diminished in enzyme-deficient cells. Hence for at least two reasons enzyme-deficient cells would be unlikely to support maximal growth of malaria parasites.

As a result, a plausible interpretation of the population genetics of G6PD deficiency can be offered. The female heterozygote is resistant to malaria and is therefore at a selective advantage, whereas the male hemizygote, being

liable to hemolysis, may actually be at a net disadvantage.

The factor precipitating hemolysis under natural conditions is unknown. In most of Africa the broad bean is not eaten, but reports that certain virus infections precipitate hemolysis in susceptible subjects may be relevant. Africans suffer from many virus diseases. Some epidemics of jaundice not due to yellow fever may have resulted from hemolysis in enzyme-deficient subjects.

Many alleged cases of black-water fever reported in immune Africans may be due to severe hemolytic episodes in G6PD-deficient subjects.

► [Within the past decade one of the exciting advances in hematology was the discovery that the erythrocytes of certain persons are deficient in glucose-6-phosphate dehydrogenase. Such persons may have acute hemolytic episodes when they ingest certain drugs or fava beans. It now appears that this "defect" may in some circumstances be advantageous in that it apparently provides some protection against malaria.—Ed.]

Nutrition and Acute Infectious Diseases are discussed by A. Omololu, I. Dema and W. R. F. Collis[4] (Rockefeller Research Unit, Ibadan). The high rate of complications in even the common acute infections like measles and the high mortality rate among Nigerian peasant children is appalling. Their staple foods are cassava and yam, the proportion depending on the yam harvest and on economic factors. Caloric intake is low. Although crude protein intake is fairly good, its utilization is limited by the lack of the sulfur-containing amino acids methionine and cystine. Methionine and cystine are the limiting amino acids, as they restrict the utilization of the other available amino acids. Utilization of total protein intake of the villagers is thus limited by the percentage of available methionine and cystine, leaving them with amounts of utilizable protein that are extremely low.

The children in the villages are not clinically ill. They run about and play with each other and most attend school. In one village, 57 of 67 persons examined had ascaris; most of these were heavy infestations, and some persons had concomitant infestation of Trichuris trichiura and hookworm. Hookworm was found in 33%, and from examination of one chance thick blood film from each villager, 25% had circulating malaria parasites and over 12% had filaria. These children are in a state of protein and caloric imbalance all the time. Malarial attacks further deplete the meager reserves

(4) West African M. J. 10:187-191, August, 1961.