THE YEAR BOOK *of* MEDICINE

(1955-1956 YEAR BOOK *Series)*

EDITED BY

PAUL B. BEESON, M.D.

CARL MUSCHENHEIM, M.D.

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DEPARTMENTS *of the* YEAR BOOK *of* MEDICINE

Infections

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The articles abstracted herein are taken from journals received between May 1954 and May 1955.

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THE BLOOD AND BLOOD-FORMING ORGANS

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THE HEART AND BLOOD VESSELS AND THE KIDNEY

INFECTIONS

PAUL B. BEESON, M.D.

PART I

INFECTIONS

IMMUNITY AND INFECTION

Properdin System and Immunity: I. Demonstration and Isolation of a New Serum Protein, Properdin, and Its Role in Immune Phenomena. Immunity may be divided into two general classes, acquired (artificial) and innate (natural). The discovery of antibodies in serum has increased knowledge of the mechanism of acquired immunity, but little is known about the factors involved in natural immunity.

In an attempt to isolate one of the components of complement, Louis Pillemer, Livia Blum, Irwin H. Lepow, Oscar A. Ross, Earl W. Todd and Alastair C. Wardlaw[1] (Western Reserve Univ.) encountered a new serum protein. Tentatively named properdin, it acts only in conjunction with complement and Mg^{++} and participates in such diverse activities as destruction of bacteria, neutralization of viruses and lysis of certain red cells. It differs from antibody in many respects, particularly in its lack of specificity and in its exact requirements for its interactions.

Human properdin is a euglobulin with a molecular weight at least eight times that of gamma globulin. It represents not more than 0.03% of the total serum proteins. Of the warm-blooded animals tested, the rat has the highest titer of properdin, the guinea pig the lowest, while that of man is intermediate. These findings suggest that properdin may be important in natural immunity, for the rat is very resistant to infection, the guinea pig quite susceptible.

In experiments on bactericidal activity of human serums, the authors used Shigella dysenteriae. All normal human serums were highly bactericidal. Serum from which properdin had been completely removed (RP) was nonbactericidal, as was properdin by itself. RP was bactericidal when sufficient properdin was again added to give the concentration

(1) Science 120:279-285, Aug. 20, 1954.

present in normal serum, indicating that properdin, acting with factors present in RP, was involved in the bactericidal activity of normal serum against the dysentery bacillus.

Severe bacteremia is common following total body irradiation of animals. Experiments to test the possibility that the properdin system might be destroyed by total body irradiation revealed that properdin falls conspicuously during the early postirradiation period. Low properdin levels reached two to seven days after irradiation suggest a causal relation between the destruction of properdin and onset of severe fatal bacteremia.

Investigation of the role of the properdin system in the heat-labile antiviral activity of human serum revealed that properdin and serum factors resembling, or identical with, components of complement are necessary for inhibition of viral hemagglutination. Inactivation or removal of any of these factors inhibits antiviral activity. Addition of human properdin to serum deficient in properdin restores its antiviral activity.

[The discovery of properdin (pro-pear'-din) appears to be a major event in immunology. We are going to hear much more of this in the next few years.—Ed.]

Absence of Serum Gamma Globulins in an Adult is reported for the first time by Jay P. Sanford, Cutting B. Favour and Melvin S. Tribeman[2] (Harvard Med. School). The first case of "agammaglobulinemia" was reported by Bruton in 1952, in a boy, 8, who had had 18 bouts of sepsis with eight different pneumococci, 5 episodes of otitis media and 3 attacks of epidemic parotitis. Deficiency in serum gamma globulin was demonstrated and recurrent infections were controlled by repeated injections of gamma globulin. Nine other male children with this syndrome have since been described.

Woman, 39 on hospitalization in 1953, had had frequent colds, with bronchitis, since early childhood, and a chronic cough had been present since age 17. At 23, anorexia, weakness, weight loss and watery diarrhea led to an ischiorectal abscess requiring surgery. In 1947, three upper respiratory infections were treated with penicillin and bilateral otitis with a sulfonamide. After hospitalization in 1948, and treatment by postural drainage, vitamins, diet and aerosol penicillin, she did reasonably well until February 1951, when myringotomy was performed for acute otitis media complicated by pneu-

(2) New England J. Med. 250:1027-1029, June 17, 1954.

monic consolidation. In June 1952, she had acute meningitis and spinal fluid culture disclosed Hemophilus influenzae. Between November 1952 and April 1953 she had repeated attacks of otitis media, pharyngitis and pneumonitis. During hospitalization in April, total serum protein of 3.8. Gm./100 cc. with globulin of 1.06 Gm. led to the first suspicion of the syndrome of low gamma globulin.

Her blood was type B, Rh positive, of subtype Rh_1, probably homozygous. Anti-A isoagglutinin titers in saline solution were all negative. Electrophoretic analysis of serum three weeks after injection of gamma globulin showed no gamma globulin peak. Quantitative immunochemical determination of gamma globulin showed 25 mg./100 cc., approximately 0.5% of plasma proteins (normal, 14%). After discharge, she received 30 cc. purified gamma globulin (0.1 Gm./kg. body weight) each month. Subjective improvement was apparent 48 hours after the first injection. No acute infections developed thereafter, chronic cough became less productive, both tympanic membranes appeared normal and chronic tenosynovitis cleared.

Replacement of gamma globulin requires approximately 0.1 Gm./kg. to reach blood levels adequate to control infection (100-150 mg./100 cc.). Lower levels are of little value. In children this dose must be given every four to six weeks; in adults, whose gamma globulin half-life may be less, treatment may be needed more often. Complexity of electrophoretic or immunochemical study of plasma proteins limits their use to the research laboratory, but suspected cases may be screened by determination of isohemagglutinin titers; persons with a measurable titer do not have an absence of gamma globulin. In the absence of isoagglutinins, the suspected diagnosis may be confirmed by quantitative determination of gamma globulin. Absence of gamma globulins should be suspected in adults as well as children with multiple respiratory and other infections, and perhaps in spruelike syndromes. Since the defect can apparently be corrected by replacement therapy, which limits disability and forestalls further complications from infections, diagnosis is of considerable importance.

[The technic of filter paper electrophoresis is becoming available in many hospitals now, and because of that we will be able to test frequently for absence of gamma globulins. The condition is probably not too rare.—Ed.]

Adult Agammaglobulinemia. Since Bruton, in 1952, reported a case in a boy of recurrent bacterial infection with no gamma globulin and an otherwise relatively normal plasma protein pattern, similar cases have been reported in male

children. Robert L. Wall and Samuel Saslaw[3] (Ohio State Univ.) report this syndrome in two adults.

CASE 1.—Man, 26, hospitalized for a third attack of pneumonia in a year, had also had recurrent erysipelas of the face. The sputum contained predominantly beta hemolytic streptococci and staphylococci. With penicillin and streptomycin therapy, he became afebrile on the third day. Electrophoretic studies of plasma showed no gamma globulin. He did not form antibodies in response to inoculations with triple typhoid, influenza and mumps vaccines. In the next few months, he had two respiratory infections.

CASE 2.—Man, 40, was first seen because of fatigue, diarrhea, nasopharyngitis and minimal lymphadenopathy. The site of a lymph node biopsy (which showed reticulum cell hyperplasia) failed to heal for 2½ months despite vigorous antibiotic therapy. In the next two years he had repeated infections, including a furuncle, upper respiratory infection with purulent conjunctivitis, bronchitis, and repeated bouts of diarrhea. Electrophoretic analysis showed lack of gamma globulin. The blood was type A and lacked anti-B isoagglutinins. Subsequent infections included three attacks of left basilar bronchopneumonia, maxillary sinusitis and bronchitis, and a recurrence of diarrhea. After immunization with typhoid-paratyphoid vaccine, there was no antibody response to O and H antigens.

These repeated infections could be attributed to gamma globulin deficiency and a concomitant poor antibody response. Whether the syndrome is a congenital or an acquired defect in gamma globulin synthesis is difficult to ascertain. With increased application of filter paper electrophoresis, more cases of agammaglobulinemia should be recognized.

Specific Agglutination of Treponema Pallidum by Serums from Rabbits and Human Beings with Treponemal Infections. Attempts to demonstrate specific antibodies to Treponema pallidum led to the discovery of the Wassermann reaction and other standard serologic tests for syphilis. However, it is now generally believed that these tests not only do not reveal a specific antibody but that they sometimes give positive reactions with serums from persons with no history of syphilis or other treponemal disease. The treponemal immobilization test provided for the first time an in vitro method for detection of specific antibodies. However, the technical difficulties of this test have limited its usefulness, and a simple, specific immunologic test is needed.

Paul H. Hardy, Jr., and E. Ellen Nell[4] (Johns Hopkins

(3) A.M.A. Arch. Int. Med. 95:33-36, January, 1955.
(4) J. Exper. Med. 101:367-382, April, 1955.

Univ.) describe in detail a method for preparation of suspensions of killed T. pallidum that are suitable for specific agglutination studies and can be stored at 4 C. for months without loss of agglutinability. The suspensions were shown to react with two distinct antibodies in the serum of syphilitic animals and man: Wassermann antibody and a specific treponeme agglutinin. The agglutination of treponemes by specific agglutinin is enhanced by heat treatment or aging of the suspension and inhibited by a divalent cation, probably Ca^{++}, normally present in serum. The inhibition was overcome by use of a chelating agent. With these findings, the authors devised a simple agglutination test for diagnosis of treponeme infections. The test was carried out with 430 human serums. Comparison of results with those of the immobilization test showed that the agglutination reaction is a very sensitive test for treponeme antibodies and that its specificity compares favorably with that of the immobilization test. Despite the necessity to absorb serums for removal of Wassermann antibody, the test is simple and can be made under conditions in which the immobilization test cannot. The specificity of the agglutination test was much greater than that of the standard serologic tests.

Final evaluation of the agglutination test must come from the critical analysis of results obtained with serums from a large number of patients who have been subject to the most searching clinical and epidemiologic study.

[The description sounds as if a really practical specific test for syphilis has been devised. It is a pity that something of this kind was not available a few years ago, when the disease was a major problem in this country. Undoubtedly many persons who did not have syphilis were given that diagnosis and treated for it on the basis of the standard serologic tests. —Ed.]

STUDIES OF ANTIBIOTIC ACTION

Mechanism of Action of Penicillin. Our understanding of this, as Harry Eagle[5] (Nat'l Inst. of Health) reminds us, lags far behind its practical application in treatment. Penicillin is only one of numerous drugs of unparalleled activity which have been discovered independently of studies of cell

(5) Journal-Lancet 75:1-6, January, 1955.

function and whose mode of action is still unknown after years of successful use. Detailed exposition of how these agents cause death of the cell would contribute materially to understanding of cellular function, both bacterial and mammalian, and might lead to more effective treatment.

The mechanism by which the agent effects cure in the infected host and its chemical action on the bacterial cell are of paramount importance. To say that penicillin cures infection primarily by direct bactericidal action is not to deny that host defenses are important, but these two mechanisms apparently operate independently. Inability of penicillin-treated bacteria to transport essential glutamic acid across the cell boundary is neither the regular nor probably the primary cytopathogenic effect. It was recently found that in cell-free staphylococcic extracts able to synthesize protein, penicillin at a relatively low concentration (1 μg./ml.) inhibited formation of an adaptive enzyme, galactosidase, as well as synthesis of ribonucleic acid. Whether a similar interference with synthetic processes is the basis of antibacterial action is unknown.

Another unexplained fact is that penicillin kills bacteria in vitro only if they are in an environment which permits active metabolism and growth. It is conceivable that penicillin blocks a metabolic reaction and thereby leads to accumulation of a metabolite, toxic in excess, that occurs only in the actively metabolizing cell. A second possibility is that if organisms are exposed to penicillin in a growing medium, after penicillin has inactivated the postulated vulnerable and essential enzyme, the cell may attempt to replace it by synthesizing new enzyme from precursor substances. The newly formed enzyme would then also be inactivated and this would continue until the cell had exhausted the precursors, thereby becoming nonviable.

With some bacteria, high penicillin concentrations are less rapidly effective than a lower, optimal concentration. If a suspension of bacteria is exposed to radioactive penicillin under standard conditions and if, at varying periods, bacteria are centrifuged out, washed and their radioactivity measured, penicillin is found to be rapidly bound and concentrated, particularly with the more sensitive strains. Correlation between sensitivity and ability to combine with penicillin

suggests a causal relationship. An interesting corollary would be that all bacteria are equally sensitive to penicillin in the sense that a given amount of bound penicillin has the same effect on all cells, sensitive or insensitive. Difference between a penicillin-insensitive and a highly sensitive organism would be in amount of penicillin which must be added to the outside fluid to effect the same lethal degree of combination. This has actually proved to be the case. At lethal concentrations all strains studied had bound the same amount. From 900-1,250 molecules of penicillin can be bound per cell without demonstrable effect on rate of growth. A slight increase in bound penicillin, 1,500-1,700 molecules per cell, results in bacteriostasis. It appears that all bacteria contain one or more penicillin-vulnerable components capable of combining with 1,500-4,000 molecules per cell, that as much as one third to two thirds of these components can be inactivated without demonstrable effect on cell function and that death results when they are almost saturated with the antibiotic. In penicillin-sensitive cells, these components are highly reactive.

Intimately related to mode of action and to the binding phenomenon is development of resistance to penicillin. Experimental evidence indicates that when change from sensitivity to resistance occurs it reflects a spontaneous mutation and selective multiplication of that rare mutant in the presence of the antibiotic.

The miraculous aspect of antibiotics is not that they kill bacteria but that they do so usually without killing the host. Mammalian cells are resistant to penicillin either because they do not contain penicillin-vulnerable components or because these components have a very low order of reactivity.

[I find it hard to select each year's batch of articles without including one or more of Eagle's contributions. Although, as he points out, there is still too little information about the mode of action of antibiotics, his own contributions to the subject are some of the best.—Ed.]

Studies of Microbial Populations Artificially Localized In Vivo. II. Difference in Antityphoidal Activities of Chloramphenicol and Chlortetracycline. In general, if a particular drug can exert powerful antimicrobial action in vivo against certain pathogens, it will be similarly effective against all pathogenic bacteria inhibited by low concentrations of the drug in vitro. Notable exceptions include typhoid fever, bru-

cellosis and tuberculosis. Although causative agents have been inhibited in vitro by low concentrations of several drugs, only a few compounds have been significantly effective against these diseases in patients or experimental animals, e.g., streptomycin has inhibited Salmonella typhosa in vitro in concentrations comparable on a weight basis to those of chloramphenicol, yet the former has been notably ineffective in treatment of typhoid fever. Similar results have been noted for streptomycin in brucellosis, subtilin in experimental tuberculous infections and chlortetracycline in typhoid fever.

Charles A. Werner, Walsh McDermott, Carol Adams and Rebeckah DuBois[6] (New York Hosp.-Cornell Univ.) report a study on comparative antityphoidal activities of chlortetracycline and chloramphenicol to explain their different therapeutic effects in typhoid fever. In vitro minimal inhibitory concentrations of the two drugs for S. typhosa were determined in parallel by the conventional serial dilution method. In vivo studies were carried out in cats, and serum concentrations after various oral and intravenous doses of the two drugs were correlated with suppression of growth of typhoid bacilli encased in triple layered agar disks inserted into the peritoneal cavities of the animals. The bacilli were found to be subsisting directly on nutriments supplied by the host in a state more closely approximating true parasitism than is possible in vitro. The agar disks were readily penetrated by both drugs from extracellular fluid of the peritoneal cavity.

Essentially equivalent concentrations of the two compounds exerted comparable bacteriostatic effect on typhoid bacilli in vitro and in vivo. Doses of chlortetracycline required to provide concentrations in the extracellular fluid inhibitory for S. typhosa were significantly greater than those of chloramphenicol and were greater than those ordinarily used clinically.

Results indicate that one explanation for the difference in therapeutic activities of chlortetracycline and chloramphenicol in typhoid fever may be the difference in the drug-host, rather than the drug-parasite, relationships of the two compounds. This drug-host difference may be a critical factor

(6) J. Clin. Invest. 33:753-758, May, 1954.