It is proposed that each article exhibited should be accompanied with a detailed account or description of it, properly illustrated by correct drawings.

In order to carry into effect the second object of the Institution, namely, *teaching the application of science to the useful purposes of life,* a lecture-room will be fitted up for philosophical lectures and experiments; and a complete *laboratory and philosophical apparatus,* with the necessary instruments, will be provided for making *chemical* and other *philosophical experiments.*

In fitting up this lecture-room (which will never be used for any other purpose than for giving lectures in Natural Philosophy and Philosophical Chemistry), convenient places will be provided and reserved for the subscribers; and care will be taken to warm and light the room properly, and provide for a sufficient supply of fresh air, so as to render it comfortable and salubrious.

In engaging lecturers for the Institution, care will be taken by the managers to invite none but men of the first eminence in science to officiate in that most important and most distinguished situation; and no subjects will ever be permitted to be discussed at these lectures but such as are strictly scientifical, and immediately connected with that particular branch of science publicly announced as the subject of the lecture. The managers to be responsible for the strict observance of this regulation.

In case there should be places to spare in the lecture-room, persons not subscribers will, on the recommendation of a subscriber, and on paying a certain small sum to be determined by the managers, be permitted to attend the public lectures, or any one or more of them.

Among the various branches of science that will occasionally be made the subjects of these public lectures may be reckoned the following, viz. These lectures will treat:

Of Heat, and its application to the various purposes of life.
Of the combustion of Inflammable Bodies, and the relative quantities of Heat producible by the different substances used as fuel.
Of the Management of Fire and the Economy of Fuel.
Of the Principles of the Warmth of Clothing.
Of the Effects of Heat and of Cold, and of hot and of cold winds, on the human body, in sickness and in health.
Of the Effects of breathing vitiated and confined air.
Of the Means that may be used to render Dwelling-houses comfortable and salubrious.
Of the Methods of procuring and preserving Ice in Summer; and of the best principles for constructing Ice-houses.
Of the Means of Preserving Food in different seasons and in different climates.
Of the Means of cooling Liquors in hot weather, without the assistance of ice.
Of Vegetation, and of the specific nature of those effects that are produced by Manures; and of the Art of composing Manures, and adapting them to the different kinds of soil.
Of the Nature of those changes that are produced on substances used as food in the various processes of cookery.
Of the Nature of those changes which take place in the Digestion of Food.
Of the Chemical Principles of the process of Tanning Leather; and of the objects that must particularly be had in view in attempts to improve that most useful art.
Of the Chemical Principles of the art of making Soap; of the art of Bleaching; of the art of Dyeing; and in general of *all the mechanical arts,* as they apply to the various branches of manufacture.

BIOCHEMICAL RELATIVITY

By W. H. MANWARING, M.D.

PROFESSOR OF BACTERIOLOGY AND EXPERIMENTAL PATHOLOGY, STANFORD UNIVERSITY

ABOUT twenty-five years ago there were introduced into certain fields of physical science radically new basic concepts, particularly in reference to atomic structure and radiant energy. Within one decade the general acceptance of these new hypotheses rendered obsolete a thousand previous conscientious researches. For two decades the new theories have been the accepted basis for a hundred hitherto impossible practical applications. To-day we are apparently at the beginning of a similar basic revolution in certain biological sciences, particularly in those fields of physiology and biochemistry bearing on the phenomena of infection and bodily resistance.

Within the last five years there have been introduced in America, Germany, Russia, France and Czecho-Slovakia radically new immunochemical hypotheses, which, if generally accepted, will render inconclusive half of forty years' accumulated immunological literature. The suggested theory of biochemistry relativity casts doubt on a hundred current therapies, challenges a score of physiological orthodoxies, suggests a new perspective in ecology and genetics, has invaded the field of educational psychology and has already led to at least one previous chemical impossibility.

I

The theory of biochemical relativity was developed to explain the origin and nature of "specific antibodies." Demonstration of the existence of highly specialized biochemical defenses in the bloods and tissue fluids of convalescent and artificially immunized animals dates from the closing decade of the nineteenth century. Serum transfer of acquired immunity, serological conviction for murder, test-tube determination of illegitimacy and cutaneous tests for hereditary idiosyncrasies are a few typical applica-

tions. Since the opening of the twentieth century, the basic problem of immunology has been the determination of the origin, nature and physiological rôle of these highly specialized, defensive serum components.

These specific antibodies have never been isolated in sufficient purity for even approximate chemical analysis. Some of them are known to be associated with the globulin fraction of an immune serum, but whether they themselves are globulins or are simpler chemical substances carried by globulins is still undetermined. No immunochemist to-day can say whether the specific antibody known as diphtheria antitoxin, for example, is monovalent, bivalent or polyvalent for diphtheria toxin, or whether or not it forms a dissociable or a non-dissociable compound with that toxin. Even the postulated therapeutic union of toxin and antitoxin to form an inert, non-toxic colloid is nothing more than a convenient therapeutic metaphor.

II

In developing our historic theories as to the origin and function of these serum defenses, immunologists were handicapped not only by this lack of knowledge as to their chemical nature, but by numerous archaic physiological beliefs.

Early pagan physiology assumed, for example, that ingested foods are ceremoniously baptized with gastric juice and by this baptism forcibly detotemized, compelled to renounce all allegiance to their plant or animal of origin and to swear fealty to human flesh. A thousand pagan therapies and pagan religious ceremonials were based on this gastric psychology. In completely detotemized state the ingested foods were assumed to be absorbed into loyal vassalage to the human soul. Mid-Victorian physiology did little more than translate this ancient pagan physiology into the nomenclature of material science. It assumed without adequate proof that under the influence of digestive enzymes ingested proteins, for example, are completely hydrolyzed or detotemized into non-specific or immunologically inert peptones and amino acids, no undigested protein being physiologically absorbed into the blood stream. For three decades no immunologist questioned the truth of this 100 per cent. perfect Mid-Victorian digestion.

Later immunologists, therefore, were surprised and humiliated by inadvertent evidence that this Mid-Victorian nutritional ideal is never realized, that almost any alien protein applied to any mucous surface is absorbed unchanged into the circulating blood at least in sufficient quantities to stimulate the formation of specific antibodies. A few milligrams of non-toxic bacterial protein, for example, dissolved in physiological salt solution and applied to the vaginal mucosa, cause specific bacterial agglutinins to appear in the circulation at the end of the usual latent or incubation period for agglutinin formation. Within twenty minutes after swallowing raw egg, undigested egg-white is carried to all parts of the body, in sufficient quantities to call forth allergic reactions in distant, locally hypersensitive organs and tissues.

What percentage of a protein meal is thus absorbed unchanged, how much is taken up after the first, second and third hydrolysis and what proportion is not absorbed till complete detotemization into peptones and amino acids no immunologist is prepared to say. Difficulty arises from the fact that gastric acidity alone is known to change protein specificity. Detection in the circulating blood may now require a new anti-serum or a new series of animal tests. With each subsequent hydrolysis one or more new specificities may develop.

III

Early pagan physiology pictured urine as a powerful spiritual force, anesthetizing, paralyzing and enslaving undesirable tissue aliens, casting them into outer darkness. A thousand pagan therapies and pagan religious ceremonials were based on this urinary psychology. Mid-Victorian physiology translated this ancient belief and extended it to include renal excretion of parenteral alien proteins. For three decades no immunologist questioned the existence of this alien-protein-excreting renal function.

Later immunology, therefore, was again surprised and chagrined by the realization that there is no convincing evidence that there is any such renal function. In the albuminaturia following excessive ingestion of raw egg, for example, normal serum albumins and serum globulins appear in the urine, usually without a detectable trace of egg-white. It is, of course, admitted that after massive doses of alien proteins, and particularly with toxic proteins, capillary and glomerular permeability are so increased as to cause mechanical leakage. But this is far from proof of a normal physiologic function.

IV

Medieval Christian physiology assumed that no non-lethal beastliness that escapes excommunication from the human body can resist transubstantiation in the presence of the divine spark vitalizing human blood. A thousand ancient therapies and religious ceremonials were based on this hemic psychology. Mid-Victorian physiology translated this ancient faith into the belief that any foreign protein retained in the animal body is completely hydrolyzed or digested by the living tissues.

For thirty years immunologists placed implicit

faith in this 100 per cent. autopurification. Judge our humiliation, then, when we began to realize that there is as yet no convincing evidence that an appreciable parenteral digestion of alien proteins takes place.

Horse proteins are relatively non-toxic for most experimental animals, a fact that has led to the selection of horses for the production of therapeutic antisera. Injected intravenously, in moderate doses, horse proteins are apparently retained quantitatively in the normal canine circulation for at least six days, as determined by quantitative tests with anti-horse rabbit precipitin. Nevertheless, by the end of four days nearly 90 per cent. of the retained horse protein is so completely denatured as no longer to act as foreign protein in canine tissue. By the end of six days, fully 95 per cent. is so denatured. Or translated into immunological terminology, the retained horse protein is no longer demonstrably antigenic for dogs, though still retaining part of its original antigenicity for other animal species.

By the end of fourteen days, 99 per cent. of the retained horse protein is so completely homologized with canine tissues that it can not be differentiated from certain normal canine proteins by routine precipitin tests. It can be so differentiated, however, by the recently introduced quantitative precipitin graphs. In this highly caninized state at least 25 per cent. of the injected horse protein is demonstrable in the canine circulation at the end of three months. Traces of homologized horse protein have been reported in human blood several years after administration of diphtheria antitoxin.

V

Our present knowledge of protein chemistry is too elementary to warrant attempted hypotheses as to the mechanism of this biochemical adaptation of alien proteins to host tissues. A few very suggestive facts have recently been determined. For example, test-tube conjugation of a single amino acid with a protein molecule may alter its immunological specificity. In other words, it now resembles a protein of another plant or animal species. Two optical isomers of the same amino acid confer different specificities.

Test-tube conjugation with a single lipoid or a single polysaccharide may have similar effects. Conjugation with the same amino acid, polysaccharide or other immunological determinant may render two unrelated proteins so nearly identical, at least in their dominant specificities, as to be indistinguishable by routine precipitin tests. Egg albumen, for example, conjugated with the characteristic polysaccharide recently isolated from the pneumococcus is a successful vaccine against pneumococcus infections in animals.

The adoption of an alien protein by host tissues, therefore, does not necessitate radical changes in internal protein structure. Superficial conjugation with a single host determinant may be all that is necessary. Or a superficial burying of a single alien determinant.

IV

Medieval Christian physiology assumed that as a result of the postulated 100 per cent. excommunication and transubstantiation of alien substances the human body is preserved in the 100 per cent. virginal biochemical purity of Adam. Mid-Victorian physiology endorsed this ancient idealism. For thirty years no immunologist questioned it. It became the basic axiom underlying all our historic immunologic theories.

Specific antibodies were, therefore, of necessity pictured as preexisting normal Adamic colloids, increased or specifically mobilized to overcome toxic or infectious agents. In other words, every specific antibody was pictured a preformed purposeful specific antidote against some human disease, an antidote breathed into the body of the first man or acquired by the postulated miracle of evolution.

During three decades a thousand logical and consistent therapies were developed from this basic faith, hundreds of them tentatively adopted by clinical research, fully 95 per cent. of them afterwards discarded as clinical disappointments.

Theoretical immunologists were soon convinced that there must be something radically wrong in their logic, but few of them dreamed that the error was not theirs, but in the basic Mid-Victorian religio-physiology in which they placed such implicit faith.

VII

Later immunologists have been forced to the reluctant conclusion that this faith is unfounded, that no man is 100 per cent. biochemically perfect. He is but an organized colony of dominant human colloids, biochemical echoes of ancient and medieval infections, ceremoniously adopted personal diseases and incompletely homologized undigested dinners. For the first time in history, therefore, it was conceivable that specific antibodies might not be hereditary specific antidotes, but might be retained modified alien entities or partially dehumanized human proteins—hybridization products between toxic or infectious agents and host tissues. This is the tentative basic hypothesis of the newer immunology.

Probably the most convincing evidence that there is at least an element of truth in this futuristic concept is obtained from the recent realization of a previous impossibility, successful test-tube syntheses of specific antibodies, by simulating the postulated biochemical hybridization in the test-tube. By incubating diph-

theria toxin with normal serum, for example, or with individual serum proteins, either alone or in the presence of commercial enzymes, at least four different specific diphtheria antitoxins have been reported within the last three years. One of these is already patented in Germany. By the same or similar technique scores of artificial specific precipitins for plant and animal proteins have also been prepared. Artificial specific agglutinins for pathogenic micro-organisms. At least one synthetic bacteriocidal antiserum.

VIII

Of course, there is as yet no proof that any of these synthetic antibodies are identical with the natural antibodies formed in the animal body during the process of immunization. But there is suggestive evidence that, in time, artificial antibodies even superior to those formed by nature may be synthesized in the chemical laboratory—another blow to Mid-Victorian idealism.

By incubating diphtheria toxin with certain normal serum proteins, for example, two different artificial diphtheria antitoxins have been reported. With other serum proteins, however, the same observers obtained, with the same technique, not the expected antitoxins, but new toxins of exalted virulence and altered specificity. There is convincing evidence that this supertoxin synthesis also takes place in the animal body. With a proper mixture of the antitoxin-synthesizing and supertoxin-forming proteins, the resulting synthetic product is physiologically and therapeutically inert. Artificial antisera superior to those formed during natural immunization might conceivably result from an initial removal of the toxin-augmenting factor from normal serum.

IX

The newer immunology is not merely concerned with protective antibodies, but is equally interested in possible applications of biochemical hybridization to pathogenic micro-organisms.

It has long been known that celloidin particles suspended in dilute protein solutions undergo changes in electropotential, presumably due to the mechanical formation of superficial or interface protein films. In the presence of alien proteins, bacteria undergo similar changes. The bacteria may even acquire a slight agglutinability with specific precipitins for the environmental proteins. That a more radical hybridization than the postulated mechanical formation of superficial proteins films is possible is shown by growing the same micro-organisms for several generations in dilute proteins. By the eighth to twelfth generation in 10 per cent. horse serum, for example, the mechanically acquired precipitin agglutinability of typhoid bacilli is increased twenty fold. At the same time the bacilli completely lose their initial susceptibility to agglutination with ordinary typhoid agglutinin.

Presumably similar hybrid specificity develops in the animal body—recently published experiences with the causative agent of a certain form of canine distemper, for example. This distemper is readily transferred to ferrets. A sublethal dose of the splenic pulp of an infected dog is a successful canine vaccine against this disease at present extensively used in England. Similarly, a sublethal dose of infected ferret pulp is a successful vaccine for ferrets. But neither of these pulps immunizes or appreciably immunizes the opposite animal species. Apparently the common causative agent is so altered, not only superficially but in internal protein specificity in the two animal species, as to become, for all practical purposes, two immunologically distinct viruses.

A hundred clinics and research laboratories are today inspired by the hope that by test-tube simulation of this postulated protein hybridization new successes may follow in the hitherto discouraging field of vaccine therapy and serum therapy.

The newer immunology introduces equal uncertainty into current theories of filterable viruses and bacteriophage. It suggests a hitherto unpostulated etiology for senility and other degenerative diseases. It tends to make logical numerous currently unacceptable heresies as to cancer, tissue transplantation and hereditary idiosyncrasy. Unfortunately, it also suggests a hundred hitherto unexploited quackeries.

X

In outlining the present trend in immunological research I have, of course, passed beyond the boundary line of adequately demonstrated fact into the uncharted field of the research pioneer. One new basic fact in this field may render illogical every alleged fact I have presented.

For example, let us suppose that some future Avery or Landsteiner proves that egg white owes its immunological character to some superficial fowl-determinant—a lipoid, polysaccharide or amino acid, for example. Let us suppose he proves that this dominant determinant is dissociated from the relatively inert colloid molecule in the gastrointestinal tract and is absorbed into the blood stream. Let us further supposed this absorbed determinant now conjugated with some normal serum protein. There might thus be synthesized in the blood stream an atypical human colloid which few immunologists could distinguish from egg white by routine serological tests. Every alleged fact herein reported regarding the apparent gastrointestinal absorption of undigested egg white becomes obsolete.

XI

To theoretical immunologists the present transitional stage is the most interesting period since Pasteur and equally pregnant with potential clinical victories. To applied immunology, however, it is a period of humiliation, loss of faith in the guiding axiom of our forefathers, a new faith not yet sufficiently grounded for clinical application. A chaos in certain immunological specialties, with few immunotherapeutists "certain in their own minds whether they should be enrolled in future medical archives as honest empiricists or as ignorant charlatans." It is little comfort for them to realize that the basic guilt is not theirs, but rests in the archaic physiology in which they placed such implicit faith.

Above all the present is the dawn of a new perspective in American philanthropy and in American research administration. During the last three decades these agencies have made lavish provision for what the coming generation will inevitably regard as superficial pseudoresearch in immunology, feverish clinical application of unproved physiological hunches. At the same time, they have made negligible provision for the basic theoretical work by which alone the truth or falsity of the accepted postulates might have been established. The recent quarter million dollar grant to an American medical school for basic theoretical research, with the specification that the grant must not be used for purely practical applications of present knowledge, heralds the dawn of a new efficiency in conventional medical research.

A NEW METHOD OF DEEP SEA OBSERVATION AT FIRST HAND

By Professor HENRY FAIRFIELD OSBORN
HONORARY PRESIDENT OF THE NEW YORK ZOOLOGICAL SOCIETY

IMMEDIATELY on the receipt of a cable announcing the first successful descent of the Barton bathysphere I cabled to Director Beebe for a brief official report to be published in SCIENCE.

This is the thirteenth expedition of the Department of Tropical Research of the New York Zoological Society under the direction of William Beebe. It is the fifth year of oceanographic research of this department, and the third season at the Bermuda Oceanographic Station at Nonsuch Island. In the year 1928 the twenty-five acre island of Nonsuch, formerly a health and quarantine station erected by the Bermuda government, was placed at the disposition of the Zoological Society for oceanographic research. The seasons of 1928 and 1929 were devoted to the study of both the shallow and deep water fauna.

The buildings at Nonsuch were "transformed . . . into a comfortable and efficient Marine Zoological Station. The two large buildings were practically new and in perfect condition. The three large rain water tanks were overflowing." The relations with the government were excellent. "We were given every assistance, even to having the wreck of a large tug raised in St. George's Harbor, towed across Castle Harbor and sunk near our landing-place, forming a perfect breakwater for protection in rough weather. We had an excellent outfit both for laboratory work, shallow water investigation, and deep-sea trawling. Our electric light plant furnished light for sixty-odd bulbs, a frigidaire, aquarium pumps, etc. A pumping engine at the landing-place furnished three hundred gallons of salt water an hour for our aquariums."

The regular staff under William Beebe included seven assistants and from time to time was aided by Dr. J. Newton Harvey, Dr. C. J. Fish, Dr. Henry P. Bigelow, Professor William K. Gregory and other visiting experts.

In the recent report of the Zoological Society it is stated: "We secured over two hundred species of shallow water fish, about two thirds of the entire fish fauna of Bermuda, and gathered much material for life histories. The midwater depths—an area which we found most difficult to study—yielded many strange organisms. The deep-sea fish were taken from a restricted locality, five miles off shore, eight miles in diameter, and one half mile to one mile below the surface. They were collected in the course of five hundred and twenty-eight hauls, and in abundance and specialization surpassed our utmost expectations."

SEASON OF 1930

Although the most modern trawling devices were used and diving methods at shallower depths were highly successful, for the two seasons past Director Beebe has felt it of great importance to be able to carry on observations at greater depths. Mr. Otis Barton and the director have been working for two years on various problems of deep sea diving, at first studying a cylinder but finally designing a sphere or diving tank, illustrations of which have already begun to appear in the scientific reports from the Station. Director Beebe's own report of June 21, 1930, is as follows: