purview. This state of mind is apt to occur after a great discovery; it occurred after that of universal gravitation; there are signs that it exists now. Yet it has always been falsified by experience, and I think always will be. There are no signs that physics is approaching an asymptotic state in which the progress gets slower and slower as time goes on. The additions to our knowledge of physics made by our generation do not get smaller and smaller as one generation succeeds another, each great discovery is not a terminus but an avenue leading to new knowledge. An improvement in technique may, as we have seen, lead to fundamental changes in our views of the nature of matter and of physical processes. There is far more in physics than is dreamt of in our theories; and nature herself, if we observe her carefully, is more suggestive of ideas than the minds of the most imaginative of us. The ideas which revolutionize science are just those of which our theories give no indications. Theories are the very life-blood of physics. Most of the researches in our laboratories originate in an attempt to test a theory; theory, however, may be injurious if it makes us concentrate our attention exclusively on the particular problem it suggested and to treat as an annoyance, to be avoided by a change in method, any anomaly in the experiment which interferes with our progress to the goal; the anomaly may be the outcrop of a vein rich in new phenomena. After Röntgen had discovered x-rays, another physicist who had been working with somewhat similar apparatus said that he had noticed that any photographic plates near his tube got fogged and spoiled; he moved his plates further away and left it at that. The discovery of argon by Lord Rayleigh arose from some vexatious discrepancies in a series of weighings.

I do not think that there is any danger of the supply of new physical phenomena being exhausted and of physicists joining the ranks of the unemployed. Rather do I believe that as each successive centenary comes round the president of section A will be able to say that the growth of physics in the century which has just passed is comparable with that in any of its predecessors.

POST-EHRLICH IMMUNOLOGY[1]

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FROM a philosophical point of view, classical immunology was equivalent to the postulate that pathogenic microorganisms and the animal body are each vitalized by a unit force, purpose, plan or will that transcends ordinary biochemical laws. Thus supermaterially stabilized, test-tube microorganisms are biochemically identical with the specific infections from which they were isolated and each and every specific serum change in convalescence and artificial immunization is a purposeful defensive hormone. Since this supermaterial somatic organization is immutable in its plan and purpose, it follows that a minute sample of each and every specific serum component that can be formed in the animal body is preexistent in its hereditary tissues, together with a physiological mechanism for its emergency increase in times of specific need. This is but a restatement of the specific receptor hypothesis in non-conventional language.

LOSS OF FAITH IN CLASSICAL THEORY

Recognizing the theological origin of this implied vitalistic theory, and its basic rôle in practical immunology and research, many attempts have been made toward its experimental verification or disproof. Expressed in conventional language, inquiry has been made as to whether or not clinicians are justified in assuming that each and every convalescent serum component is preexistent in normal animal tissues, and whether or not each specific convalescent serum property is a purposeful defensive hormone.

To technical specialists probably the most convincing evidence against this ancestral logic is Otto's alleged separation of "specific sensitizin" from "specific precipitin" by electroosmotic methods. This separation proves that these two convalescent serum components are not chemically identical, and, therefore, can not be mere quantitative variations of the same hereditary defensive hormone.[2] To non-specialists equally suggestive evidence is contained in the war-time researches of Ostromyschlenski and Petroff. These two Russian biochemists incubated mixtures of diphtheria toxin and normal horse serum and found that among the numerous resulting chemical products there are certain denatured serum colloids apparently identical with diphtheria antitoxin.[3] Such test-

[1] Presented before the Society of American Bacteriologists, Pasadena, California, June 18, 1931.

[2] R. Otto and T. Shirakawa, *Ztschr. f. Hyg. u. Infektionskrankh,* 103, 426, 1924.

[3] Ostromyschlenski and Petroff, *Rus. Gesell. f. physical. Chemie,* 47, 263, 1915. (This work was not brought to the attention of international medical science till 1925, and not confirmed in Russian laboratories till 1929, when Kryshanowski prepared several variants of the Ostromy-

tube synthesis would be inconceivable, if diphtheria antitoxin can be formed only as an internal secretion from fixed tissues. Subsequent immunochemists have reported similar test-tube syntheses of specific precipitins, agglutinins and bacteriolysins.[4]

Accumulating evidence of this type has justified the post-Ehrlich denial that each and every convalescent serum change is a desquamated preexistent normal cellular component[5] and has led to the current belief that there are normally present in the animal body enzymic, hormonal and genetic factors capable of synthesizing new or previously non-existent protective specificities.[5,6,7]

Since antitoxins, precipitins, agglutinins, opsonins and other so-called "antibodies" are known or assumed to be specialized proteins, post-Ehrlich immunology assumes that, as a result of natural infection or artificial immunization, new, previously nonexistent protein specificities are synthesized, "induced" or "grafted onto" the animal body, and that some of these exogenous or endogenous "mutant" proteins are specifically defensive in character. This, of course, does not exclude the probability that there are numerous relatively inert "mutant" specificities, and even "induced" specificities injurious to the body.

RECENT ADVANCES IN PROTEIN PHYSIOLOGY

In approaching problems suggested by this current denial of super-material stabilization and motivation of animal tissues, post-Ehrlich immunologists have to their advantage numerous facts not known to earlier theorists. Probably the most significant of these facts are the recent hints as to the probable nature for protein specificity. Within the last five years, artificial conjugation of a protein molecule with a single amino-acid, lipoid or polysaccharide has been shown to confer upon it a new immunological specificity, the "ongrafted" or "induced" character being to a large extent independent of the nature of its protein carrier. By absorption methods, the conjugated amino-acid, lipoid or polysaccharide can be diagnosed, irrespective of this carrier.[8] The conjugated group may even dominate immunological specificity; egg albumin, for example, conjugated with the complex polysaccharide recently isolated from typed pneumococci, being successful vaccine against experimental pneumococcus infection in rabbits.[9]

Protein specificity, therefore, is no longer regarded as a test of complete protein individuality. It is apparently a composite picture of superficial colloidal "determinants," protein characteristics differing from the composite protein pattern of the animal used for the test. Human proteins, for example, may well be 99 per cent. identical with rabbit proteins, the rabbit precipitin being merely a test for the 1 per cent. human characteristic. Two proteins giving the same serological reaction are no longer necessarily identical. nor are identities revealed by sera or anaphylactic tests with one animal species necessarily the same as relationships revealed by different animal tests. Serological classification of animal and plant proteins is but a classification relative to the animal species selected for the production of the diagnostic antiserum.

Equally significant are the new views as to the probable interrelationship of normal serum colloids. An intravascular conversion of serum albumin into serum globulin is now known to take place, with postulated orderly intravascular syntheses from the simplest nitrogenous compound to the most complex serum colloid. Antigens, therefore, are no longer injected into a static colloidal environment, but into a dynamic protein mixture, with a hundred orderly syntheses and disintegrations, conjugations and dissociations that may conceivably modify their chemical properties.[10]

Older immunologists assumed that absorption of undigested food proteins does not take place through the normal gastro-intestinal mucosa, any apparent absorption being *ipso facto* pathological. Within the last three years, however, it has been definitely proved that gastro-intestinal absorption of undigested food proteins is a normal physiological process[11,12,13] and that alien protein absorption also takes place through other mucous surfaces.[14,15] The normal animal of current immunology is no longer a specific immunological zero, but an animal with a dozen constantly exercised antiprotein functions, a hundred well-developed tolerances or immunities, with the probability that many of these physiological tolerances are directed against minor characteristics of any natural infection or injection antigen.

schlenski artificial diphtheria antitoxin. *Centralb. f. Bakt.*, 110, 1, 1929.)

[4] For bibliography see *Jour. Immunol.*, 19, 155, 1930.

[5] W. H. Manwaring, *Jour. Immunol*, 12, 177, 1926; 19, 155, 1930. (See also, Jordan and Falk, "The New Knowledge of Bacteriology and Immunology," Chap. 81, p. 1,078, 1928.)

[6] A. Locke, E. R. Main and E. F. Hirsch, *Arch. Path.*, 2, 437, 1926.

[7] G. Ramon, *Compt. rend. Soc. biol.*, 102, 381, 1929.

[8] K. Landsteiner and J. van der Scheer, *Jour. Exper. Med.*, 48, 315, 1929; 50, 407, 1929.

[9] O. T. Avery and W. F. Goebel, *Jour. Exper. Med.*, 50, 533, 1929.

[10] J. L. Azevedo, *Proc. Soc. Exper. Biol. and Med.*, 27, 4, 1929.

[11] M. Walzer, *Jour. Immunol.*, 14, 143, 1927.

[12] H. H. Donnally, *Jour. Immunol.*, 19, 15, 1930.

[13] A. Cocoa, *Jour. Immunol.*, 19, 405, 1930.

[14] J. Finder, A. F. Lash and J. Simons, *Proc. Soc. Exper. Biol. and Med.*, 27, 368, 1930.

[15] M. B. Cohen, E. E. Ecker and J. B. Breithart, *Jour. Immunol.*, 18, 419, 1930.

DYNAMIC PROTEIN SPECIFICITY

Classical physiology assumed that the human body is static in its protein specificity. To maintain this stasis it was endowed with a 100 per cent. efficient alien protein excretory function in the kidneys, and a 100 per cent. efficient alien protein destructive function in internal tissues. Current immunology challenges both assumptions. For example, in the albuminurea following excessive protein diet, the urine has been shown to be free from food proteins, apparently containing only normal serum albumins and normal serum globulins, presumably escaping as a result of increased glomerular permeability.[16] Parenteral hydrolysis of alien proteins would be hard to conceive without postulating a multiplicity of highly specialized enzymes, beyond the range of present biochemical knowledge.

There is both direct and indirect experimental evidence that such automatic tissue purification does not take place. It has long been known, for example, that alien proteins injected intravenously into rabbits can not be detected in rabbit tissues later than the fourth day by the ordinary precipitin or anaphylactic tests.[17] This is far from being proof of their quantitative destruction or elimination, however, since a slight change in one or more surface characteristics might conceivably alter the specificity of the injected proteins and thus account for their apparent disappearance. That this is the probable fate of certain alien proteins is shown by injecting horse serum intravenously into dogs and studying its possible retention with specific rabbit precipitin. By the end of six days, the alien serum proteins are so far denatured as to be wholly non-antigenic for dogs, while still retaining part of their original horse protein specificity for rabbits.[18,19] The concentration of these retained, partially "caninized" horse proteins decreases to about 10 per cent. by the end of three months, but with quantitative curves from which their mathematically complete elimination or destruction can not be predicted during the lifetime of the animal.[20]

Indirect evidence in support of such parenteral denaturization and retention may be drawn from recent studies of the so-called "serological ripening" or "physiological maturation," the apparently spontaneous appearances of new serum specificities during adolescence[21] in both man and laboratory animals.[22] So marked is this change in rabbits that old-age rabbit serum injected into younger rabbits is alleged to stimulate the formation of specific precipitins for old-age rabbit proteins.[23] Such new specificities prove retention or environmentally "induced" new specificities, unless one is prepared to postulate a phylogenetic recapitulation of ancestral protein specificities not complete till late adult life.[24]

That such "ongrafting" or "induction" of new specificities is a biological possibility is proved by recent studies of "induced" or "mutant" bacterial specificities; a mixed culture of colon bacilli and dysentery bacilli, for example, with dysentery specificity "grafted" onto the colon bacilli, and persisting for at least seven test-tube generations after separation of the two microorganisms.[25] Probably a more convincing example is the alleged "induction" of diphtheria specificity in associated streptococci, the quasi-diphtheria characteristic persisting for at least twelve test-tube generations after separation of the two microorganisms.[25] Experimentally induced new specificities are also reported in erythrocytes.[26]

The so-called "bacteriophage" furnishes another suggestion example. In time "bacteriophage" may be pictured as a dissociated protein pervert or a dissociated "mutant gene," of slightly different specificity from the parent microorganism.[27] This "mutant" pro tein is apparently incapable of self-multiplication, but multiplies or is multiplied when absorbed into active symbiosis with intact bacteria.[28] Thus multiplying, it eventually perverts microbic specificity, thus functioning as a lethal factor. For half a century, geneticists have speculated on such possibilities.

PRACTICAL APPLICATIONS

One of the major puzzles of the last two decades has been the numerous inconsistencies and irreconcilabilities in "anaphylaxis" and immunity.[29] To the newer immunology "sensitivity" is due to accelerated humoral and cellular reactivity, with no preconception as to whether or not such acceleration acts to the specific advantage or disadvantage of the individual.[30,31,32]

[16] H. G. Wells, *J. A. M. A.*, 53, 863, 1909.
[17] R. M. Pearce, *Jour. Exper. Med.*, 16, 349, 1912.
[18] W. H. Manwaring, H. D. Marino, T. C. McCleave and T. H. Boone, *Jour. Immunol.*, 13, 357, 1927.
[19] W. H. Manwaring, H. D. Marino and J. L. Azevedo, *Jour. Immunol.*, 15, 109, 1928.
[20] H. C. Sox and W. H. Manwaring, *Jour. Immunol.* (in press).
[21] E. Friedberger, G. Bock and A. Furstenheim, *Ztschr. f. Immunitätsforsch.*, 68, 480, 1930.
[22] E. Friedberger and D. Gajzago *Ztschr. f. Immunitätsforsch.*, 67, 67, 1930.
[23] T. C. Picado, *Compt. rend. Soc. biol.*, 102, 631, 1929.
[24] Editorial, *J. A. M. A.*, 96, 950, 1931.
[25] G. W. Wygodtschikoff and N. S. Mannilowa, *Ztschr. f. Immunitätsforsch.*, 68, 480, 1930.
[26] C. Hallauer, *Ztschr. f. Immunitätsforsch.*, 67, 15, 1930.
[27] C. W. Jungeblut and E. W. Schultz, *Jour. Exper. Med.*, 69, 127, 1929.
[28] A. P. Krueger and J. H. Northrop, *J. Gen. Physiol.*, 14, 223, 1930.
[29] A. R. Rich, *Arch. Path.*, 7, 552, 1929.
[30] W. H. Manwaring, H. D. Marino, T. C. McCleave and T. H. Boone, *Jour. Immunol.*, 13, 357, 1927.
[31] W. H. Manwaring, H. D. Marino, J. L. Azevedo and H. C. Torbet, *Jour. Immunol.*, 15, 351, 1928.

While classical vaccine therapy and serum therapy were justly proud of their few spectacular victories, they were humiliated by wholly illogical and much more numerous clinical failures. To post-Ehrlich immunology, test-tube "mutants" are not necessarily specific immunizing agents against corresponding infections, nor are serum "antibodies" in the horse necessarily directed against the antigenic "determinants," pathogenic for man.

Recent studies have shown that pathogenic microorganisms not only multiply in the corresponding specific immune serum but often multiply much more rapidly than in control tubes with normal serum.[33] A specific growth-stimulating bacterial retention product in convalescent animals is no paradox to modern theorists.

Recent tests have shown that tuberculous animals are not only resistant to superinfection with tubercle bacilli, but are apparently equally resistant to influenza, anthrax, streptococci and diphtheria toxin.[34] If in time it should be shown that there is no appreciable specific protective factor in tuberculosis, that the increased resistance to superinfection is largely nonspecific, it will be no surprise to current theorists.

Classical immunology is to-day puzzled by the apparently spontaneous appearance of diphtheria immunity in adolescent Eskimo children in an environment demonstrably free from diphtheria bacilli.[35] Post-Ehrlich immunology is prepared to consider a phylogenetic recapitulation of ancestral immunity not necessitating personal contact with specific infections.[36]

SUMMARY

Future bacteriologists can not assume without convincing experimental evidence that any pathogenic microorganism is necessarily static in its biochemical specificity, but must consider the possibility that immunochemical specificity varies with test-tube conditions, animal species, organ or tissue infected and stage of infection.

Future serologists can not assume without convincing experimental evidence that any specific serum component or property is necessarily a specific "antibody" or "defensive hormone"; but must consider the possibility of a wide range of "ongrafted," "induced" or "mutant" specificities, with no preconception as to their probable immunological rôle.

Future immunologists can not assume that the formation or "induction" of new protein specificities is the only important adaptive factor in specific immunization; but must emphasize the relative importance of collateral hypertrophies of non-specific enzymic, hormonal and genetic factors.

Finally, future clinicians must be cautious in endorsing any infectious theory which assumes or implies that the animal body is static in its biochemical specificity; but must be receptive of the accumulating evidence that specificity varies in different tissues, organs and body fluids, and at different stages of anatomical and physiological growth.

OBITUARY

DAVID STARR JORDAN

DAVID STARR JORDAN was born on a farm near Gainesville, Wyoming County, New York, on January 19, 1851. He died at his home, Serra House, on the campus, Stanford University, California, at 9:45 o'clock on Saturday morning, September 19, 1931, at the ripe age of 80 years and eight months.

On July 3, 1929, Dr. Jordan became very seriously ill, due in large part to the unusual extreme heat which prevailed during the first few days of that month at Stanford. For some time he was confined to his bed and his life was despaired of, but, in spite of renewed attacks, he recovered from each to some extent, but never quite fully; each relapse left him a little weaker than before. During these periods of partial recovery he was able to be taken in a wheelchair out into his flower garden, where he would remain some time each day in comfort in the pleasant surroundings. On one or two occasions he was taken to the quadrangle and to various places about the campus so familiar to him during his long connection with the university. The last of these little visits to old familiar scenes was only a few days before the end came.

Until toward the last he retained his interest in world affairs, and in certain ichthyological studies upon which he was engaged when first stricken. His last considerable contribution to ichthyological literature is a "Check-List of the Fishes of North and Middle America," a volume of 670 pages, the manuscript of which was finished only shortly before what he jokingly referred to as his "unceremonious collapse." He was pleased when the "Check-List" appeared in print (February 8, 1930), and he autographed three copies on March 27.

I first met Dr. Jordan in the spring of 1877 at

[32] A. Besredka, "Le choc anaphylactique," Masson et Cie, Paris, 1930, Chap. 7, p. 263, *et seq.*

[33] M. Nocolle and E. Cesari, *Annal. d. Inst. Pasteur,* 40, 43, 1926.

[34] T. Hirayama, *Ztschr. f. Immunitätsforsch.,* 68, 218, 1930.

[35] Bay-Smith, *Klin. Wochenschr.,* 21, 947, 1929.

[36] Editorial, *J. A. M. A.,* 96, 950, 1931.