ing), and bacteriolytic (bacteria-dissolving) substances, opsonins and agglutinins, and grouping them under the term "bacteriotropic substances," the lecturer referred to them as the natural immunizing constituents of the body. He had found, moreover, that when a given virus was injected into the blood, these bacteriotropic substances increased in amounts, in proportion, to a certain extent, with the quantity administered.

Three years ago, in an address before the Chelsea Clinical Society of London, Sir A. E. Wright[222] stated that *while their origin in the body was unknown,* "all the protective substances which were involved in the cure of disease were to be regarded as produced by internal secretion." Alluding to various disorders, including tuberculosis, in which "the blood was deficient in protective substances," he held that if they [pathologists, I presume] "knew the laws by which such substances were produced," we could "call forth a production of those substances" in the patient. In all of some thirty cases—boils, acne and sycosis—which he had treated by inoculations, "there had not been one of them in which there had not been produced enough of that internal secretion to enable the body to kill off the staphylococcus," while "patients with tuberculosis recovered if they produced enough of the internal secretion to render their bodies uninhabitable by the tubercle bacillus." He held, moreover, that "it should be recognized that chronic or local infection was a symptom of defective internal secretions, and that those secretions could be elaborated in the body when there was youth, strength and health, by the application of the appropriate stimulus given in proper quantities."

Now, a year earlier, I had pointed out in the first volume of the present work[223] and elswhere,[224] that the blood's immunizing bodies[225] were the internal secretions of the ductless glands and formulated the principle that "the power of the organism to antagonize the constitutional effects of pathogenic germs, their toxins and other poisons, is directly proportionate to the functional efficiency of the adrenal system," the latter being composed of the thyroid gland, the anterior pituitary and

[222] Sir A. E. Wright: Brit. Med. Jour., Mar. 19, 1904.
[223] *Cf.* vol. i, pp. 609 to 666, 728 to 751, in the first three editions.
[224] Sajous: Monthly Cyclo. of Pract. Med., Jan., March., 1903; Phila. Med. Jour., Mar. 7, 1903.
[225] *Cf.* vol. i, p. 765, in the first three editions.

the adrenals. I laid stress, at the time, on the fact that[226] "all forms of vaccination endow the inoculated subject with enhanced activity of the adrenal system, and, therefore, of all structures which take part in the defense of the body" and ascribed the immunizing influence of Pasteur's method against hydrophobia, vaccination against small-pox, the effects of Coley's mixture of erysipelas and bacillus prodigiosus toxins in sarcoma, Koch's tuberculin, etc., to this process. I repeatedly emphasized the fact that the cure of disease should be considered as produced by internal secretions, that bacteria could not live where the immunizing substances were present in sufficient quantity, etc. That Dr. Wright's researches have confirmed my conclusions is self-evident.

That he should be unable, however, to point to the source or identity of the immunizing bodies is but normal. Elsewhere[227] I had occasion to write: "Pathologists will continue to work in the dark, as they have now been doing several years, until they realize that the very few substances, to which various names have been given: Buchner's alexins, Ehrlich's complement, Metchnikoff's cytase, Ehrlich's intermediary body or amboceptor, Bordet's sensitized substance, etc., *are* internal secretions in the true sense of the word: *i.e.,* products of *ductless glands.*" To this series, as shown in the preceding section, "opsonin" is also to be added.

What is, under these conditions, the nature of the immunizing substances that appear in the blood under the influence of toxins?

In the light of the evidence previously adduced, when a poison or toxin appears in the blood, a fraction of the poison will reach the pituitary body (with the plasma or with the leucocytes) and, if the dose be not excessive, it will excite the test-organ and provoke a protective reaction in the body at large. This reaction being produced through the adrenals, the first substance to appear in the blood is of course adrenoxidase. As this entails increased oxygenation of all organs, their secretory and formative activity is augmented; as a result of this, the pancreas produces more trypsinogen. The leucocytogenic

[226] *Cf.* vol. i, p. 765 *et seq.*, in the first three editions.
[227] Sajous: Monthly Cyclo. of Pract. Med., Apr., 1904.

organs create more leucocytes—mainly neutrophiles and eosinophiles. This double leucocytosis was noted by Muir,[228] who remarked, as a result of his observations, that "whether they act as direct phagocytes or indirectly, the eosinophiles evidently play an important part in the defense of the body." As I interpret the rôle of these cells: they migrate from the iodine reserves (the bone-marrow) to the thyroid and parathyroid glands, to hasten the formation of the sensitizing secretion of these glands. This secretion being taken up by the red corpuscles in the lungs, the blood-plasma receives the first of its "immunizing" substances, viz., adrenoxidase, bound up with the sensitizing thyro-parathyroid secretion. Now, this identical combination is a prominent factor in all the experimental work recorded by pathologists, as the following cursory review of this research will show.

Adrenoxidase plus sensitizing substance. Adrenoxidase, as we have repeatedly seen, is only destroyed at 100° C., while the second substance, opsonin, is, according to Wright and Ross, destroyed at from 60° to 65° C. Now, Metchnikoff,[229] as previously stated, refers to the presence of the thermostable 100° C. substance as "circulating in the blood-plasma" as Pfeiffer's "specific immune body." On the other hand, the latter, which has also been termed "amboceptor" by Ehrlich, "substance sensibilisatrice" by Bordet, "copula" by Metchnikoff, "desmon" by Müller, etc., is destroyed at 65° C. This paradoxical fact finds an explanation in the presence of two substances, adrenoxidase and the sensitizing substance, the more readily observed phenomena being carried on by the latter because of its destruction at the lower temperature.

Still, if this be true, both these bodies should originate from the red corpuscles: Metchnikoff clearly differentiates the 100° thermostable substance as a constituent of the plasma from other substances, referred to below, which originate from leucocytes. More clearly specified in this particular, however, is the source of the sensitizing substance or immune body. While Bordet and von Dungern[230] held that the red corpuscles

[228] Muir: Glasgow Med. Jour., Jan., 1905.
[229] Metchnikoff: Cited by Lazarus Barlow: *Loc. cit.*, p. 469.
[230] von Dungern: Münch. med. Woch., Bd. xlvi, S. 405, 1899; Bd. xlvii, S. 667, 962, 1900.

excited the production of this substance, Nolf[231] showed that it was a product of these cells. The rôle of this substance is evidently that ascribed by myself to the thyro-parathyroid secretion and by Wright to the "opsonin," for, as stated by Wassermann,[232] according to Bordet, "the substance sensibilisatrice plays the rôle of mordant. It makes the blood-cells [and also bacteria, toxins, wastes, detritus, etc., I should add] vulnerable to the alexin, so that the latter can attack the cells and dissolve them."

This brings us to the next stage of the defensive process:—

Phagocytosis, carried on by the intracellular digestive triad, trypsin. A multitude of neutrophiles are now present in the circulation ready to ingest and digest the sensitized bacteria, toxins, cells, wastes, etc.—Metchnikoff's phagocytes. We have seen repeatedly that they contain what I have termed the "digestive triad," viz., trypsinogen, nuclein, and adrenoxidase, which, combined, constitute the ferment trypsin. Charrin and Levaditi,[233] von Zaremba[234] and others have demonstrated the digestive activity of pancreatic juice on bacteria and toxins; Metchnikoff, Arthus, Mouton[235] and others found trypsin in leucocytes. Moreover, the labors of Bordet, Metchnikoff, Ehrlich and Morgenroth have demonstrated that the destruction of bacteria, etc., was due to the presence in the phagocyte of a digestive substance. "This substance, a sort of digestive ferment," writes M. Labbé,[236] "attacks and destroys the cells and bacteria that are sensitive to its action; thanks to it, pathogenic elements are destroyed within the leucocytes." As is well known, the efficiency of phagocytic protection is proportionate with the relative number and activity of the phagocytes present, and if these cells increase promptly in the blood, they soon dispose of the bacteria; conversely, if the latter are too numerous, or too virulent, the phagocytes are overwhelmed, partly by bacterial toxins, and general infection occurs. Phagocytes, therefore, owing to the digestive triad they contain, play a leading part in the defense of the body, in accord with Metchnikoff's doctrine.

[231] Nolf: Ann. de l'Inst. Pasteur, vol. xiv, pp. 297, 492, 1900.
[232] Wassermann: "Immune Sera," Transl. by Bolduan, p. 5, 1904.
[233] Charrin and Levaditi: Semaine méd., Mar. 22, 1899.
[234] von Zaremba: Archiv f. Verdauungskrankheiten, Bd. vi, S. 403, 1900.
[235] Mouton: Ann. de l'Inst. Pasteur, T. xvi, p. 457, 1902.
[236] M. Labbé: "Le Sang," p. 44, Paris, 1902.

The third stage of the auto-protective process is now in order; the appearance in the blood of:—

The digestive triad as the bacteriolytic constituent of the plasma. While Pfeiffer, Fodor, Nuttall and others found that the blood-plasma possessed bactericidal properties, Buchner and Hankin isolated the active substance, and termed it "alexin." As stated above, this is the trypsic body, or digestive triad which destroys bacteria within the phagocytes. The experimental demonstration by Bordet, Metchnikoff and others that the phagocytic alexin was a trypic ferment is further sustained by Buchner's own labors (1899), which showed that there existed a close connection between the leucocytes and the presence of alexins in the plasma. Buchner showed, moreover, that alexins were derived from leucocytes, a conclusion sustained by the investigations of Bail, Schattenfroh and others, and now generally accepted. As to the manner in which alexins leave the leucocytes, Metchnikoff and Gengou have held that they were liberated by breaking up of the cell. We have seen, however, that this view can no longer hold. Indeed, Buchner showed that they were secreted by the cells, a conclusion sustained by Ehrlich's investigations and those of other observers. On the whole, it is evident that while leucocytes use their intracellular trypsin to digest the bacteria they ingest, and, as I have pointed out, convert them into nutrient granules which they carry to all tissue-cells; they can likewise secrete their digestive triad or trypsin with their granulations, into the plasma, thus endowing the latter with its bactericidal property. The interrelations of these various substances in the blood will be referred to in the next chapter.

From start to finish, therefore, it becomes possible to account for the auto-protective or "immunizing" process in disease by means of substances derived from the ductless glands: adrenoxidase, the thyro-parathyroid secretion, and the pancreatic internal secretion.[237] Even the phagocytes which utilize the latter are ductless glands, since they also secrete their bacteriolytic substance in the blood. Moreover, one salient fact has asserted itself, viz., that the intra-phagocytic and plasmatic bactericidal and antitoxic triad is the identical one which, as I

[237] *Cf.* this vol., p. 854.

have pointed out, fulfills the cardinal function in the vital process with the adrenal active principle as the chief factor. Here, again, the paramount influence of this principle prevails, since it is to its identity as the ferment of the bactericidal ferment, *i.e.*, as a catalytic, that it can protect the body whose life it serves to initiate and sustain.

Wright's subdivision of the "bacteriotropic substances" into bactericidal and bacteriolytic bodies, opsonins and agglutinins, may be reduced to three, under these conditions, since a pathogenic organism is necessarily killed by the trypsin whether in the phagocyte or in the blood-stream, as they are in the intestinal canal, viz., the digestive triad, trypsin, the thyro-parathyroid secretion, opsonin, and agglutinin.

We are left, however, with an unknown quantity: "agglutinin." What are the nature and mode of action—both unknown—of this substance?

As interpreted from my standpoint, agglutination is the initial phenomenon of bacteriolysis, and is also caused by the thyro-parathyroid secretion. It is a coincident phenomenon of, or succeeds the sensitization of pathogenic organisms or of any substance to be dissolved by the digestive triad in the plasma. Clumping and digestion of the red corpuscles—hæmolysis—are due to the same factors, these cells sharing the fate of the bacteria when the digestive activity of the plasma becomes excessive.

The landmarks of the thyro-parathyroid secretion are readily traced in the experimental history of agglutinin. Thus the temperature at which the latter is destroyed is the same. Wassermann,[238] for instance, writes: "The agglutinins are fairly resistant substances which withstand heat to 60° C., and lose their power only on heating to 65° C. It is possible, therefore, to make a serum hæmolytically inactive by heating to 55° C., and still preserve its agglutinating power." It is not to adrenoxidase alone that it is due, since the latter is only destroyed at 100° C.; nor can it be the digestive triad which is destroyed at 55-56° C. On the other hand, 60° to 65° corresponds with opsonin, which, as we have seen, is the parathyroid secretion. Its intimate functional relationship with adrenoxi-

[238] Wassermann: *Loc. cit.*, p. 36.

dase is also suggested by the fact that Baumgarten[239] was led experimentally to conclude that agglutinin and Ehrlich's complement (adrenoxidase) were identical, while Bordet and von Dungern held that hæmolysins might originate from the red corpuscles. Again, we have seen that it was in the lungs that the thyro-parathyroid secretion was taken by the plasma and red corpuscles: Deutsch found that the lungs of *non-immunized* guinea-pigs were the only organs which exceeded in agglutinating activity that of the blood-plasma, and therefore of all other body fluids.

The presence of agglutinin in plants suggests the active agent in the process. Ricin, obtained from the castor-bean, is very active in this particular, as are abrin, the phallin of mushrooms, and other plant albumoses. All plants containing more or less iodine, oxidases, and nuclein, as we have seen, the conditions therein are such as to permit the elaboration of an iodine-ferment (which may be very powerful, as in the plants mentioned) very similar, in its chemical properties, with those of the thyro-parathyroid secretion. This involves the conclusion, however, that iodine (the main active agent of the secretion and of the vegetable compound corresponding with it) should like ricin, abrin, etc., produce hæmolysis: "Iodine," writes Cushny,[240] "is said to dissolve the red blood-corpuscles when it is brought in contact with them outside the body, and to form a combination with hæmoglobin." The corpuscles themselves and the plasma in which they bathe affording the other constituents for the formation of an iodine ferment, the effect is the same as if an energetic blood hæmolysin had been used. Exception has been taken to Ehrlich's suggestion that the agglutinin of plant albumoses (phallin, ricin and abrin) was the same substance as hæmolysin; his view is perfectly warranted, however, since, as stated above, plants contain not only the iodine ferment, but also trypsin, etc., to follow up agglutination with digestion, *i.e.*, hæmolysis. Indeed, Baumgarten found that partial hæmolysis of the red corpuscles occurred after they had been agglutinated with ricin and abrin when the mixture was energetically shaken.

[239] Baumgarten: Berl. klin. Woch., Bd. xxxviii, S. 1240, 1901.
[240] Cushny: "Pharmacol. and Therap." third edition, p. 519, 1899.

That agglutination is a precursor of hæmolysis is a recognized fact. Thus, Bordet[241] found that "agglutination of the red corpuscles occurs previous to their solution," that "the solvent power of the specific hæmolysins depended on the combined action of *two* constituents of the specific serum," and, moreover, that "when the fresh hæmolytic serum was warmed for half an hour at 55° C., it lost its power."* That both the amboceptor (adrenoxidase) and the complement (the digestive triad) are necessary for the production of hæmolysis has in fact been demonstrated by Ehrlich and Morgenroth.[242] All the more recent investigations have not only served to confirm these fundamental features of the problem, but they have sustained Ehrlich's view that hæmolysis is a fermentation process analogous to digestion. This applies as well to bacteriolysis, as is well known. Agglutinin stands out prominently as an independent substance in this connection, since it does not itself immunize. Durham[243] found that the presence of large quantities of agglutinins in the blood of animals did not prevent death from infection. It is plain, therefore, that agglutination is but an initial phenomenon of the immunizing process.

The identity of agglutinin as the thyro-parathyroid secretion thus asserts itself in various ways. The two bodies correspond: as to the temperature at which their action ceases, 60° to 65° C.; their source in the blood-stream, the lungs; the identity of their main active agent, iodine; their mode of distribution, the red corpuscles; and finally, their sensitizing property. Having shown in the preceding section that opsonin was also the thyro-parathyroid secretion, it is plain that opsonin and agglutinin likewise represent the one substance.

Returning to Wright's subdivision of the "bacteriotropic substances" of the blood into four bodies, it has become evident that we need only take two into account, viz., the thyro-parathyroid secretion (opsonin, agglutinin, substance sensibilisatrice) and the digestive triad (trypsin, cytase, alexin, com-

* The experiments of several investigators to determine the part taken by the red corpuscles in agglutination and hæmolysis are rendered valueless by the fact that, unlike Bordet, they failed to use fresh serum or exposed the latter or the corpuscles to contact with substances which annulled the activity of their secretion.—S.

[241] Bordet: Cited by Wassermann: *Loc. cit.*, p. 3.
[242] Ehrlich and Morgenroth: Berl. klin. Woch., Bd. xxxvii, S. 681, 1900.
[243] Durham: Brit. Med. Jour., Sept. 3, 1898.

plement, etc.). Adding thereto phagocytosis, we have the three active factors of the immunizing process which are brought into action when bacteria, *i.e.,* their toxins or endotoxins, or any other poison capable of exciting the test-organ of the pituitary body, enters the blood-stream.

In the first volume, over four years ago, I advanced the view that a poison or toxin capable of stimulating the adrenal center, *i.e.,* the test-organ, protected the organism by increasing the proportion of immunizing substances in the blood, and that various diseases developed because of the deficiency of such substances. Wright's researches have demonstrated that during infection by certain bacterial species, the proportion of "bacteriotropic substances" is below normal, the patient's blood being then in what he terms the "negative phase," while—and this is the most important result of his valuable researches—by means of bacterial vaccines, tuberculin, etc., judiciously employed as to quantity and intervals between the doses, the immunizing substances can be so increased in the blood that they exceed greatly the normal limits. This raises the patient's defensive powers to such a degree, *i.e.,* brings them up to the "positive phase," that the invading bacteria and toxins are more or less promptly destroyed.

Wright, however, found that great precautions were necessary. By what he terms the "opsonic index," *i.e.,* the average number of bacteria taken up by each leucocyte, he is able to gauge the proportion of bacteriotropic substances in the blood. He observed also that while inoculations cause the "bacteriotropic pressure" to rise, the latter tends constantly to return to normal. This imposes the need of regulating carefully the intervals between the doses in order to keep the bacteriotropic activity of the blood above normal—a fact which in itself imposes the need of frequently examining the blood. The use of large doses in no way tends to sustain the blood's immunizing power; experience has shown that these are dangerous, particularly in the negative phase, and that they may even cause death. Again, Wright[244] refers to what he terms another "serious aspect of the question" as follows: "Here is an inoculation after which the resisting power runs down; but after a time it rises and

[244] Wright: Canadian Practitioner and Rev., Nov., 1906.

the patient is re-inoculated with a large dose; the resistance goes down further, and before he can recover another dose is given and the resistance goes down still further. So anybody can inoculate with successive doses and reduce the resisting power to anything he likes. It is quite easy by this method to reduce the resisting power of the blood enormously."

In the first volume and elsewhere,[245] I laid stress on the importance of recognizing the two phases of action to which Wright refers. I wrote at the time that "the majority of drugs, toxins, physiological toxalbumins, etc., *stimulated* the adrenal system when the proportion of these agents in the blood did not exceed a certain limit, and that *when this limit was exceeded, i.e.,* when the dose administered, or the amount of toxins secreted by bacteria, etc., was excessive, it either *inhibited or arrested* the functions of this system." Briefly, the observations of Wright are clearly accounted for when the functions of the test-organ and the adrenals are taken into account: *Each toxin* or *drug* capable of exciting the test-organ can raise its functional activity *up to a certain limit;* beyond this it paralyzes its functions whether the dose administered be excessive or whether it be given in smaller doses too frequently, thus leading to cumulative action.

The result in both cases is either gradual or sudden adrenal insufficiency with its consequences: more or less rapid diminution of adrenal secretion, *i.e.,* of adrenoxidase. This means that the protective or immunizing substances, which are simultaneously the life-sustaining constituents of the body, are quantitatively inadequate. The auto-protective functions always working hand in hand with the vital processes, the general symptoms of poisoning invariably include, as I have already pointed out,[246] those that follow removal of the life-sustaining organs, the pituitary and the adrenals, viz., marked adynamia, hypothermia, lowered vascular pressure with weak and small pulse, dyspnœa, cyanosis and convulsions,—the number and violence of the symptoms depending upon the extent to which the functions of the test-organ are inhibited.

In the first volume[247] I wrote: "Artificial immunization

[245] Sajous: Phila. Med. Jour., Mar. 7, 1903.
[246] *Cf.* vol. i, p. 773, in the first three editions.
[247] *Cf.* vol. i, p. 764, in the first three editions.

means the introduction not of bacteria, but of their products: the toxins themselves. These do not reproduce any more than the alkaloids of plants reproduce; they act with more or less vigor upon the adrenal system, precisely as do these alkaloids or other drugs. Indeed, if, instead of 'toxins' they were called as are the alkaloids, 'medicines,' their use would inspire no more fear of complications than do the former, and their true position in therapeutics would be accorded them." But this refers to uncontaminated toxins. Are we sure that tuberculin, for instance, is always free of pathogenic, living, organisms? Karl von Ruck,[248] who can speak authoritatively in such matters, writes in this connection, after referring to the inconstancy of the results obtained with tuberculin R.: "Another danger from its use was soon shown to exist by Trudeau,[249] who found living, virulent tubercle bacilli in the preparation, after I had myself[250] directed the attention of the profession to the probability of such an occurrence."

Again the question of technique is an important one. The safeguards urged by Prof. Wright will surely be utilized by men who have acquired his skill, and insure comparative safety; but when we take into account the small proportion of such men among the hundreds of thousands of practitioners in civilized countries, and the fear of the great majority of medical men and their patients that the inoculation itself may prove a source of disease, it becomes plain that pending at least the disappearance of these untoward circumstances, our *armamentarium pharmacopœiæ* should remain our standby.

Summarizing the evidence and conclusions bearing upon the question I have so far submitted, the following conclusions seem warranted:—

(1) *Certain drugs, however introduced into the body, can, by stimulating the test-organ of the anterior pituitary, increase the bacteriolytic and antitoxic properties of the blood;* (2) *the immunizing agencies thus increased are* (*a*) *the thyro-parathyroid secretion, an iodine-ferment (now known as the sensitizing substance, opsonin and agglutinin) which sensitizes and softens pathogenic organisms, preparing these, and probably all poisonous or otherwise harmful substances, broken-down cells, wastes, etc., for ingestion and digestion by the phagocytes;* (*b*) *the phagocytes, which ingest the bacteria to digest them by means of their intracellular trypsin;* (*c*) *the trypsin secreted by phagocytes or other leucocytes into the blood-stream and which digests therein what bacteria, toxins, toxic wastes and other noxious substances are not destroyed by the phagocytes.*

[248] Karl von Ruck: Med. Record, Jan. 20, 1906.
[249] Trudeau: Medical N ws, Aug. 28 1897.
[250] Karl von Ruck: New Orleans Med. Jour., July, 1897.

Concerning the poisonous effects: (3) *drugs which are capable of stimulating the test-organ and are therefore able to enhance the efficiency of the immunizing substances directly or indirectly, differ in no way in this particular from inoculations of bacterial cultures, tuberculin, etc., and can only excite the test-organ up to a certain degree, varying more or less with each drug;* (4) *when this limit is exceeded owing to the use of excessive doses or of small doses given in too rapid succession, poisoning occurs;* (5) *the earlier symptoms of poisoning are those of excessive activity of the drug used or of the chemical combinations it may form in the alimentary canal, the blood, the leucocytes, the subcutaneous tissues, etc;* (6) *sooner or later, according to the drug or poison, general symptoms appear which are common to all agents, drugs, toxins, etc., capable of stimulating the test-organ, viz., great weakness with flaccidity of the muscles, hypothermia, lowered vascular pressure, rapid and weak pulse, dyspnœa, swarthiness, cyanosis, convulsions (due to accumulation of toxic wastes) and coma;* (7) *these symptoms are due to diminution or cessation of tissue respiration, i.e., of general oxygenation, the result in turn of depression or cessation of the functions of the test-organ and of the thyro-parathyroid apparatus,*—owing to factors which are considered in succeeding chapters.

With Prof. Wright I fully concur when he contends[251] that "we have in the power of raising the antibacterial power of the blood with respect to any invading microbe, out of all comparison the most valuable asset in medicine." But I hold that we have among the remedies that have been at our disposal many years, agents eminently capable of raising the bacteriolytic and antitoxic power of the immunizing constituents of the blood beyond even the limits required to antagonize any infec-

[251] Wright: Cited by C. P. Aaron: N. Y. Med. Jour., Dec. 1, 1906.

tion or any other form of toxæmia. Indeed, so intense is this action in the case of some of these agents that the blood-cells themselves are digested (hæmolysis) along with the bacteria. The practical experience accumulated by clinicians during the many years—centuries in some instances—that these agents have been employed, and the researches of therapeutists into their physiological action, have given us a working field which it will take decades of steady labor upon all questions relating to the use of tuberculin or other bacterial products by inoculation even to approach. We need not, therefore, deprive the present generation of the advantages that the magnificent lore of our profession affords. Within our reach are weapons whose every part is known to all and which, in power to destroy the greatest enemies of mankind, are second to none—provided their present empirical use give way to their scientific use, viz., with the test-organ of the pituitary and the organs which it controls as the foundation of the body's auto-protective resources. This binds indissolubly pharmacotherapeutics to the general principle of immunity—precisely the field I opened in the first volume of this work. We must learn to bow to Nature's powers; had her mode of work—the doctrine of Hippocrates—inspired all researches since his time, Medicine would not only rank as a Science to-day, but it would exceed all other sciences in perfection.

As a final conclusion of this chapter, I would submit, therefore, that *immunizing medication is the foundation of rational therapeutics.*

CHAPTER XVIII.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PHARMACODYNAMICS.

THE PRESENT STATUS OF THERAPEUTICS.

In a Presidential Address[1] A. H. Bampton said recently (1907): "Scepticism is in the air. Even in this society, if any daring member has introduced a subject bearing on medical treatment, it has been with an apologetic air and humble mien, well knowing that if his remarks had any reference to the utility of drugs in the treatment of disease they would be subjected to good-humored banter, and received by those sitting in the seat of the scornful with amused incredulity." That the same spirit reigns on this side of the ocean hardly needs to be emphasized. But few years had elapsed since Frank Billings, also in a Presidential Address,[2] declared that "drugs, with the exception of quinine in malaria and mercury in syphilis, are valueless as cures," and what has been termed Osler's "black, hopeless, helpless, therapeutic pessimism," is quite as applicable to a large proportion of the medical men of our country. The present work, in fact, was begun under the influence of a very similar state of mind. It would be unfair, however, to incriminate only pharmacological knowledge on this score; pathology is quite as invalid when the relations of cause to effect are scrutinized. Indeed, Lewellys F. Barker's previously quoted estimate that "drugs of *unknown physiological action* cannot conscientiously be set to act upon bodily tissue *in disease in which we are ignorant of deviations from the normal,*" exemplifies succinctly the dual cause of the rather ignominious position in which practical medicine finds itself. The contents of the foregoing chapters account for this: they show that functions of the first order have been overlooked: functions which, in pathogenesis and therapeutics, play the leading part, and without which these fundamental branches must remain inscrutable.

[1] A. H. Bampton: Leeds and West Riding Medico-Chirurgical Soc., Lancet, Jan. 19, 1907.
[2] Billings: 54th Annual Session of the Amer. Med. Assoc., 1903.