logical and pharmocodynamical experiment and the indefatigable efforts of the manufacturing chemist to supply new drugs," says Barker,[208] "the view is prevalent and rightly so, that in the treatment of internal diseases we have more to hope for the future than to entrust to the present." Referring to Skoda's dictum "We can diagnose disease, describe it and get a grasp of it, but we dare not expect by any means to cure it," he adds: "In such a temper *drugs of unknown physiological action* cannot conscientiously be set to act upon bodily tissues in disease in which *we are ignorant of the deviation from the normal* of the chemical and physical processes going on in the cells. The death-blow came first to polypharmacy; to-day, with many, pharmacotherapy, as a whole, is almost moribund."

[208] Barker: Johns Hopkins Hosp. Bull., July, Aug., 1900.

CHAPTER XVII.

THE LEUCOCYTES, PITUITARY, THYROID, PARATHYROIDS, AND ADRENALS, AS THE FUNDAMENTAL ORGANS IN PATHOGENESIS, IMMUNITY AND THERAPEUTICS.

THE LEUCOCYTES AS THE DISTRIBUTORS OF REMEDIES AND POISONS.

In the first volume of the present work and elsewhere,[1] I pointed out that the anterior pituitary was the governing center of the body's auto-protective or immunizing mechanism, and that by means of our remedies its functional activity could be enhanced at will, and thus caused to activate the antitoxic properties of the blood. An eminent French clinician, Hayem,[2] wrote recently: "Therapeutic weapons are wanted which will *reinforce the defensive power of the organism* by increasing the functional activity of the leucocytes or by developing chemical antidotes"—the trend of our day being in harmony with Hippocrates's belief in the *vis medicatrix naturæ*. That this is precisely the underlying thought of my own doctrine is self-evident; but it does what no other doctrine has done: it points to the identity of Nature's mechanism and to the means she adopts to attain her object.

We have reviewed the main features of this mechanism. We have seen that the pituitary contains a test-organ related by nerve-paths with the adrenals, which in turn govern, through their secretion, the activity of all metabolic processes in the blood as well as in the tissues. As the thermogenic center, this test-organ also presides over the febrile process—which is but an exacerbation of catabolic activity, raising it when need be—to destroy, not only tissue-wastes, but all toxic substances which adventitiously gain access to the blood-stream. The process through which the protective activity of the test-organ

[1] Sajous: Monthly Cyclo. of Pract. Med., Jan., 1903; Phila. Med. Jour., Mar. 7, 1903.
[2] Hayem: Presse médicale, Aug. 12, 1903.

is awakened suggests itself as the next question in point, but before it can be taken up an important feature must receive attention, viz., the manner in which the substances which provoke this reaction enter the blood and reach the tissues. As drugs and poisons are identical as far as the test-organ is concerned—both being noxious agents—the absorption and distribution of drugs will serve to illustrate the same processes in the case of poisons.

We have seen that leucocytes take up food-products from the intestine to convert them into granulations which they carry to all tissues and deposit therein. I showed furthermore, in the fifteenth chapter, that these granulations not only penetrate all cells, but that they become part of their structure. That ingested drugs or poisons should also be taken up from the intestinal canal by leucocytes and distributed to the various tissues is shown by the fact that MacCallum traced leucocytes which had englobed albuminate of iron in the intestine to the spleen, liver, etc., an experiment repeated successfully by other investigators with proteids and other food materials. This applies as well, as far as distribution is concerned, to drugs injected subcutaneously or directly into the blood: they are more or less promptly engulfed or absorbed by leucocytes and distributed to various parts of the organism.

"Recent experiments in France show," says an editorial writer,[3] "that leucocytes fulfill a very important function in distributing medicinal drugs to all parts of the body. . . . This is shown by various experiments. Here, for instance, is a rabbit under whose skin is injected a little strychnine or atropine. At the end of, say, half an hour, some of the blood is drawn off and divided by centrifugal treatment into its three parts—leucocytes, red globules, and plasma. Equal quantities of each are injected into three animals, and it is seen that the one that receives the leucocytes is poisoned, while the others are not. The leucocytes transfer these drugs from one part of the body to another, and this is their greatest utility. It is the more so that the place where they transport these substances varies according to circumstances. In normal conditions—that is, in health—the leucocytes carry the drug to the liver and marrow. In illness they carry it to the affected points, to the centers of irritation, where the arrival of the leucocytes is most desirable. . . . . But we can depend on them to carry iron to the blood-making organs, iodoform to tuberculous lesions, salicylate of soda to affected points, etc. . . . . There is another fact that must be taken into account: the leucocytes, it is true, carry drugs to affected points, but they carry them also, with special insistence, to certain organs. Different organs attract different drugs; the liver, iron; the thyroid gland, arsenic and iodine; while the skin, the spleen, the lymphatic ganglia, and other organs seem to constitute regions of choice for several chemical substances." Indeed, Morel[4] found that finely powdered nux vomica was engulfed by leucocytes as well as any other substance foreign to the blood. Besredka,[5] having injected a soluble salt of arsenic into rabbits, found analytically that while the red cells and the plasma contained none, the leucocytes had absorbed it. Silver salts also were found to be ingested by leucocytes by Samoïloff.[6] Montel[7] obtained a similar result with sodium salicylate. Lombard[8] obtained corresponding results with atropine and strychnine. Marcel Labbé and Lortat-Jacob[9] injected iodides subcutaneously and into the peritoneum and found that leucocytes absorbed these salts. Calmette obtained similar results with atropine; Metchnikoff, with soluble iron; Stassano, with mercurial salts; Neisser, with an oleate of calomel; Carles,[10] with ferrous iodide and other preparations of iron, colloidal silver, morphine, olive oil, rhubarb, and biniodide of mercury; Lancelin[11] and Lombard, with morphine, etc.

[3] Editorial: Cleveland Med. and Surg. Reporter, Aug., 1904.

Can we accept as sound, however, the belief that leucocytes modify their itinerary, so to say, when a given area is diseased and carry to that area drugs that may be beneficial to it? M. Labbé[12] states that "while cinnabar injected into the circulation is, in normal animals, taken to the liver, the bone-mar-

[4] Morel: "Recherches expérimentales sur les leucocytes," Paris, 1892-98.
[5] Besredka: Ann. de l'Inst. Pasteur, T. xiii, pp. 49, 209, 1899.
[6] Samoïloff: Lubarsch u. Ostertag, "Ergebnisse der allg. Path., etc.," Bd. iv, S. 107, 1899.
[7] Montel: "Thèse de Bordeaux," 1900-1901.
[8] Lombard: Thèse de Paris, 1901.
[9] Marcel Labbé and Lortat-Jacob: C. r. de la Soc. de biol., July 4, p. 830, 1902.
[10] Carles: "Du rôle des leucocytes dans l'absorption, etc.," 1904.
[11] Lancelin: Thèse de Bordeaux, 1902.
[12] M. Labbé: Presse médicale, Aug. 10, 1904.

row, etc., (Cohnheim, Ponfick, etc.), in diseased animals it is deposited in the morbid foci (Schüller, Ribbert, Orth, Wyssokowitch)." It is upon this principle that Landerer based his theory that sodium cinnamate reached the pulmonary foci in tuberculosis; that mercury is believed to seek out syphilitic eruptions, that iron adjusts itself to hæmatopoietic organs in anæmia, that iodoform proceeds at once to tubercular regions, that sodium salicylate selects the joints, etc. The drug-laden leucocyte is, according to this view, capable of intelligently and wilfully selecting the area to which it is to proceed; or, it can be drawn to the morbid focus through chemiotaxis; or, again, owing to the vulnerability of such a focus to bacterial invasion, it can be attracted thereby, as are other phagocytes, irrespective of their contents. Analysis of the question shows that while there can be no doubt that leucocytes take up drugs as they do any useless or noxious agent that appears in the blood, the belief that they are specifically attracted to any diseased focus because they happen to contain a substance that may be beneficial to it is erroneous.

The observations of Schüller, Ribbert and others, that cinnabar, which, in normal animals, is distributed in the liver, bone-marrow, etc., is deposited in the morbid foci in diseased animals, only prove that local leucocytosis has occurred—a common phenomenon observed even in the absence of any drug in the organism. This means only that leucocytes laden with the drug in more or less great numbers are diverted from their normal haunts to invade the diseased area to act as phagocytes, to sustain nutrition, rebuild tissue, etc. That the drug-laden leucocytes travel everywhere is moreover shown by the fact that in the experiments of Lombard, Calmette and Besredka, the blood examined was taken from the *general* circulation, and its leucocytes were found to contain the drugs injected. On the other hand, Landerer,[13] referring to Schüller, states that "he found cellular deposits in *predominating* numbers in inflamed or injured areas," simply meaning thereby an excess of leucocytes as compared to other regions.

A very interesting phase of the problem presents itself in this connection, viz., additional proof that leucocytes secrete

[13] Landerer: "Le traitement de la tuberculose," 1899.

the products they absorb as they do their nucleo-proteid granules in the tissues—drugs, more or less modified, replacing the nutrient particles, and being secreted automatically in lieu of the latter.

Carles[14] injected subcutaneously fine grains of carmine in the leg of a frog, then cut slightly the foot of the opposite side and introduced small pieces of glass in the wound. Fifteen hours later the latter was found to contain a large number of leucocytes stuffed with carmine. Another incision on the opposite side, led to a similar result after twelve hours. This experiment was repeated several times with the same result, the injections being made in different parts of the body. Carmine-laden leucocytes were also found in the liver. Cohnheim resorted to the same procedure forty years ago; carmine injected in the lymphatic sac of frogs appeared in the leucocytes in an ulcerated cornea. Carles then tried the experiment with sulphide of mercury and collargol, with the same result. He attributes these phenomena to chemiotaxis; but interpreted from my standpoint, it is due, as stated above, to a less obscure process, *i.e.*, the *function* of the leucocytes to carry to the tissues as nutrient material, whatever they absorb and digest, and in greater quantities to diseased tissues to facilitate the process of repair.

This is further shown by the fact that leucocytes migrate through the walls of vessels to reach the tissue-cells and deposit their load therein, whether this be composed of nutrient granules or a drug. Thus Stassano and Billon,[15] after injecting lecithin in frogs, observed a profuse leucocytosis of cells laden with this substance. "A curious fact, however," says Carles, referring to this experiment, "is that leucocytes containing lecithin are also found outside the vessels. As true alimentary carriers they drop their charge, therefore, in the various tissues in order to nourish them; they even reach those that are deprived of capillaries thanks to diapedeses"—precisely as I had stated the previous year.

The leucocytes may be killed, however, by the drugs they absorb. Alluding to powdered drugs of various kinds, Carles

[14] Carles: *Loc. cit.*
[15] Stassano and Billon: C. r. de l'Acad. des sciences, p. 623, 1902.

states that "they take them up as well as any other inert substances, but that they subsequently die without rejecting them," as observed by Morel with powdered nux vomica. Carles noted a similar effect with rhubarb.

That the substances or drugs absorbed by the leucocytes that are harmless to them are actually secreted by them in the tissues was first observed by Schüller, who, as stated, observed that they deposited a larger quantity of their contents in diseased areas than elsewhere, solid elements being reduced to a state of extreme division. M. Labbé[16] also states that "insoluble drugs are absorbed and dissolved in the leucocytes" as shown by their influence on calomel and arsenic. Besredka, having provoked tuberculous abscesses in rabbits, then injected arsenic into the animals at intervals. He found the drug not only in the leucocytes, but also in the pus of the abscesses. Carles repeated these experiments and obtained similar results; he found that mercury and copper followed the same course as the arsenic—a fact, by the way, which emphasizes the absence of specificity as far as the distribution of the drugs is concerned. That the leucocytes secrete their granulations (Hankin, Kanthack, Hardy and Keng, Ehrlich, Hardy and Wesbrook, and others) explains how these drugs, irrespective of those derived from broken-down cells in the pus, are deposited in the tissues—precisely, I may add, as if they were nutritive particles.

Pathogenic organisms may likewise be transported by leucocytes to any part of the body and initiate morbid processes. Four years ago,[17] in an article opposing Koch's views concerning the non-infectivity in man of bovine tuberculosis, I emphasized the fact that direct infection of the lungs can occur through bacilli ingested by leucocytes in the intestinal canal, and reached the conclusion that "contaminated milk and foods are, therefore, as active sources of infection as air-borne germs." As is well known, the bacillus of tuberculosis is pathogenic when dead, and the endotoxin is liberated when the germ is disintegrated. Landerer, referring to Schüller's observation[18] that the contents of leucocytes were deposited in rela-

[16] M. Labbé: *Loc. cit.*

[17] Sajous: Monthly Cyclo. of Pract. Med., Jan., 1903; Phila. Med. Jour., Mar. 7, 1903.

[18] Landerer: *Loc. cit.*

tively large quantities in inflamed or injured tissues, states that these observations were confirmed as to bacteria by Ribert, Orth and Wyssokowitch. Carles, who mentions these authors, writes in this connection: "Recently acquired knowledge of the physiology of leucocytes explains the predisposing rôle of traumatism as to the localization of Koch's bacillus. The staphylococcus (Wyssokowitch, Orth, Weichselbaum), the pneumococcus (Netter, Banti, Vanni), and many other microörganisms have since been found to have the same tendency to invade the damaged areas owing to the chemiotactic power of the leucocytes which had ingested them. This fact has been placed beyond question by numerous confirmatory clinical and experimental facts (Gabbi, Tournier and Courmont, Chauveau, Rosenbach, Becker). Widal and Ravaut[19] witnessed a case in which a tuberculous focus thus became infected by the bacillus of Eberth, etc.—all due doubtless to imperfect phagocytosis or to the death of the leucocytes containing living bacteria, or dead bacteria containing endotoxins. Many examples of this kind are available in literature, as every one knows.

Can we say in the face of this evidence that leucocytes carry drugs to the diseased sites, where their arrival "is most desirable"? If such were the case, how could we account for the distribution of bacteria and for inert substances to the same regions? That substances such as iron, arsenic, iodide, phosphorus, etc., which fulfill a physiological rôle in the organism are taken by these cells to the tissues where they are stored, or back to the intestinal canal for elimination if they are not required, is doubtless true, but that agents such as mercury, sodium salicylate, atropine, opium, strychnine, etc., which are totally foreign to the tissue elements, should accumulate in any morbid tissue otherwise than as a result of the local leucocytosis that attends all morbid processes seems illogical. This is an important feature from the standpoint of therapeutics, for while some advantage may be derived from the use of appropriate remedies because they must reach the diseased area through the intermediary of the leucocytes, this does not represent, as the authors who have studied the leucocytes in this connection seem to believe, the manner in which drugs—includ-

[19] Widal and Ravaut: Soc. méd. des hôpitaux, Jan., 1902.

ing those known to be carried to the morbid tissues—produce their main physiological effects.

This is further shown by the fact that the effects of most drugs (the exceptions being those such as iron, phosphorus, etc., which form part of our tissues) are produced mainly through their action on the central nervous system.

Digitalis, for example, is thought—irrespective even of any participation of the leucocytes in the process—to act directly upon the heart muscle, but Traube, in 1871, showed that transsection of the cord high up annulled its effects, and Boehm[20] found that the same procedure arrested its action when it had become manifest. This indicates plainly that the action of the drug is not direct, *i.e.*, on the heart-muscle itself. This may be shown in another way. Hebdom,[21] for instance, found that digitalin acted on an isolated heart when a 1 to 50,000 solution was used. But can we assert that a corresponding dose in man will act in the same way? The minimum estimate of the quantity of blood in the body of an adult is 13 pounds; *i.e.*, 100,000 minims. This quantity would thus have to contain a *full grain* of digitalin to react directly upon the heart, granting that no waste occur either in the stomach, intestines, liver, or blood, before reaching that organ. Now, $^1/_4$ grain of Merck's digitalin, according to Wood,[22] "represents the full therapeutic dose." In the blood this would make a solution of 1 to 400,000, which is inactive on the detached heart. Again, if the view that the drug acts directly on the heart-muscle were sound, the hypodermic use of a sufficient quantity to make Hebdom's 1 to 50,000 solution should at least be required. In truth, a dose thus administered and making a solution in the blood *but one thirty-second as strong* as this, is a powerful one. Thus, Deucher[23] found that a dose of digitalis given hypodermically produced the same effects as a dose four times as great administered by the mouth. Inasmuch as $^1/_4$ grain of digitalin is stated by Wood to produce the full therapeutic effects of the drug, $^1/_{16}$ grain should thus provoke equivalent effects hypodermically. This is equal to a 1 in 1,600,000 solu-

[20] Boehm: Arch. f. gesammte Physiol., Bd. v, S. 153, 1872.
[21] Hebdom: Skand. Arch. f. Physiol., Bd. vii, S. 169, 1898; Bd. ix, S. 1, 1899.
[22] Wood: "Therapeutics," eleventh edition, 1900.
[23] Deucher: Deutsches Archiv f. klin. Med., Bd. lviii, S. 47, 1897.

tion in the blood mass. And yet this does not allow for the diminution of the dose in the latter. Can we consistently admit, in view of the antitoxic properties of the blood (especially active in the leucocytes) which underlie immunizing processes now engaging the attention of the whole scientific world, that a glucoside will suffer no chemical change? Even if defibrinated blood-serum be used as a menstruum for digitalin in experiments, such as Hebdom's, on the isolated heart, the environment of the drug is greatly modified through the absence of blood-cells, fibrin, etc. Thus, variation of temperature provokes precisely contrary effects. Masi showed that, while digitalin arrests the frog's heart in *systole* at the normal temperature, at a lower one it arrests it in *diastole*. Moreover, how do we know that the supposed direct action of the drug will always manifest itself on the mammalian heart as it does experimentally on the batrachian? Masi found that at identical temperatures digitalin arrested the frog's heart in diastole and the mouse's heart in systole. All this shows distinctly that the prevailing view that digitalis acts directly on the heart cannot bear close scrutiny. Indeed, the action of this drug has remained obscure. "In our experiments upon the mammalian heart," writes H. C. Wood,[24] "we have seen in the final acts of digitalis drama happenings so curious and unexpected that at present no proposed theory as to the action of the drug is sufficient."

The drugs which, as shown in the foregoing pages, are distributed by leucocytes—excepting as stated, agents which take part in general nutrition—also produce their main effects through the central nervous system. Thus, Cushny[25] states that "*atropine* acts as a stimulant to the central nervous system and paralyzes the terminations of a number of nerves." Of the aromatic series to which the *salicylates* belong, he also says: "They are all possessed of a more or less marked action on the central nervous system." Wood,[26] referring to *strychnine*, writes: "The fullest permissible doses stimulate very powerfully the respiratory centers, and also slightly increase blood-pressure by stimulation of the vasomotor centers and probably also of the heart itself." Of *silver*, the same author

[24] Wood: *Loc. cit.*
[25] Cushny: "Pharmacology and Therapeutics," fourth edition, 1906.
[26] Wood: "Therapeutics," twelfth edition, 1905.

says the symptoms of poisoning are "those of gastro-enteritis with violent disturbance of the nervous system due to a direct action of the poison upon the cerebrum and the spinal cord." He also states that "sometimes the influence of *mercury* falls almost exclusively upon the nervous system, and produces a peculiar train of paralytic phenomena." In his section on opium (we have seen that leucocytes were found to carry morphine to the tissues), Wood says: "It is undoubtedly a stimulant to the spinal cord; but . . . . the cerebrum in man is so infinitely more susceptible to its influence than is the spinal cord that this spinal effect is rarely perceptible in man." The physiological action of morphine emphasizes strongly the question in point, for although taken up and carried by leucocytes to all parts of the organism, it is only through its action on the central nervous system that its effects, including the relief from pain, are produced.

A still more striking example of this fact is the physiological action of the coal-tar antipyretics and analgesics, antipyrin, acetanilid, etc. Although these drugs are widely used in practice, their action, as stated by Cushny,[27] "is very imperfectly understood." Now, Sawadowski[28] showed that removal of the brain *above* the basal ganglia, the optic thalami and the striated bodies did not prevent the action of antipyretics. He found, however, that when these ganglia were detached from the lower part of the spinal system, the antipyretics no longer reduced fever. An important fact imposes itself in this connection, viz., the experimental incision inevitably destroyed the nerve-paths from the pituitary body to the upper spinal structure, and, therefore, the nerve-path connecting it with the adrenals.

This evidence, supplemented by that submitted in the first volume and in the preceding chapter, seems to me to warrant the following conclusions: (1) *that leucocytes, acting as phagocytes, absorb not only food-products in the alimentary canal and in the blood-stream, but also drugs, poisons and pathogenic organisms;* (2) *that whatever substance a leucocyte engulfs or absorbs, including pathogenic elements, is submitted therein to*

[27] Cushny: *Loc. cit.*, p. 373.
[28] Sawadowski: Centralbl. f. med. Wissensch., Bd. xxvi, S. 145, 161, 1888.

whatever action its digestive constituents may have on that substance, the product being secreted broadcast in the tissues as if it were invariably a nutritive substance; (3) *that if the intracellular digestive process be imperfect or if the leucocyte be killed by them, living pathogenic bacteria may thus be disseminated by leucocytes;* (4) *that drugs and poisons more or less modified chemically, dissolved, or triturated in the leucocytes, may thus be distributed by them to all tissues;* (5) *that while in some instances this may cause remedies capable of promoting local resolution to reach diseased areas—especially in view of the local leucocytosis of which such areas are the seat—this does not represent the process through which drugs, poisons, and bacterial toxins and endotoxins produce their main physiological effects;* (6) *that these physiological effects and the beneficial influence of remedies are due mainly to their action upon the central nervous system.*

THE ANTERIOR PITUITARY AS A LYMPHOID ORGAN IN WHICH THE PRODUCTS OF LEUCOCYTES AND ANY DRUG, POISON OR TOXIN THESE CELLS MAY CONTAIN ARE EXPOSED TO THE TEST-ORGAN.

In the preceding chapter I referred to the anterior lobe of the pituitary body as an "organ of special sense," owing to the presence therein of a sensitive organ which I assimilated to the "test-organ" found by zoölogists in Tunicata, the lower Chordata and other animals far down in the phylogenetic scale. Spengel, who first described the structure in these ancestral forms, referred to it as an "olfactory organ" and concluded that its function was to test the water which supplied them with oxygen—a view now generally accepted by zoölogists. Gentès, we have seen, though unaware of the fact that I had attributed functions similar to those of the test-organ to the anterior pituitary body—and probably of the views of zoölogists regarding it—found, in the partition separating it from the posterior lobe of the higher mammals, cat, dog, etc., a sensory organ which could also have been termed an "olfactory organ," since its cellular elements recalled "precisely," he said, those of the olfactory area of the nasal mucous membrane. The data contributed by zoölogists, my own—based on clinical, physiological