CHAPTER XXII.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PHARMACODYNAMICS (*Continued*).

THE BLOOD-PLASMA OF TERRESTRIAL ANIMALS AS THE FUNCTIONAL HOMOLOGUE OF SEA-WATER.

The kinship between the blood-plasma of vertebrates and sea-water was referred to in the first volume. I wrote at the time:[1] "The many vestigial structures which the human frame exhibits as relics of its evolutional past not only include evidences of a primitive aquatic existence, the embryonic branchial or gill-clefts and the pituitary bodies, for instance; but the plasma in which all the cells of the organism bathe may be said also to typify the original medium." Since then, the question has received considerable attention, as shown by the quotations submitted below, which indicate that the subject as a whole harmonizes perfectly with the soundest teachings of many branches of science.

René Quinton, who pointed out this similarity between sea-water and the blood-plasma, in 1900 at the XIII International Congress, more recently presented the results of additional investigations before the Paris Academy of Sciences. "In M. Quinton's view," says a correspondent,[2] "sea-water is the natural source from which, as Haeckel believes, those elementary bodies have their rise, which in turn develop into every other species, human beings included. The environment in which the anatomical elements of living creatures exist is neither more nor less than a marine one. Our tissues and cells continue to exert their functions in a fluid the composition of which presents the closest resemblance to that of sea-water. Hitherto the number of elements entering into the composition of a living body has been considered to be about fifteen. But the researches of M. Quinton have shown the existence of traces of at least some fourteen other elements which

[1] *Cf.* vol. i, p. 788, 1903.
[2] Paris Correspondent: Lancet, Apr. 16, 1904.

are also found in sea-water, such as copper, lead, silver, gold. and others. Further, if an animal be bled to exhaustion and the place of the blood be supplied by sea-water, on the morrow the animal will have regained its strength, and at the end of five days its recovery is complete. M. Quinton has injected into animals a quantity of sea-water greater than their own body weight without any toxic effects, whereas an injection of pure water brings about death. Sea-water then appears to be the nutrient fluid of animals, their natural plasma in fact."

Other observers have lately taken up the question. Macallum, of Toronto,[3] finds from geological evidence "that in the ocean of the earliest period the relative proportions of the elements: sodium, potassium, calcium and magnesium approximated to those found in river discharges or in fresh water shed from areas covered with archæan rocks. This condition must have continued until living forms made their appearance in the ocean, when the gradual elimination of the magnesium, and particularly of the potassium and calcium, began. The living forms were in all probability unicellular; and 'as the period must have been of great duration, the organisms and their protoplasm acquired a fixed relation to the four elements.' In the transition from the ocean of the more ancient composition to that of the present, the unicellular forms became multicellular, and developed circulatory systems, the vascular fluids of which were at first simply modified sea-water. Professor Macallum lays stress on the resemblance between the blood-plasma of vertebrates and sea-water as regards the relative proportions in which sodium, potassium and calcium are present, and considers this similarity to be due to heredity, 'the proportions of the saline constituents of the plasma being a reproduction of the proportions which obtained in sea-water when circulating plasmata were developed.' He thinks the same general principle holds good for protoplasm as well, and maintains that both animal and vegetable protoplasm derive their relations to the elements, sodium, potassium, calcium and magnesium, from the composition of sea-water which obtained when all forms were unicellular."[4]

[3] Macallum: Trans. Canadian Institute, p. 181, vol. 1903-4.
[4] Editorial: Brit. Med. Jour., July 9, 1904.

The researches of Jacques Loeb,[5] and the investigations of Matthews, Fischer and others, have also shown that "the solution which is most favorable to the life of the tissues is one which contains a number of salts, and these in the same concentration in which they exist in sea-water. The excess, deficiency or removal of one or more of these salts disturbs the equilibrium of the solution, which becomes toxic for the animal cell. The practical application of this fact is obvious. The normal salt solution of the future will be one having practically the same composition as sea-water, if not sea-water itself.

"It is easy to explain the reason for this predilection of the animal cell for an environment having the same saline content and concentration as the water of the ocean. During the dawn of life all cells lived amid this environment, and the chemical and physical structure of protoplasm became adapted to the chemical and physical characteristics of the surrounding medium. In spite of the enormous lapse of time, and the complex elaboration of the simple protoplasmic units into the higher animal forms, the former still retain the ingrained habits of their primitive life."[6]

Professor Bunge, of Basle,[7] states that he is "convinced that the remarkably high percentage of salt in vertebrate animals, as well as the desire to take salt with our food, can only be satisfactorily explained by the theory of evolution." He also remarks in this connection: "The land vertebrates are all remarkably rich in salt, in spite of the scanty supply around them. But even these are only apparent exceptions. We need but remember the fact that the first vertebrates on our planet all lived in the sea. Is not the large amount of chloride of sodium found in the present inhabitants of dry land another proof of the genealogical connection, which we are forced to accept from morphological facts? There is no doubt that each of us in his individual development has gone through a stage in which he still possessed the chorda dorsalis and the branchial arches of his sea-dwelling ancestors. Why may not the high average of salt in our tissues be also inherited from them?

[5] Jacques Loeb: Pflüger's Archiv, Bd. cvii, S. 252, 1905.
[6] Editorial: Med. News, Sept. 9, 1905.
[7] Bunge: "Physiologic and Pathologic Chemistry," Eng. Trans. by Starling, pp. 101, 102, 1902.

"If this interpretation be correct, we should expect that the younger the vertebrates are in their individual development, the more salt they would possess. This is in fact the case. I have convinced myself by numerous experiments that an embryo of a mammal contains more salt than a new-born animal, and that it gradually becomes, after birth, poorer in chlorine and sodium as it develops. Cartilage contains the most sodium of any tissue in our bodies, besides being also the tissue of greatest antiquity. It is histologically identical with the tissue which still survives in the skeleton of the Selachians, a sea-water animal, during its whole life. The human skeleton, as every one knows, is originally also composed of cartilage, and even before birth much of this is replaced by bone. This phenomenon cannot be understood on teleological grounds; it can only be explained by the theory of evolution."

These quotations—purposely used to preserve the full force of the evidence they contribute—indicate how far-reaching was Claude Bernard's conclusion[8] that the blood is "an internal medium in which anatomical elements live as do fishes in water." Indeed our own bodies are but colonies of aquatic animals, of unicellular organisms that live precisely as do unicellular organisms in their primordial habitat, the seas. Here these minute cells absorb their food from the surrounding medium; they assimilate it and reject their wastes as do our cells in the lymph of the intercellular spaces. Immobilized, however, when, as cell-colonies, they constitute organs, they are unable to provide for themselves; we have seen how Nature meets the needs of this new state of things: even in the lowly sponge, free amœboid cells, leucocytes, act as food-purveyors—the type of the nutritional process (as interpreted from my standpoint) in all multicellular organisms, including our own. In the lower form the amœboid messengers gather the food-stuffs from the marine medium; in the higher, they collect them from the alimentary canal. But the walls of this identical channel, where antecedent living matter is taken up to be carried where it will again assume the living state, are the seat of another phenomenon: the absorption of water which, with what

[8] Claude Bernard: "Leçons sur les propriétés des tissus vivants," pp. 55-58, 1866.

salts the food contains—sodium chloride mainly—serves to elaborate the original fluid in which our "anatomical elements can live as do fishes in water," and differing only from that of the ocean, as to constituents, in that it courses in canalicular systems.

It would appear as if, gradually as the cells are grouped into increasingly complex colonies until an organization such as that of man is reached, their chances of life should be correspondingly reduced. Especially does such a conclusion seem to impose itself when we realize that long before the higher mammals are reached, the preservation of the living state depends upon a multitude of factors; that the structure as a whole is disposed into organs having totally different functions, secretory, contractile, nervous, etc., which in turn are disposed into systems whose functions include chemical processes of various kinds, respiratory, digestive, excretory, etc. Yet such does not appear to be the case under normal conditions, *i.e.*, when the physiological functions of even the higher animal are carried on in accord with provisions of Nature. The normal longevity of the parrot, of the elephant, of man and other animals attests to this: it affords proof that increased complexity does not entail increased vulnerability. The reason for this becomes apparent when function is reduced to its simplest expression in the light of my own views: whenever an exacerbation of activity becomes manifest, it is always evoked by an increased flow of an oxygen-laden fluid whose physical and chemical properties are those of the sea, around cells specifically disposed to determine the function. Even the nerve-cell with its elongated axis-cylinder, its tufts of dendrites, the minute fibrils that connect it with other cells, the neuroglia, etc., (as I interpret them) are channels for the adrenoxidase-laden plasma analogous, as to its qualitative attributes, to the primordial seas —a small cosmos, it is true, but a cosmos nevertheless.

If a living muscle, a nerve, etc., be immersed, as was done by Overton,[9] in solutions of various salts, a striking fact asserts itself, viz., that the nearer the composition of sea-water is approached, the longer does the organ preserve its functional activity. Need we wonder that the effect of saline solution,

[9] Overton: Pflüger's Archiv, Bd. cv, S. 176, 1904.

which, injected into our tissues, meets therein all the other salts of sea-water, should, as another editorial writer[10] says, be "little short of miraculous?" It is but a bit of the ocean that the moribund receives, but to his cell—marine-cells—it is the one medium compatible with life.

MARINE SALTS AS ACTIVE PARTICIPANTS IN THE BODY'S DEFENSIVE FUNCTIONS.

The defensive properties of all the body fluids, the blood, lymph, serum, etc., including the digestive ferments of phagocytes, can only be exercised efficiently when the alkalinity of these fluids is adequate.* When, owing to the presence of a pathogenic substance, a toxin, a poison, toxic wastes, etc., the proportion of auto-antitoxin is augmented in the blood,* the alkalinity of the latter must increase proportionally; otherwise the bacteriolytic and antitoxic action of the antitoxin is inhibited* and the defensive process is weakened in proportion.

The alkalinity of the blood, lymph, etc., is due to the presence of *sodium and potassium phosphates,* which are intimately associated, and generally referred to as the "alkaline phosphates." Closely associated with these salts are the *alkaline carbonates* (sodium carbonate and bicarbonate, and potassium carbonate). They assist the former in giving the blood and lymph their alkalinity, but they also enable the plasma to absorb carbonic acid from the tissues and to eliminate this gas. After fulfilling their functions the alkaline phosphates are excreted in the perspiration and urine: about 4.5 gms. (68 grains) being eliminated in the latter daily by a normal adult.

The relationship of the blood's alkalinity to the defensive functions of the body has been urged by several experimenters. Charrin[11] gives the blood's alkaline reaction the first place in the immunizing processes of the body. It increases leucocytogenesis, and, therefore, the number of phagocytes available. Löwy and Richter[12] noted that the leucocytes increased in number in proportion as the alkalinity became more marked. We have seen that trypsin is the active proteolytic agent in the germicidal and antitoxic substance—including Buchner's alexin. Metchnikoff[13] states that alexin "acts only in the presence of salts. When relieved of its salts by dialysis, the serum loses its hæmolytic power, but as soon as these salts are restored to it, this power reappears." As (in the light of my views) these same defensive substances are the active

* *Author's conclusion.*
[10] Editorial: Medicine, Sept., 1901.
[11] Charrin: "Les défenses naturelles de l'organisme," 1898.
[12] Löwy and Richter: Virchow's Archiv, Bd. cxlv, S. 49, 1896.
[13] Metchnikoff: "L'Immunité dans les mal. infectieuses," p. 93, 1901.

agents in tissue metabolism, a corresponding relationship between this process and the blood's alkalinity should exist. Gautrelet[14] noted an absolute parallelism between metabolism and the alkalinity of the blood, *i.e.*, nutrition was found low when the alkalescence was low, and *vice versa*, both in man and in the lower animals. The blood's alkalinity is intimately related with the energizing agent in auto-antitoxin, namely, adrenoxidase. Thus, while Orlowsky[15] found that the alkalinity of the blood in various diseases is proportionate with the number of red corpuscles, declining when these are few and increasing as their number increases (the leucocytosis influencing the alkalinity in no way), Mylius[16] found that, although the red corpuscles themselves were neutral or acid, the *blood-platelets* were strongly alkaline. Now, I have shown[17] that these platelets were droplets of adrenoxidase.

The experimental application of these facts in infection proves their importance. The researches of Behring and Nissen,[18] for example, concluded that the resistance of the white rat to anthrax was due to the intense alkalinity of its blood. Paul found that when the alkalinity of the rabbit's blood was neutralized, its germicidal power disappeared. Calabrese[19] found that the alkalinity of the blood increased with the degree of immunization, and that the blood reacted against a toxic by a steady increase of alkalinity. In comparative experiments in a large number of animals, von Fodor[20] found that their resistance to the anthrax, cholera, tubercle and streptococcus inoculations was greatly increased when sodium bicarbonate was administered, either subcutaneously or orally.

Sodium Chloride, though a neutral salt, is a most important inorganic constituent of the body fluids: Owing to the smallness of its molecules (58.5) and its chemical inertia, it is preëminently the salt which maintains the osmotic equilibrium between the tissues and the blood. When the supply is inadequate, all the functions are hampered, since it is the solvent of adrenoxidase* (serum globulin). By holding the latter in solution it insures its free circulation as a constituent of the plasma in all vessels down to the minutest capillary networks distributed to cellular elements, including those of the nervous system: the axis-cylinders and other neuro-fibrils, the networks of neurons, their dendrites, etc.* This also enables the adrenoxidase-laden* plasma to transude freely through the capillary walls in order to reach the tissue-cells, *i.e.,* to carry on the life process. The free osmotic properties which the lymph in the tissue-spaces also owes to sodium chloride insures another important function, viz., that of sweeping away by the lymph-current of all wastes derived from the cell.

* *Author's conclusion.*
14 Gautrelet: Arch. gén. de méd., Mar. 27, 1906.
15 Orlowsky: Deut. med. Woch., Bd. xxix, S. 601, 1903.
16 Mylius: Cited by Labbé: Presse méd., vol. ix, p. 999, 1902.
17 *Cf.* vol. i, p. 715, in the first three editions, and this volume, p. 826.
18 Behring and Nissen: Zeit. f. Hygiene, Bd. viii, S. 412, 1890.
19 Calabrese: La semaine méd., vol. xv, p. 467, 1895.
20 Von Fodor: Centralbl. f. Bakt. u. Parasit., Bd. xvii, S. 225, 1895.

The influence of sodium chloride on osmosis is so well known that evidence to that effect is not required. The extent to which it enhances the efficiency of the protective processes in infection may be illustrated by a few examples. Lubomoudrov[21] found that a saline solution composed of 0.5 per cent. of sodium chloride and 1 per cent. of sodium sulphate in distilled water, injected intraperitoneally or subcutaneously, caused leucocytosis and increased phagocytosis. They retarded the development of typhoid and cholera bacteria, and in some instances caused its destruction. Prophylactic injections, given twenty-four hours before inoculation, enabled guinea-pigs to resist a dose from two to three times as large as that which killed controls. It becomes a question, however, which of the two salts mentioned insured these results. It is evidently not the sodium sulphate, for *sodium and potassium sulphate,* though found in practically all the fluids of the body and eliminated at the rate of about 4 gms. (60 grains) daily in the urine, are in reality but excretory products derived from the oxidation of proteids and other organic substances containing sulphur.

Conversely, a multitude of clinical facts on record—some of which will be submitted later—have shown that sodium chloride in "decinormal saline solution" produces precisely the effects noted by Lubomoudrov.[22]

Experimental researches point in the same direction. Lesné and Richet, Jr.,[23] for instance, found that if, after injecting a solution of potassium iodide into two dogs, sodium chloride solution was also injected in the blood of one of the dogs, toxic phenomena came on in the latter only after 1.16 gm. (17 grains) per kilo of animal had been given, whereas in the dog deprived of the saline they appeared when 0.32 gm. (5 grains) per kilo had been reached. Ercklentz[24] also found that animals given fatal doses of a toxic and saved by saline solution, showed little pathological trace of the intoxication when killed, while animals left to die, *i.e.,* without saline solution, showed marked histological alterations. F. J. Bosc and V. Vidal,[25] in fact, ascertained experimentally that the solution of sodium chloride and sodium sulphate, equal parts (7 per mille), did not present any difference in results from those of the ordinary saline. Their researches imposed the conclusion that simple saline solution of the above strength possesses the minimum of harmful effects and the maximum of physiological effects, and should be the solution of choice for massive intravenous injections.

Therapeutics.—*Sodium chloride* is a potent adjunct in many morbid processes, especially in *febrile diseases,* because it maintains the fluidity and circulatory freedom of the auto-antitoxin-laden plasma.* It insures the access of the plasmatic adrenoxidase to the diseased area and, owing to the thyroidase it contains, it sensitizes (as opsonin) the bacteria, detritus, etc., thus facilitating their ingestion and destruction by the phagocytes.* It also enables these cells, as well as the leucocytes, which supply nucleo-proteid granules and trypsin to the plasma,

* *Author's conclusion.*
21 Lubomoudrov: Annales de l'Inst. Pasteur, vol. xix, p. 573, 1905.
22 Lubomoudrov: *Ibid.*
23 Lesné and Richet, Jr.: Progrès méd., Mar. 28, 1903.
24 Ercklentz: Therapie der Gegenwart, Jan., 1903.
25 F. J. Bosc and V. Vidal: Arch. de physiol., 5 série, vol. viii, p. 937, 1896.

to migrate freely to the exposed region and carry on their protective function efficaciously.*

Over one-half ounce of sodium chloride being eliminated daily with the urine, the sweat, fæces, etc., the reduced diet and the anorexia prevent, especially during febrile diseases, its being replaced through its normal source, the food.* The body's supply becoming inadequate very soon, the protective functions are hampered in proportion as the deficiency of the salt is marked.* *This is a fruitful cause of death in all infections.**

This applies as well to the *alkaline salts*, the elimination of which proceeds at the rate of about 68 grains daily in the urine alone. Gradually as their proportion in the blood becomes reduced, both the nutrition of the body and the activity of its defensive process, plasmatic and cellular, are correspondingly inhibited, irrespective of the remedies administered.*

In accord with the teachings of physiology, Hutchison[26] states that the considerable increase of alkalinity during the ingestion of food is synchronous with the appearance of the "alkaline tide in the urine." He explains this alkalinity, at least in part, "by the absorption of alkaline salts from the food." The quantity thus eliminated is very large. Thus Halliburton[27] says of sodium chloride (common salt), that "about 16 gms. (247 grains) are daily excreted in the urine, and smaller quantities in the sweat and fæces." Halliburton also says in this connection that "during its passage through the body, it facilitates the absorption of proteid food, and increases tissue metabolism." This applies as well to morbid states. Thus, Fornaca and Micheli[28] found that the physiological salt solution increased nutrition in convalescents, and the proportion of red corpuscles. The anorexia and reduced nutrition which accompany febrile diseases necessarily follow from the well-known fact mentioned by Labbé[29] that during digestion the alkalinity decreases, while it is lowered during fasting.

In diseases in which the intake of food is reduced, the proportion of the various salts in the blood should not, as is now the case, be taken as guide for the elaboration of artificial sera, since the excretion of these salts with, or as, wastes, does not correspond with this proportion.* The aim should be to compensate for the salts of which the body is deprived through the reduced diet, to enable it to carry on its bacteriolytic and antitoxic functions to the best advantage.* *To neglect this factor in a febrile case is to compromise the issue.*

* *Author's conclusion.*
[26] Hutchison: Lancet, Mar. 7, 1896.
[27] Halliburton: Schäfer's "T. B. of Physiol.," vol. i, p. 77, 1898.
[28] Fornaca and Micheli: Riforma medica, vol. xviii, ii, p. 374, 1902.
[29] Labbé: Presse médicale, Oct. 18, 1902.

Since I urged in 1903,[30] the importance of supplying the patient in all febrile diseases, *from the beginning*, the salts he fails to receive owing to the reduced diet which his sickness entails, a number of clinicians have carried out this plan, as to the sodium chloride, with marked advantage, as will be shown under "Treatment" of the various diseases in which this measure is indicated. J. B. Todd, of Syracuse, having found that saline solutions were as effective when used as beverages, as when given subcutaneously or by enema, while J. Madison Taylor, of Philadelphia, found that the ordinary saline solution tablets fulfilled the object admirably for the preparation of the beverages, there is no ground, on the plea of complicated technique, to deprive the patient of a measure which *in acute fevers is of greater importance than any drug.*

On the whole, the proportion of sodium chloride and alkaline salts to be administered should correspond with the diminution of nourishment which the disease, in one way or another, entails.* If the patient receives in the twenty-four hours one quarter of his usual food, the salts given should be three-quarters of the quantities excreted, taking into account size, sex and age; if the food-intake is reduced only one-half, but one-half of the salts excreted are necessary, etc. The proportions would then be as follows:—

An adult man taking in 24 hours	Sodium Chloride	Sodium Phosphate
¾ Food	60 grains (4 gms.)	15 grains (1 gm.)
½ "	120 " (8 ")	30 " (2 gms.)
¼ "	180 " (12 ")	45 " (3 ")
0 "	240 " (16 ")	60 " (4 ")

These salts may be added to the milk, broths, or other beverages and foods. It is most important that the patient should drink water freely, especially in febrile processes, to preserve the normal specific gravity of the blood and other fluids. This serves also to insure a low specific gravity of the urine, notwithstanding the free elimination of acids and other wastes, thus protecting the kidneys.

When the salts cannot be administered entirely by the mouth, they should be given by enema, and, if necessary, subcutaneously or endovenously, injecting in the latter cases the classic saline solution—approximately one teaspoonful (or more exactly, 69 grains) of common salt to one pint of sterilized water at *not less* than 110° F.—and *very slowly*. It does not

* *Author's conclusion.*
[30] *Cf.* vol. i, p. 787, in the first three editions.

itself raise the temperature, as is now taught: it enables the blood suddenly to resume its antitoxic functions, the hyperthermia being but an expression of the life-saving process.*

For hypodermoclysis or intravenous injection the plain saline solution is the most satisfactory and safest. The addition of *sodium bicarbonate*, recommended by some, tends to cause local gangrene, as shown by Baish[31] and others, but this salt may be given advantageously by the mouth when there is acidosis. Another salt, *sodium sulphate*, appears in many foreign formulæ, but, as we have seen, it is a waste-product and useless. *Calcium*, which, according to Howell, Jacques Loeb and others, stimulates the heart, is eliminated in such small quantities that it need not be replaced. It tends, in fact, to promote the formation of emboli. *Potassium*, as shown by Loeb, Matthews, Fischer and others, prolongs cellular life; but a very minute quantity suffices for this purpose, and as milk contains potassium chloride, it supplies the needs of the body. The precautions to be observed in injecting saline solution are the following: The solution and apparatus should be sterilized, and the skin be thoroughly cleansed at the place of injection. The temperature should be 110° to 115° F. The passage of air into the tissues or vessels should be avoided. Never more than half a pint should be injected in one place in the cellular tissue. The infusion should be carried out slowly; about one ounce a minute can be safely introduced into the veins or the subcutaneous tissue.

Contraindications and Untoward Effects.—The contraindications are self-evident: if there exists any œdema, pericardial, pulmonary, peritoneal, etc., especially if this is due to renal disorder, the addition of a large quantity of fluid and a marked increase in the osmotic property of all body fluids will naturally increase the trouble. When nephritis is present, the enhanced metabolic activity which saline solution causes will aggravate the renal disorder by increasing the waste-products. When the patient is liable to hæmorrhages, pulmonary, uterine, cerebral, etc., to increase the osmotic properties of the blood will augment the danger. In arteriosclerosis, cardiac degeneration, etc., they are believed to be dangerous, but evidence to this effect is lacking.

The latter belief is based on the mistaken theory that the solution distends the arteries, but Sollmann[32] found that intravenously injected solutions of sodium and potassium disappeared in great part from the circulation *per se* and passed into the tissues by physiological filtration as injected, then out with the urine. Even large quantities failed to augment the fluid contents of the vessels. J. B. Briggs[33] ascertained sphygmomanometrically that "it is useless to infuse with any idea of filling up the depleted vessels [in shock]; the water and salt are excreted probably quite as rapidly as they pass into the circulation."

* *Author's conclusion.*
[31] Baish: Deut. med. Woch., Sept. 4, 1902.
[32] Sollmann: Archiv f. exper. Path. u. Pharm., Bd. xlvi, S. 1, 1901.
[33] J. B. Briggs: Johns Hopkins Hosp. Bull., Feb., 1903.

The supposed untoward effects are really not such.* As previously stated, the elevation of temperature produced is not due to a direct action of the saline solution, as now believed: it is due to the fact that the blood is enabled by it to resume its bacteriolytic and antitoxic functions, a process which entails a rise of temperature.* The rise of vascular tension is but a normal outcome of this process, the muscular coat of all vessels and the cardiac muscle itself being also the seat of enhanced metabolic activity.* The glycosuria is also but a proof that the adrenal system itself is suddenly liberated,* since we have seen that adrenal extractives provoke glycosuria.

REMEDIES USED TO INFLUENCE SPECIAL ORGANS.

All remedies acting, in the light of my views, through one or more nerve-centers, no drug ingested and absorbed from the alimentary canal, or administered subcutaneously, intravenously, etc., should act specifically upon any one organ without influencing others in the same way. This fact is emphasized by the physiological effects of the drugs analyzed below—which are usually referred to as "local remedies."

Purgatives are shown to act in various ways. The first of these is by their direct irritating action on the intestinal mucosa, which causes its glandular elements and the organs forming part of the digestive system to increase their activity reflexly. Here the drug is not absorbed, however; it acts precisely as would an irritant applied to the conjunctiva. An important feature is illustrated in this connection, viz., that the main action of purgatives is to provoke an increase of auto-antitoxin in the intestinal fluids which tends to asepticize the contents of the canal. It applies as well to purgatives, such as mercury, which are absorbed, since, as we have seen, this metal stimulates powerfully the adrenal mechanism and enriches all secretions in auto-antitoxin.

Emetics may likewise act as local stimulants, the irritation of the gastric mucosa causing vomiting reflexly, as is well known. Others, apomorphine, for instance, are shown to produce the same effect in another way: they depress markedly the sympathetic and vasomotor centers, and cause such marked

* *Author's conclusion.*

general vasodilation through relaxation of their walls that blood enters freely into all glandular elements. Those of the gastric mucous membrane, among others, becoming hyperæmic, a condition similar to that produced by direct irritants, such as mustard, is awakened, and vomiting occurs.

Diaphoretics differ from emetics in that they depress the sympathetic center only. All arterioles being dilated, an influx of blood occurs into all glandular capillaries, including those of the sweat-glands. Whereas emetics cause passive hyperæmia only, diaphoretics cause local increase of function, owing to the normal condition of all vessels except the arterioles. The secretory activity of the sudorific glands, among others, is therefore markedly raised, and sweating occurs.

Oxytocics, of which ergot is the main type, produce their effects by stimulating actively the vasomotor center. They thus drive a large amount of blood to the various organs, including the uterus. The contractile power of the uterine muscle being thus greatly enhanced, it responds with correspondingly greater energy to the periodical impulses it receives during parturition. The influence of oxytocics on hæmorrhage is due to this potent constrictor action on the smaller vessels governed by the vasomotor center; but the fact that blood is forced peripherally by these drugs renders them dangerous for this purpose.

Diuretics.—These agents are shown to produce their effects in various ways. Saline solution, for instance, indirectly enhances metabolism through its influence on osmosis. An excess of waste-products being produced, the kidneys are caused reflexly to increase the excretory activity—a process aided by the excess of water introduced into the blood. Digitalis also causes diuresis by increasing metabolism, since we have seen that it stimulates the adrenal mechanism. Mercury, another diuretic, is also, as shown, a powerful adrenal stimulant. These remedies all raise indirectly the vascular tension—an active factor in the production of diuresis.

PURGATIVES.

Physiological Action.—Most purgatives increase the secretory activity of the intestinal glands by causing irritation of the intestinal mucosa, *i.e.*, by augmenting reflexly the local blood-

supply through the vagus, the stricto-dilator nerve* of the alimentary system. As the intestinal juice, owing to the presence therein of adrenoxidase (secretin), nucleo-proteid (which with adrenoxidase forms enterokinase), and pancreatic juice, including trypsin, all of which jointly form auto-antitoxin, the physiological purpose of this increase of secretion is evidently a protective one, viz., to rid the intestine of an irritating substance.* If this canal happens to contain pathogenic organisms, toxins or other harmful substance, they are likewise exposed to the action of the auto-antitoxin in the intestinal juice. This is one of the most important functions of the intestinal juice, and the therapeutic value of purgatives is mainly due to the fact that they accentuate the efficiency of this function.*

Thiry[34] found that slight mechanical irritation, as tickling with a feather, sufficed to cause an exposed area of the mucosa of the small intestine to secrete. The influence of local irritation is further shown by the fact that in herbivora, the large proportion of refuse or residuum left in the intestine causes the stools to be loose, while in carnivora they are habitually dense, with a tendency to constipation. Thiry failed to increase the secretory activity of the intestinal mucosa by the local application of purgatives, but several other observers have obtained positive results. In accord with Moreau,[35] Vulpian,[36] for example, found that a solution of magnesium sulphate or jalap injected into the small intestine caused a local catarrhal congestion with the effusion of much fluid, which was found to contain red corpuscles and leucocytes. Lauder Brunton[37] also found that Epsom salt, gamboge, elaterium and croton oil stimulated the secretory activity of the small intestine. Manquat[38] states that all the experiments performed to demonstrate that irritation was produced could be summarized as follows: when an exposed coil of small intestine was ligated in four places a few inches apart, thus forming three segments, the injection of a cathartic substance into one of the three caused this segment alone to become filled with liquid. H. C. Wood, Sr. and Jr.,[39] state (1906) that "the evidence, both experimental and clinical, is indeed overwhelming in favor of increased secretion."

That the secretory activity of the intestinal mucosa is due to nervous action, and that the secretory nerve is the vagus, is shown by the fact that H. C. Wood, in 1870, found that division of the vagus on both sides, in the neck, prevented the action of purgatives. Vulpian,[40] as a result of the experiments recited above, concluded that the increase of secretion produced by the local irritation of cathartics was due to reflex action.

The presence of the various constituents of what I have since termed "auto-antitoxin" in the intestinal juice was shown in the fourteenth chapter,[41] to which the reader is referred.

* *Author's conclusion.*
34 Thiry: C. R. de l'Acad. de méd., vol. xlvi, 1868.
35 Moreau: *Ibid.*, July 5, 1870; Sept. 12, 1871.
36 Vulpian: Gaz. méd., vol. xliv, p. 300, 1873.
37 Lauder Brunton: Cited by Wood: *Loc. cit.*, thirteenth edition, p. 645, 1906.
38 Manquat: "Thérapeutique," vol. i, p. 677, 1903.
39 Wood, Sr. and Jr.: *Loc. cit.*, thirteenth edition, p. 646, 1906.
40 Vulpian: *Loc. cit.*
41 *Cf.* this volume, p. 850.