CHAPTER XXX.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PATHOGENESIS AND THERAPEUTICS (*Continued*).

THE ADRENAL SYSTEM IN THE DISEASES OF THE ALIMENTARY CANAL.

The series of diseases embodied in the present chapter is intended to illustrate three salient facts: (1) the cardinal rôle which the intestinal canal fulfills in the defence of the body at large against infection by increasing, when necessary, the proportion of auto-antitoxin in the intestinal juice; (2) that certain toxins, endotoxins or other poisons can depress and even paralyze the vasomotor and sympathetic centers precisely as is the case with depressing drugs; and (3) the fact that the *deprivation of auto-antitoxin* which maternal, or at least breast-milk, entails when infants are hand-fed accounts for the fatality of intestinal diseases among them besides, as already shown in the preceding chapter, rendering them highly vulnerable to infection.

CHOLERA ASIATICA.

SYNONYMS.—*Epidemic Cholera; Cholera Algida; Cholera Maligna.*

Definition.—Asiatic cholera, an infectious disease caused by Koch's comma bacillus, is due to paresis of the test-organ and the vasomotor and sympathetic centers by the endotoxin of this pathogenic organism.*

Symptoms.—After an incubation period varying from two to five days, the disease sets in by a *premonitory diarrhœa* often accompanied by slight colicky pain and borborygmus. The patient feels well otherwise. After a period varying from a few hours to a few days, however, he becomes weak, experiences fleeting cramps in the extremities and chills, and, perhaps, vertigo or faintness. This is accompanied by a change in the character of the stools.

* *Author's definition.*

This introduces the stage of *serous diarrhœa,* in which the stools, from fæcal or bilious, become fluid and serous, devoid of fæcal odor and laden with rice-like flakes, thus constituting the "rice-water" stools. Several of these stools, each representing a large quantity of blood-serum, may be passed without pain, but soon abdominal cramps are experienced and vomiting sets in—also of "rice-water"—accompanied by a feeling of intense exhaustion. Gradually as the loss of serum increases, thirst becomes greater, until it is intense and insatiable, and the urine becomes scanty or absent. The face is at first pale, but it soon assumes a leaden hue. As the flux increases, the patient grows steadily weaker, the pulse being small, weak and rapid, and in some cases irregular. The muscular cramps may also become severe and the extremities cold. This may prove to be but an attack of "choleraic diarrhœa" or "cholerine," often met with during cholera epidemics. If this be the case, the symptoms gradually improve and the patient finally recovers. On the other hand, collapse may occur more or less suddenly, followed by death. Such a case may last from six hours to two days.

If the case prove to be one of true cholera, it lapses into the *algid stage.* As described by a clinician who has observed many such cases, "this is announced by a lessened frequency and abundance of the dejections, which sometimes cease altogether. In a few hours, however, the patient's condition grows rapidly worse; the countenance is altered—the cheeks become hollow, the eyes sink deeper in the sockets, are encircled by a black ring; there are pains in the head, ear-tinglings, dizziness and blurred vision; the voice becomes hoarse and is soon extinguished. A feeling of anxiety assails the patient, who suffers from the most excruciating vomiting, hiccough and cramps in the calves. Cooling of the surface increases, all external parts being, as it were, frozen; but the patient feels an internal, very troublesome heat, explained by the fact that the temperature of the skin, mouth, etc., is much lowered, while that of the internal organs is raised and even febrile. At the same time the skin takes a bluish tinge with black marble-like veins coursing over the hands, feet, penis, and with increasing cyanotic dark hue of the nails. The pulse becomes weaker and smaller, until it disappears, first from the radial arteries and then from the

crurals and even the carotids, while the heart-beats gradually disappear, the sounds becoming weaker until finally only the second sound is heard. To this, great emaciation is added, the body growing thin and the skin wrinkled. Breathing is frequent and difficult; every secretion is dried up, with the exception of that of the sudoriferous glands, a cold and clammy sweat covering the cutaneous surface. At the end of this stage the patient becomes extremely apathetic and somnolent, loses consciousness, slowly turning his eyes toward a person speaking to him, and at times answering some words with great fatigue, but immediately falling again into stupor. A period of agitation, during which the patient tries to rise and utter vague words, sometimes precedes this stage of collapse, which generally —in more than three-fourths of all the cases—grows worse, and ends in death. The whole duration of the algid stage is from a few hours to two or three days."

When the patient survives the algid stage, the *reaction stage* begins, *i.e.*, general improvement of all the symptoms and after a few days convalescence. In some cases, however, several of the symptoms persist, the anuria, hypothermia, dyspnœa, etc., and the patient may suffer a relapse which may prove fatal[1]. In others, again, symptoms recalling those of typhoid fever occur—the so-called "cholera-typhoid," attended by delirium, a dry tongue, etc. This also may terminate fatally. Finally, the convalescence may be protracted and be attended by various *complications* which include many forms of cutaneous eruption, gastro-intestinal disorders, inflammatory disorders of the throat, lungs and brain, cerebral softening, insanity, tetany, palsies, etc.

Various clinical types occur, but they differ mainly through the intensity of the symptoms. Thus *cholera siderans,* observed sometimes in India, may run its course in a few hours, and in rare cases in a few minutes. Again, there are cases in which there is no diarrhœa, the so-called *dry cholera,* the absence of flux being due merely to the fact that the fluids accumulate in the intestine, because paralysis of the latter prevents their expulsion.

The clinician referred to in the text is Professor Rubino, of Naples.[1] He clearly defines in his description of the algid stage several features which are of special importance when interpreted from my standpoint.

[1] Rubino: Sajous's "Analyt. Cyclo. of Pract. Med.," vol. ii, p. 210, 1898.

Pathogenesis and Pathology.—Asiatic cholera is due to poisoning by an endotoxin contained in Koch's comma bacillus, which is liberated after death and disintegration of this micro-organism. Although infection occurs through the alimentary canal, even large quantities of specific bacteria may be ingested and be found in the stools without causing the disease, provided the functional efficiency of the body's auto-protective mechanism be perfect.* Children are vulnerable to cholera because this mechanism is not fully developed; the aged are vulnerable because it has become weakened in them, as it does under the influence of any debilitating condition, ill-health, overwork, alcoholism, deficient food, etc., all of which also predispose to the disease.*

The gastric juice does not afford protection against water-borne cholera bacilli as believed by some. The main protective influence is exercised by the auto-antitoxin of the intestinal juice.*

It is now generally recognized that the poison is an *endotoxin* freed only by death and disintegration of the germ. Pfeiffer[2] found this poison intensely toxic. Cantani and Gamaleia[3] and others have made similar observations. Its identity is not established, however, but, as shown by Nicati and Rietsch,[4] Van Ermengem,[5] Koch, Pfeiffer and other investigators, the injection of pure culture of the bacillus into the intestine or the peritoneal cavity of animals evokes pathological changes and symptoms similar to those observed in cholera Asiatica: marked weakness, feebleness of the heart's action, marked coldness of the head and extremities, etc. Moreover, Koch's bacillus is always found in the stools of cases of Asiatic cholera, and in this disease *only*. Pettenkofer and Emmerich, Hasterlik[6] and others, however, as is well known, not only swallowed without evil results large quantities of cholera cultures, but as shown below, various observers have found that normal stools may contain virulent cholera vibrios though the patient show no sign whatever at the time or subsequently of cholera. That it is only under certain predisposing conditions, therefore, that the disease can develop, is obvious. As stated by Tyson,[7] "general ill-health, fatigue, the alcoholic habit, depression of spirits, fright or anxiety, any one or all may be predisposing causes. All ages and sexes are liable to be infected, but young children seem most vulnerable," and, I would add, aged people, the poor and ill-fed likewise.

When, therefore, emigrants, pilgrims, etc., coming from regions in which the disease is always endemic, as it is on the borders of the

* *Author's conclusion.*

[2] Pfeiffer: Zeit. f. Hyg. u. Infects., Bd. xi, S. 393, 1891.

[3] Cantani: Cited by Gamaleia: Arch. de méd. expér. et d'anat. path., vol. iv, p. 173, 1892.

[4] Nicati and Rietsch: Arch. de physiol. norm. et path., 3 série, T. vi, p. 72, 1885.

[5] Van Ermengem: Bull. de l'Acad. roy. de méd. de Belge, 3 série, T. xviii, p. 1221, 1884.

[6] Hasterlik: Wiener klin. Woch., Bd. vi, S. 167, 1893.

[7] Tyson: "Practice of Medicine," third edition, p. 92, 1903.

Ganges, into communities containing such debilitated subjects, especially when the local hygienic conditions are defective, they communicate it to them indirectly, *i.e.*, through the intermediary of the soil, the water and the food which they contaminate with their germ-laden discharges, their soiled linen, etc. Rubino[8] writes in this connection: ''Cholera vibrios can live only for a short time in fæcal matter, seldom longer than two or three days;" . . . "they live, on the contrary, very long in the soil, especially when they find in it a proper nutritious material; it seems rather that their virulence is then heightened, the elaboration of their poison becoming more rapid and intense. They can live also on the outer surface of fruits and vegetables (the duration being then from one to six days), and even on the cut surface of these, where their life may last for a time ranging from one hour (on very acid fruits) to two weeks. Cholera vibrios can grow freely in water, especially when it is stagnant and polluted with organic matter." This emphasizes the fact that infection occurs in predisposed individuals mainly through the alimentary canal, when the *true* cholera vibrio, Koch's comma bacillus, is present.

The first citadel of the alimentary canal, the stomach, is thought by some observers to protect the body through the bacteriolytic action of its gastric juice. Schultz-Schultzenstein[9] found that water containing pepsin and traces of acid killed the vibrio if .019 per cent. of hydrochloric acid is present, and that in 75 per cent. of his experimental cases 600 c.c. water ingested on an empty stomach became bacteriolytic, *i.e.*, it acquired an acidity of 0.03 per cent. In the remaining 25 per cent., however, it was only .0142 per cent.—a solution which does not kill the vibrio even in *one and one-half hours*. Now Howell[10] states that, as shown by von Mering, water introduced into the stomach begins *at once* to pass out into the intestine; and moreover, that when 500 c.c. of water were given to a large dog, by the mouth, 495 c.c. had passed into the duodenum, and out through a fistula in the latter, within *twenty-five minutes*. It is evident, therefore, that contaminated water carries the pathogenic organism directly to the intestine in at least 25 per cent. of all exposed individuals. The gastric juice does not even protect those in perfect health, since, as already stated, various investigators have found bacilli in normal stools in individuals who never developed the disease. The experiments of Pettenkofer and Emmerich on themselves demonstrate the same fact. An abundance of cholera vibrios having been found in their stools, their gastric secretions evidently did not kill the ingested cultures.

Conversely, it is believed that the alkaline juice of the intestine is necessary to develop the germ, and that it is a suitable culture fluid. But in the light of the evidence I have adduced to the effect that the intestinal juice is rich in trypsin, nucleo-proteid and adrenoxidase, this cannot be the case. This accounts for the fact that Klemperer[11] found in experiments on guinea-pigs, rabbits and dogs, that the normal intestine is strongly resistant to the cholera bacillus—an action which he attributed to a substance he found in the epithelial cells, *i.e.*, nucleinic acid and nuclein. This is obviously the nucleo-proteid, and as no one would deny the presence of trypsin in the intestine, nor since the labors of Pawlow, Delézenne, Camus and Gley, and others, that of enterokinase (trypsin plus adrenoxidase), the three constituents of the digestive triad which in the blood constitute the auto-antitoxin are evidently present. *It is the intestinal juice, therefore, which is the first serious barrier to infection.*

[8] Rubino: *Loc. cit.*
[9] Schultz-Schultzenstein: Centralbl. f. Bakt., Bd. xxx, S. 785, 1901.
[10] Howell: "T. B. of Physiol.," p. 698, 1905.
[11] Klemperer: Deut. med. Woch., Bd. xx, S. 435, 1894.

If we now inquire into the cause of this, we are brought back to debility of the adrenal system, the result of the many untoward conditions grouped as "predisposing causes." The formation of adrenoxidase being deficient, the pancreas and the leucocytogenic organs are inadequately nourished, so that trypsin and nucleo-proteid are formed in insufficient quantities.

Cholera is not, as generally believed, an intestinal disease,* the symptoms referable to the alimentary canal being, in keeping with all the other characteristic symptoms, the result* of a general intoxication by the endotoxin of the coma bacillus. It is, therefore, by penetrating the intestinal walls and into the body fluids that the comma bacillus provokes the disease. As it is the function of the digestive leucocytes to ingest food-products in the intestinal canal in order to complete the digestive process and prepare the end-products for assimilation by the tissue-cells,* they ingest likewise in the intestine what bacteria happen to be present in the food. Infection occurs when this intracellular process is inadequate, *i.e.*, when the digestive leucocytes ingest living comma bacilli which they are unable to digest or even kill.*

The number of bacilli ingested by leucocytes is not a prominent feature of their inability to destroy these germs, since enormous quantities of the latter may be swallowed by a man in normal health without giving rise to the disease. The ruling factor of infection is deficiency of the digestive triad: trypsin, nucleo-proteid and adrenoxidase, both in the intestinal juice and in the digestive leucocytes, and infection occurs when the bacilli have, as a result, remained unaffected by the bacteriolytic action of these bodies.* It is not in the blood, as now believed, that the organisms proliferate;* the digestive leucocytes carry the living comma bacilli directly to the lymph-spaces, as if they had been digested and converted into tissue-cell granulations.* Being unassimilable, however, they are swept away as wastes by the torpid lymph-stream, and as lymph is practically blood-serum, and an excellent medium for their growth, they rapidly pullulate therein.* When, with the lymph current, they reach the blood and ultimately the arterial system, they are rapidly killed and disintegrated, and their endotoxin being liberated, general intoxication follows.*

* *Author's conclusion.*

It is now believed that cholera is essentially an intestinal disease; yet, as observed by Karlinski[12] in his own case, while studying cholera in Arabia, the comma bacillus can be present in one's stools without provoking the disease. This was confirmed by Sawtschenko and Sabolotony,[13] Abel and Claussen,[14] Rumpel[15] and other observers. Hasterlik[16] repeated on himself and three others Pettenkofer's experiment, and as was the case with the latter, suffered no inconvenience, though the baccilli were found in the stools. The doses were gradually increased until one of the experimenters ingested an entire culture of a third generation. This caused abdominal pain and diarrhœa after thirty-six hours, but nothing more. As observed by Guttmann,[17] Kolle[18] and others, this was true cholera, since large quantities of bacilli were found in the dejections, and many such cases are observed during epidemics.

Again, while Pettenkofer, Emmerich, Hasterlik and his associates observed no effects after swallowing large quantities of comma bacillus cultures, Pfeiffer and Pfuhl[19] suffered moderately severe attacks of cholera after being accidentally inoculated with cultures. Deaths have also occurred from this cause. As "inoculation" means the introduction into the blood of a relatively very small number of bacilli, while enormous quantities of them were included in the cultures swallowed, it is self-evident that it must be *in the body fluids* that the proliferation occurs. Indeed, the bacilli were found in Pfeiffer's discharges for thirty-three days after the inoculation, and Thomas[20] has shown that all the symptoms and pathological lesions of cholera could be produced in rabbits by intravenous injections of pure cultures of comma bacilli obtained from cholera dejections.

Now is it in the blood, as generally believed, that the proliferation of the bacteria occurs? Bacteriologists have found that, as stated by Vincenzi,[21] "the cholera vibrio develops luxuriantly in the blood-serum of healthy animals" *in vitro, i.e.*, in serum deprived of its bacteriolytic activity by removal of its cells. This does not mean that a similar result can occur in the blood-stream, but that proliferation can take place in the *lymph*-stream. This becomes apparent when the functions of the digestive leucocytes, as I have described them, are taken into account. Interpreted from this standpoint, every leucocyte which happens to ingest one or more living bacilli in the intestinal canal becomes a source of infection, an inoculating agent, on entering the blood if *it does not* absorb in the intestinal canal a *qualitatively efficient supply of the digestive triad*, trypsin, and its activators, nucleoproteid and adrenoxidase, constituting auto-antitoxin, to kill the microorganisms.

In the light of the evidence adduced in the seventeenth chapter, the leucocytes do not deposit their end-products in the blood; they leave the blood-stream by migrating through the walls of the capillaries and deposit them in the tissue-spaces in contact with the tissue-cells. Unsuitable products, wastes, etc.—including the cholera vibrios in this condition—being of course unabsorbed by the latter, they are swept away by the lymph-stream. Now lymph being, as stated by Stewart, practically "blood deprived of its cells," *i.e.*, serum, we have

[12] Karlinski: Centralbl. f. Bakt., Bd. xv, S. 751, 1894.
[13] Sawtschenko and Sabolotony: Centralbl. f. allg. Pathol. u. pathol. Anat., Bd. iv, S. 625, 1893.
[14] Abel and Claussen: Centralbl. f. Bakt., Bd. xvii, S. 77, 1895.
[15] Rumpel: Berl. klin. Woch., Bd. xxxii, S. 73, 1895.
[16] Hasterlik: *Loc. cit.*
[17] Guttmann: Med. Press and Circular, Jan. 25, 1893.
[18] Kolle: Zeit. f. Hyg. u. Infects., Bd. xviii, S. 42, 1894.
[19] Pfeiffer and Pfuhl: Cited in Med. Press and Circular, Sept. 5, 1894.
[20] Thomas: Arch. f. exp. Pathol. u. Pharm., Bd. xxxii, S. 38, 1893.
[21] Vincenzi: Deut. med. Woch., Bd. xix, S. 418, 1893.

in the torpid current of the lymph vessels a vast field wherein, at the ideal laboratory temperature, 37° C. (98.6° F.), the cholera vibrio can also develop "luxuriantly." As to the fact that the germs finally reach the blood, Bosc[22] found that the blood-serum of severe cases contained "an enormous quantity" of a substance which, injected into animals, produced all the typical signs of cholera and finally death. This poison was evidently derived from dead bacilli, for serum taken from the cases which furnished the poison failed to develop cultures.

While the functional debility of the adrenal system is the primary cause of the body's vulnerability to the disease because the specific organisms are thus allowed to reach the lymphatic vessels, proliferate therein and permeate the blood with their endotoxin,* the latter gives rise to the symptoms of the disease by paralyzing directly the functions of the vasomotor and sympathetic centers.

By inhibiting the functions of the vasomotor center, the cholera endotoxin causes, indirectly, dilation of all vessels of the body, and therefore accumulation of the blood in the great central vessels, particularly those of the splanchnic area.* The peripheral vessels and capillaries being deprived of a corresponding volume of circulating blood, the marked symptoms of ischæmia of various organs appear: coldness and pallor as to the skin; vertigo and faintness as to the brain; weakness and exhaustion as to the muscles; weakness and rapidity of the cardiac action, or anuria as to the kidneys; and dyspnœa as to the lungs.* Conversely, the accumulation of blood in the deep trunks* gives rise to the sensation of intense internal heat and the high rectal temperature, which may reach 104° F. (40° C.) or more.

Inhibition of the functions of the general sympathetic center by the endotoxin, coincides with the appearance of the serous diarrhœa.* As this center governs the caliber of the arterioles, its inhibition causes relaxation of all these terminal vessels and flooding of all the organs they supply.* The bulk of the blood of the body being accumulated in the greater central vessels, *i.e.*, those of the splanchnic area, however, as stated above, the effects of the sympathetic paresis become manifest only in the organs adjoining the congested region, and the vessels of which are themselves engorged through this contiguity.* As the vessels of the intestines form part of the engorged splanchnic area,

* *Author's conclusion.*
[22] Bosc: Annales de l'Inst. Pasteur, vol. ix, p. 507, 1895.

their mucous membrane becomes markedly hyperæmic and the arterioles of its secreting elements being widely dilated and relaxed, the blood-serum, which forms the liquid portion of their secretion, and sometimes pure blood literally pour into the intestinal canal, forming the serous diarrhœa.* Mixed with the discharge are rice-like masses composed of desquamated epithelium, comma bacilli and leucocytes.

Other symptoms are due to the relaxation of the arterioles, viz.: the cold sweats which occur before the blood has lost much of its serum; the abdominal muscular cramps, owing to the admission of an excess of blood-plasma and adrenoxidase into the muscular elements; the hiccough due to a similar condition of the diaphragmatic muscles; and the vomiting, partly caused by the accumulation, in the stomach, of serous fluids similar to those eliminated by the intestines.*

In the first volume[23] I showed by means of a chart that the nine cardinal symptoms of cholera were identical to those that follow removal of both adrenals in mammals. This coincidences, however, only with the corresponding, *i.e.*, the advanced stage of the disease, when the functions of the adrenals are paralyzed. Indeed, the violence of the morbid phenomena and the rapidity with which they lead to a fatal issue in some cases indicate, however, that other general centers are primarily assailed by the poison. This rapid course cannot be due to primary paresis of the adrenal center, since the disease would not in that case cause death in a few hours, or even a few minutes, as observed in some instances. Though Strehl and Weiss[24] and others have found that compression of the adrenal veins—thereby arresting the supply of adrenal secretion—caused an immediate fall of the blood-pressure, etc., it is nevertheless true that the circulation of the adrenals is not arrested even by paralysis of the adrenal center, and that the mere passage of blood through the adrenals is sufficient to sustain for some time, though inadequately, the vital process. We will see farther on, however, that arrest of the adrenal circulation finally does occur, and that this entails death.

That the vasomotor center is primarily paralyzed is shown by the early pallor, which occurs coincidently with the peripheral hypothermia and the central hyperthermia—the skin being cold while the rectal temperature is 104° F. (40° C.) or over. This points to accumulation of the blood in the great central trunks, the splanchnic area, and its normal consequence, depletion of the peripheral capillaries. This interpretation meets the teachings of experimental evidence, for Pfeiffer,[25] basing his opinion on the effects of dead bacilli on guinea-pigs, concluded that the poisons liberated acted as paralyzants to the centers governing the circulation and the temperature. It accounts also for various paradoxical phenomena that prevailing conceptions fail to elucidate. Thus Stiller,[26] during the Hamburg epidemic of 1892, observed the disappear-

* *Author's conclusion.*
[23] *Cf.* vol. i, p. 773, in the first two editions.
[24] Strehl and Weiss: Arch. f. d. ges. Physiol., Bd. lxviii, S. 107, 1901.
[25] Pfeiffer: Zeit. f. Hyg. u. Infekts., Bd. xvi, S. 268, 1894.
[26] Stiller: Berl. klin. Woch., Bd. xxx, S. 181, 1893.

ance of a splenic swelling in each of three cases of typhoid fever when the patients were also attacked by cholera. Obviously, the splenic swelling was due to engorgement incident upon the fever, the deeper vessels being intensely contracted; as soon as the cholera poison depressed the vasomotor center and caused relaxation of these deeper vessels, the spleen was depleted; there was a simultaneous fall of the peripheral temperature to 95° F. (35° C.), and the organ resumed its normal volume. So plain also is the depletion of the peripheral vessels, that Klebs[27] was led to conclude that contraction of the arteries was a pathogenic sign of cholera.

Conversely, as observed by Simmonds[28] in 300 autopsies at the Hamburg Hospital, there was hyperæmia of the intestinal serous membrane; so great is the engorgement of the intestinal structures at times, that blood is mixed with the glandular exudation, as noted by Gamaleia.[29] Indeed, as is well known, the passages are sometimes bloody. The large intestine is also, as stated by Rubino,[30] "extremely hyperæmic." It is not due to a direct action of the bacilli or their toxins on the intestine, since the local lesions are most pronounced late in the disease. Nor is the congestion restricted to the intestine. Rusi[31] found microscopically marked engorgement of the vessels of the female genital organs with extravasation. The cause of this is plain when we take into account the result of the vasomotor paresis, *i.e.*, accumulation of blood in the deep vessels, and particularly those of the splanchnic area.

The vasomotor paresis does not account, however, for the serous diarrhœa. We have seen that a number of familiar drugs, veratrum viride, chloral, the bromides, etc., also depress the functional activity of the vasomotor center.* In toxic doses they also cause marked peripheral hypothermia, a high central temperature, etc.—symptoms similar to those just described. Yet none of these drugs, even in toxic doses, cause the serous diarrhœa or flux; the cholera endotoxin must, therefore, provoke this symptom in another way. It cannot be ascribed to irritation of the intestinal canal by the specific microörganism; for, as we have seen, the normal stools of individuals in good health can contain virulent cholera vibrios, though no signs of the disease appear. Moreover, as shown by Denys and Sluys,[32] the comma bacillus does not alter the intestinal mucous membrane. Cholera occurring, as pointed out above, only when the immunizing properties of the digestive leucocytes and blood are deficient, and when the endotoxin of the dead germs is diffused in the blood, the flux can only be due to paresis of the center which governs the flow of plasma into the intestinal secretory elements. As the arterioles are the vessels which supply these structures with blood, the nerve-center paralyzed is the general sympathetic center. That the blood-serum should, under these conditions, flow in such quantities as practically to deplete the whole body (as shown by the shrunken condition of the latter after death) is self-evident.

Inhibition of the general vasomotor and sympathetic centers is not, however, the immediate cause of death. This is due to the fact that the loss of serum gradually causes the blood to become too viscid to circulate in the capillaries, and particularly, owing to their extreme minuteness, in those of the adrenals.

* *Author's conclusion.*
[27] Klebs: Cited by Stiller: *Ibid.*
[28] Simmonds: Münch. med. Woch., Bd. xxxix, S. 845, 1892.
[29] Gamaleia: C. r. de la Soc. de biol., 9 série, vol. iv, p. 739, 1892.
[30] Rubino: *Loc. cit.*
[31] Rusi: Russ. Zeit. f. Geburtsh. u. Gynäk., Bd. vii, Hft. i, 1904.
[32] Denys and Sluys: La cellule, Brussels, vol. x, No. 1, 1894.

(See colored plate opposite page 32, Vol. I.)* Hence the insatiable thirst, and the shrinking of the body as the loss of fluid increases; and, owing to gradual cessation of adrenal functions, the algidity, the cyanosis, the darkness of the blood,* and the steady decline of all vital functions, which finally cease when the physical conditions of the blood are such that the latter can no longer carry on its functions. The main cause of death which asserts itself, therefore, is the *viscidity of the plasma, which prevents its circulation in the capillaries, including those of the pituitary and adrenals.**

That it is simply to the lack of plasma, including of course its salts, that these symptoms are due, is shown not only by the highly beneficial influence of intravenous injections of saline solution, but also by the excretions and the condition of the blood. While Rubino[33] states that sodium chloride is included in the salts found in the rice-water stools, Carrieu[34] found the urine poor in chlorides during convalescence, thus showing a loss during the disease. Gradually as the patients improved the chlorides were found to increase. Moxon[35] found the blood in the great vessels and heart "remarkably viscid and tarry." Renvers[36] also found the tissues very dry and the blood greatly thickened. That such a condition of the blood should paralyze function is self-evident. As to the adrenals, as long as the blood can circulate freely through them, some secretion is produced—even though the adrenal center be paralyzed—as it does when the gland is grafted into an animal from which the adrenals have been removed. Gradually as the blood thickens, however, the minuteness of the intrinsic vessels of these organs causes the circulation through them to become increasingly difficult, until their secretion, the *pabulum vitæ*, is no longer produced, when life ceases.

Treatment.—The primary effect of the cholera endotoxin being to depress the functions of the body's protective mechanism, the adrenal system, the most powerful of drugs must be employed to prevent this action, viz., mercury.* *Calomel* has, in fact, given excellent results.

Surgeon-General Francis[37] states, referring to calomel, recommended by Ayres, of Hull, that Dr. Alderson in 1867 wrote to the Lancet, pointing out that statistics showed it to be the best, and that his own experience (1865) has sustained this conclusion, his mortality being 15 to 20 per cent. lower than that of his colleagues who depended upon astringents and alcohol. Calomel was also found very beneficial by Lieut. Col. F. W. A. de Fabeck of the Indian Medical Service. F. Peyre Porcher[38] recalled, at the time of the Hamburg epidemic, the treatment recommended by Calhoun also many years before, which, he says, though heroic, "obtained far superior results to those reported as

* *Author's conclusion.*
[33] Rubino: *Loc. cit.*
[34] Carrieu: Nouveau Montpelier méd., vol. ii, pp. 788, 825, 1893.
[35] Moxon: Fagge's "Pract. of Med.," vol. i, p. 313, 1886.
[36] Renvers: Deut. med. Woch., Bd. xx, S. 52, 1894.
[37] Francis: Med. Press and Circular, Sept. 23, 1896.
[38] F. Peyre Porcher: Med. Record, Nov. 26, 1892.

far as the proportion of cured cases is concerned." The method was "calomel, 10 grains (0.6 gm.); gum camphor and tannin, each 5 grains (0.3 gm.) every half-hour or hour, as the urgency of the symptoms demanded, until the diarrhœa was checked and the secretions were restored to a healthy state." Pasalsky[39] found, however, that the tannin was useless without the calomel, and gave 10-grain (0.6 gm.) doses hourly for a few hours. Porcher used the calomel alone and astringent injections, plus mustard, to abdomen and extremities, and he states that by pursuing this plan in the premonitory stage, he did not lose a single patient. Van Hasselt[40] treated 51 cases with but fifteen deaths. He advised the immediate use of calomel, not forgetting to give hydrochloric acid at the same time. The calomel is mixed with a little water and gum powder, placing the mixture on the tongue, thus avoiding touching the teeth. The first dose is 1 gram (15 gr.) repeated several times. Even in convalescence 0.01 gram ($^1/_6$ gr.) is given hourly. Leyden[41] ascribed the better results obtained during the last Hamburg epidemic in part to the use of calomel. Many other clinicians have spoken in the same vein.

Administered by the mouth, however, especially when the serous diarrhœa has begun, the drug is greatly exposed to being washed down the intestinal canal and thus fail to be absorbed. The effects would be rendered far more certain and prompt* by giving the *biniodide of mercury* intravenously, the quantity administered being at least $^1/_2$ grain (0.03 gm.) frequently repeated, until the stools become greenish, *i.e.*, bile-stained.* Dissolved in thirty drops of warm, sterilized water, this quantity can be injected into the veins at the bend of the elbow without causing the least pain, while reaching the test-organ within a minute.*

The fact that calomel administered by the mouth proves ineffective—for the reason suggested in the general text—has caused its use to be abandoned by many practitioners. Thus Surgeon-General Francis[42] states that "many practitioners condemn it," on the plea that "the drug lies inert in the intestine." The mode of using mercury recommended above is used in the treatment of syphilis. Of various salts of mercury used intravenously in this disease in the course of 408 injections, the biniodide was found, better than any, to meet the conditions of this procedure: perfect solubility; failing to coagulate albumin; ready sterilizability; painlessness, and rapidity of action.

Mercury not only counteracts the paralyzing influence of the cholera bacillus endotoxin on the test-organ, but it increases its functional activity, thus causing an accumulation of autoantitoxin in the blood.* The cholera bacillus being easily destroyed by the immunizing constituents of the blood, the infec-

* *Author's conclusion.*
[39] Pasalsky: St. Peters. Inaug. Dis., No. 24, p. 55, 1892-93; Provincial Med. Jour., Nov. 1, 1893.
[40] Van Hasselt: Sajous's "Annual of the Univ. Med. Sci.," vol. i, D. 26, 1894.
[41] Leyden: Deut. med. Woch., Bd. xx, S. 37, 1894.
[42] Francis: *Loc. cit.*