

de Renzi,¹²⁸ Galippe¹²⁹ and others found that the local application of mercurial preparations cured stomatitis due to ingested mercury. Nemser¹³⁰ ascertained experimentally, through gastric fistulæ, that the gastric juices had little or no effect on calomel, even when the salt was left in the stomach over an hour.

MERCURIALISM.—When the therapeutic use of mercury is injudiciously prolonged and in subjects who are exposed by their occupations to the continuous absorption of this metal, another order of phenomena is introduced, *i.e.*, those due to chronic poisoning—another manifestation of uncontrolled metabolism.*

The earliest symptoms of this condition include a metallic taste, soreness and swelling of the gums, a bluish-red or gray color along the peridental sulci and the fœtid breath which mark the onset of *active* mercurialism. Unless the use of the drug ceases, the destructive process extends downward and around the teeth, causing these to fall out; gangrene of the gums and jaws, and hæmorrhages may then ensue. The tongue, the entire mucosa of the mouth, especially where it overlies considerable soft tissue, *i.e.*, the cheeks and lips, undergo a similar destructive process. If the use of the drug be persisted in, death may follow from exhaustion and inanition. If its use be stopped when the ulcerative process has penetrated the cheeks, the patient remains scarred and disfigured.

Gastro-intestinal disorders, anorexia, nausea, vomiting, gastric pain, colic, diarrhœa alternating with constipation, and intestinal ulceration similar to that observed in the mouth are also observed. Marked anæmia and pallor, emaciation and great muscular weakness occur, even though gastro-intestinal disorders be mild, and death may ensue.

All these phenomena are due to excessive oxygenation and to the proteolytic activity of the blood's auto-antitoxin.* They are especially marked where the epithelium of the gums is destroyed by the contact of "tartar," carious teeth, etc., and the underlying elements are exposed to the air.* The adrenoxidase being greatly in excess in all tissues, the air furnishes

* Author's conclusion.

¹²⁸ de Renzi: *Revista clinica e therap.*; Physician and Surgeon, Apr., 1889.

¹²⁹ Galippe: *Jour. des Conn. Médic.*, pp. 188, 195, 203, 1890.

¹³⁰ Nemser: *Zeit. f. physiol. Chemie*, Sept. 6, 1906.

an endless quantity of oxygen to its catalytic agent, *i.e.*, the adrenal principle, and the gums and other tissues are destroyed through a local digestive process.*

The destructive process is very active in the blood, owing to the presence of adrenoxidase in the plasma, and of the red corpuscles, which deal out adrenoxidase as fast as needed to sustain the morbid process.* Both the red corpuscles and the leucocytes are actively digested, and the general nutrition is correspondingly impaired. The broken-down cells, etc., being no longer converted into eliminable products, they form the fatty, fœtid substance found in the vessels after death.

That the proteolytic, *i.e.*, digestive activity of the blood, is greatly increased by mercury has been sufficiently emphasized by the evidence already submitted. The morbid effects are evidently not due to a local action of the drug, since it is most likely to occur when it is given by inunction. The rôle of adrenoxidase in the morbid process is also shown by the pernicious influence of concomitantly-given adrenalin, emphasized by Moulinier.¹³¹

The oxidizing action of the blood-fluids on mercury has been repeatedly noticed by investigators. It has, in fact, been considered a necessary factor of its combination with the albumins of the tissues, into which, we have seen, it is secreted by the leucocytes after being submitted to the action of the ferments—including adrenoxidase—in these cells. Thus, Hermann¹³² states that "we must suppose some supplementary oxidation as a result of the tissue juices."¹³³ Cushny¹³⁴ also states that "even the metal may be oxidized and absorbed when it is applied to the living surfaces or injected into the blood in a state of fine division."

That the destructive action cannot be a local one is shown by the smallness of the dose that is capable of producing it, along with general phenomena. Thus Lewin¹³⁵ reported the case of a man who, after a subcutaneous injection of $\frac{1}{4}$ grain (0.016 gm.) of salicylate of mercury, had stomatitis, with ulceration, together with acute nephritis (anuria and albuminuria). The temperature rose to 40° C. (104° F.) and death was barely averted. The biniodide employed in intra-uterine injections, 1 to 3000 solution, caused acute mercurial poisoning in a case of Young's.¹³⁶ Inunctions of the gray ointment are particularly dangerous in this connection. Out of 630 cases in which mercurial ointment was used by the medical officer of a workhouse in Belgium¹³⁷ to rid the inmates of vermin, 50 were made very ill, one case proving fatal, although the quantity used was but a trifle more than a drachm (4 gms.). Kraus¹³⁸ observed a case in which, after the second hypodermic injection of 0.1 gm. ($\frac{1}{2}$ grains) of calomel, intense intestinal symptoms accompanied by perforation and anuria, occurred. Repeated 1-grain (0.065 gm.) doses of calomel used hypodermically, caused death

* Author's conclusion.

¹³¹ Moulinier: *Loc. cit.*

¹³² Hermann: *Loc. cit.*

¹³³ Manquat: *Loc. cit.*, vol. i, p. 171, 1903.

¹³⁴ Cushny: *Loc. cit.*, third edition, p. 639, 1899.

¹³⁵ Lewin: *Deut. med. Woch.*, vol. xix, p. 922, 1893.

¹³⁶ Young: *Brit. Med. Jour.*, June 13, 1903.

¹³⁷ *Lancet*: Nov. 26, 1898.

¹³⁸ Kraus: *Deut. med. Woch.*, Bd. xiv, S. 227, 1888.

in a case observed by Runeberg.¹³⁹ The old and feeble are especially vulnerable to the toxic action of mercury.

In the blood it is not the albuminate of mercury that does the harm, but as stated, the excess of auto-antitoxin which provokes hæmolytic. That hæmolytic affecting both the leucocytes and red corpuscles occurs under the influence of toxic doses of mercury was observed experimentally by Detre and Sellei¹⁴⁰ and others. Again, "the blood suffers very decidedly," says Wood,¹⁴¹ "becoming more fluid and watery than normal." "According to the researches of Wright," continues the author, "its solid constituents are notably diminished, including albumin, fibrin and the red corpuscles, and it contains a large quantity of fetid, fatty material."

NERVOUS DISORDERS.—The exaggerated proteolytic activity of the plasma, besides reducing the proportion of the blood's corpuscles, entails an untimely consumption of granulations secreted by the leucocytes, including those supplied to the neurons and the myelin throughout the entire nervous system, and to the muscular elements.* The interference with nutrition thus caused may be followed by muscular weakness, or by some form of paralysis or shaking palsy when the destructive action becomes marked. In individuals whose occupation exposes them to the constant absorption of the metal, the latter may occur before other symptoms of mercurialism, even stomatitis, appear. The muscles of the upper and lower extremities, then those of the face and tongue, are successively involved until the patient's every movement is carried out tremblingly.

The brain being likewise imperfectly nourished,* vertigo, hallucinations, insomnia and headache, and in some cases convulsions, owing to accumulation of toxic wastes, are observed. The mental phenomena are peculiar: the patient is abnormally irritable, timid and morose, melancholia ultimately developing in some instances. The senses are more or less influenced; anosmia, amblyopia and deafness being sometimes noted. Pains in the muscles, along the nerves and in the joints, and areas of anæsthesia are to be found in practically every case.

The observation of Wright, that the blood's solid constituents are notably diminished, including albumin, fibrin and the red corpuscles, has been confirmed in animals by Wilbouchewitch¹⁴² and Hughes Bennett.¹⁴³ "Fibrin" here is obviously fibrinogen—the absence of which accounts for the fluidity of the blood and the predisposition to hæmor-

* Author's conclusion.

¹³⁹ Runeberg: *Ibid.*, Bd. xv, S. 4, 1889.

¹⁴⁰ Detre and Sellei: *Berl. klin. Woch.*, July 25, 1904.

¹⁴¹ Wood: *Loc. cit.*, thirteenth edition, p. 485, 1906.

¹⁴² Wilbouchewitch: *Archives de physiol. norm. et path.*, Sept., 1874.

¹⁴³ Hughes Bennett: Wood, *Loc. cit.*, thirteenth edition, p. 485, 1906.

rhages noted in mercurialism. Wood¹⁴⁴ says, for instance, that "in these cases passive hæmorrhages often recur again and again, and may contribute largely to a fatal issue."

Charcot¹⁴⁵ considered trembling palsy as typical of hydrargyrism among the toxæmias of metallic origin. That, in addition to the hæmolytic previously referred to, the destruction of myelin also occurs, was emphasized by Letulle,¹⁴⁶ who noted absence of the sheath composed of this substance in the peripheral nerves. As it is to the reaction between the phosphorus-laden myelin and the oxygen-laden adrenoxidase of the axis-cylinder that, as I have pointed out, the formation of nerve energy is due, their functions are necessarily impaired. The axis-cylinder was found unharmed, however, by this investigator—a normal result, since, as I have shown, it contains only adrenoxidase-laden plasma. The other constituents of auto-antitoxin being absent, the adrenoxidase is harmless.

Acute Poisoning.—This is usually due to the ingestion of corrosive sublimate. When a large toxic dose of the salt has been taken, the first symptoms are usually localized in the tissues over which the poison passes, these being the seat of marked irritation or corrosion. A sharp metallic taste, a burning sensation in the mouth, pharynx, œsophagus and stomach, nausea and vomiting follow one another in more or less rapid succession, the vomited matter often containing blood. There is also violent diarrhœa with tenesmus, the stools containing shreds of mucous membrane and blood, accompanied by severe pain in the stomach and abdomen.

Sooner or later the symptoms of general poisoning appear: there is great prostration, the pulse is soft, small, rapid, and perhaps irregular, the respiration is shallow and rapid, the skin grows cold and clammy, there is almost complete anuria, the temperature is subnormal, and the patient passes rapidly into coma, dying sometimes within an hour. This constitutes the symptom-complex of excessive activity of the adrenal system and of the intense vasoconstriction (due to hypermetabolism in the vessel walls, especially the muscularis) which results. The caliber of the vessels which admit blood into the pituitary, thyroid and heart being greatly reduced, the functions of these organs are inhibited, and the vital process is arrested.*

When the quantity ingested is not very large, the gastrointestinal symptoms occur, but the prostration fails to lapse into coma, the constriction of the arterioles being inadequate

* Author's conclusion.

¹⁴⁴ Wood: *Loc. cit.*, thirteenth edition, p. 485, 1906.

¹⁴⁵ Charcot: *Médecine méd.*, p. 292, 1892.

¹⁴⁶ Letulle: *Arch. de physiol. norm. et path.*, Apr., 1887.

to arrest the vital functions. Within a period varying from one to twenty-four hours, therefore, the symptoms described under "Mercurialism" appear, including, in some cases, marked trembling. The renal symptoms are very marked, and suppression of urine may begin within a few hours (owing now to acute nephritis, in which the convoluted tubules are mainly involved) and persist to the end. In most instances the anuria disappears within twenty-four hours, but the urine is then found to contain, if the intoxication be sufficiently severe, hyaline and epithelial casts and more or less albumin. The salivation, stomatitis and glossitis are no less marked than in mercurialism. The convalescence may last several weeks, during which the patient may lose several teeth, a large quantity of hair and become considerably emaciated.

When the poison is introduced into the system through wounds, with the dressings, or through mucous surfaces, the vagina or rectum, by injections, the gastro-intestinal disorders appear nevertheless, but later in the history of the case, and generally along with the renal symptoms.

The corrosive action of bichloride of mercury, especially on mucous membranes, is well known. Even the skin may succumb to it. "When very strong solutions come in contact with tender parts of the skin," says Cushny,¹⁴⁷ "and in particular, when the salt itself is allowed to lie in contact with it for any length of time, deep corrosion, necrosis and sloughing may follow."

The process through which the other symptoms described are produced is similar to that which prevails in "mercurialism."

This identical corrosive action is that which causes the bichloride to act with greater violence than the other salts of mercury, as a toxic. Being transmitted to the test-organ by leucocytes, it is probable that it reaches this organ but slightly, if at all, modified by the auto-antitoxin in these cells, since, as observed by Stassano,¹⁴⁸ the sublimate in leucocytes derived from the blood of dogs poisoned with this salt, can be converted into the red iodide by appropriate treatment. Again, though as stated by Carles¹⁴⁹ notwithstanding the "marked resistance to the action of poisons which kill all other cells," they are themselves killed or weakened under the influence of very active poisons. In acute poisoning, therefore, the sudden invasion of the blood by the toxic endows it with almost as active irritating properties as the toxic itself. Such blood is no longer, like the albuminate, an inert agent, and its action on the adreno-thyroid center being active in proportion, so great a volume of auto-antitoxin accumulates in the blood that the vascular disorders described in the general text are produced. Hence the intense capillary hyperæmia observed in various organs, and the erythema, dermatitis, œdematous swellings, etc., to which mercurialization gives rise.

¹⁴⁷ Cushny: *Loc. cit.*, p. 643.

¹⁴⁸ Stassano: *Loc. cit.*

¹⁴⁹ Carles: *Loc. cit.*, p. 85.

The treatment of poisoning by mercury is described in a special section at the end of this volume.

Therapeutics.—The beneficial effects of mercury are obtained with doses which increase sufficiently the auto-antitoxin of the blood to destroy the cause of the disease, whether it be a microorganism and its toxins or endotoxins, toxic waste products, etc.* When this limit is exceeded, mercury is a poison: it raises the functional activity of the adrenal center to such a pitch that the body's auto-protective system is converted into an auto-destructive system.*

In *syphilis*, a disease in which, owing to the mode of infection, the adrenal system is for a time inactive,* each case requires a given quantity to excite the test-organ, and this quantity must be carefully adjusted to the needs of the condition present, the object being to raise the immunizing potential of the blood to the degree required to destroy the pathogenic elements, but not beyond.*

Mercury has been used in syphilis by some clinicians on the general principle that the quantity introduced into the system would antagonize a correspondingly active morbid process.* Being a formidable malady, it is thought that "a greater impression is made on the disease"—using the words of a recent writer—when large quantities are administered by inunctions, subcutaneously, etc. As will be shown, this is quite unnecessary and may prove very harmful.

Owing to the external use of mercurial preparations as antiseptics, the belief that they might act similarly in *biliousness*, *gastro-enteritis*, *summer diarrhœa*, etc., has caused them to be tried, and, in many instances, with gratifying results. These should not be attributed to a direct action of the preparations used, but to their influence on the test-organ, and to the bacteriolytic and antitoxic action of the blood's auto-antitoxin, the production of which they promote.* By enhancing metabolism, small doses have likewise proven valuable in *anæmia*, *sthenic inflammation*, and kindred disorders.

This is well shown in the condition known as "*biliousness*," due to hypometabolism of physiological toxic wastes; 10 grains (0.66 gm.) of blue mass, followed by a saline aperient to remove any excess of the drug in the intestine, promptly corrects this disorder by stimulating the body's auto-protective mechanism. Such a large dose is not needed, however, to insure this action: $\frac{1}{10}$ grain (0.0065 gm.) of calomel with a little soda bicarbonate every hour, five times, will act as efficiently, since a minute dose suffices to excite the test-organ. If flushing of the

* Author's conclusion.

intestine is desired, *i.e.*, a copious flow of antitoxic intestinal juice in addition to the hepatic action, larger doses: $\frac{1}{8}$ to $\frac{1}{2}$ grain (0.01 to 0.03 gm.) every 15 or 30 minutes until 1 or 2 grains (0.065 to 0.1 gm.) are taken, may be ordered. In the *gastro-enteritis* due to the presence of fermentative toxic products of digestion $\frac{1}{50}$ to $\frac{1}{60}$ grain (0.0013 to 0.001 gm.) doses of the yellow oxide in sugar of milk, or in the *summer diarrhoea* $\frac{1}{500}$ grain (0.00013 gm.) of the bichloride every hour in solution until relief is obtained, are very effective through a similar process. In *gastric irritation* from the same cause, or where there is also *vomiting*, either in adults or children, $\frac{1}{100}$ grain (0.00065 gm.) of the bichloride is often curative given every hour five times, then at longer intervals; provided, of course, dietetic errors be corrected. In *gastric ulcer* $\frac{1}{60}$ to $\frac{1}{30}$ of the bichloride before meals promotes cicatrization of the ulcers.

To increase the nutrition in *asthma*, especially in children in whom the stools are pasty and ill-smelling, $\frac{1}{60}$ grain (0.001 gm.) given every hour five times, and repeated at one week's interval, is very beneficial. The powder may be mixed with a little sugar and applied to the tongue. In *anemia* $\frac{1}{60}$ to $\frac{1}{40}$ grain (0.001 to 0.0016 gm.) of the bichloride three times daily is of recognized value. Mercurials were long in favor to counteract *sthenic inflammation*, but, except in iritis due to syphilis, are now seldom employed. The use of excessive doses accounts for this fact, very small doses alone being indicated.

The bacteriolytic and antitoxic activity which the blood and the intestinal juices acquire under the influence of mercurials, accounts for the beneficial effects observed in various infectious diseases, *typhoid fever*, *diphtheria*, *acute tonsillitis*, *puerperal septicæmia*, *etc.*

In *typhoid fever* German practitioners give 10 grains (0.66 gm.) of calomel daily for three days. Others have also found that small doses, $\frac{1}{10}$ grain (0.0065 gm.), four times in the twenty-four hours diminished considerably the intensity of the disease and its duration. The Germans regard the drug as an antipyretic, owing to the effects observed. In the light of my views the reduction of the temperature is due to the fact that the pathogenic organisms and their toxins are greatly reduced through the increased activity of all immunizing processes. Among others, Rondot¹⁵⁰ observed a decided shortening of the disease in 21 cases, and diminution of the severity of the symptoms by the use of $\frac{1}{12}$ grain (0.005 gm.) of bichloride daily, divided in very small doses given at short intervals.

Ackley¹⁵¹ found that a mixture of $\frac{1}{12}$ to $\frac{1}{10}$ grain (0.005 to 0.0065 gm.) of the biniodide and 10 grains (0.66 gm.) of saccharated pepsin every six hours checked the marked symptoms and greatly shortened the duration of the disease.

Before antitoxin—which should always be given the preference when available—was introduced, one of the most effective agents in *diphtheria* was calomel in large doses. The cyanide, $\frac{1}{100}$ to $\frac{1}{30}$ grain (0.00065 to 0.0013 gm.), every hour, or the bichloride, $\frac{1}{40}$ to $\frac{1}{10}$ grain (0.0016 to 0.0065 gm.), can be given one or two days, even to children, with less danger of causing salivation. The simultaneous use of depressing drugs should be avoided.

¹⁵⁰ Rondot: Gaz. heb. des Sci. méd.; Boston Med. and Surg. Jour., Feb. 23, 1888.

¹⁵¹ Ackley: Pittsburgh Med. Rev., June, 1890.

Daly¹⁵² recommended Reiter's method: 2 to 5 grains (0.13 to 0.3 gm.) of calomel every hour until the stools acquire a greenish hue, when the intervals are lengthened. Selldén¹⁵³ reported 1400 cases treated by colleagues and himself with the cyanide of mercury, in which the mortality was only 4.9 per cent. A teaspoonful of a 1 in 10,000 solution was given every half to one hour, according to the age of the child. The importance of avoiding other drugs is that various agents that have been tried in diphtheria tend to depress the protective functions.

Among other disorders distinctly influenced by mercurials owing to the increase of immunizing substances their use provokes, are *acute tonsillitis*, *puerperal septicæmia*, the *exanthemata* of childhood, and *cerebro-spinal meningitis*.

IODINE AND THE IODIDES.

Physiological Action.—Iodine and its preparations, in whatever way administered, are taken up by the leucocytes, and it is through the intermediary of these cells that they—or rather the substances into which the leucocytes convert them—penetrate into the circulation. The thyroid and parathyroid glands being the organs which utilize iodine for the elaboration of their secretion, thyroidase, all the iodine ingested with foods is distributed to these glands. When iodine or its preparations are administered, however, these organs do not necessarily utilize the quantity ingested; as iodine is one of the substances which the body stores for future use, they admit only enough blood (and, therefore, iodine-laden leucocytes) to supply their momentary need.*¹⁵⁴ As a result, the thyroidase cannot become overrich in iodine; its sensitizing influence on all the cellular elements of the body, including those of the pituitary, and its stimulating action on the test-organ of the latter are always the same under normal conditions.* If from any cause, however, the food fails to supply enough iodine to satisfy the needs of the thyroid apparatus, therapeutic doses of this halogen prove beneficial through this apparatus, by enabling it to restore to the blood what proportion of thyroidase it may be lacking.*

The main therapeutic action of iodine and its preparations, however, is of another kind. It is due to the direct action of the iodine compound (secreted by the leucocytes

* Author's conclusion.

¹⁵² Daly: "Trans. Amer. Laryn. Assoc.," vol. viii, p. 73, 1886.

¹⁵³ Selldén: Wiener med. Presse, Bd. xxix, S. 522, 1888.

¹⁵⁴ Cf. this vol., p. 1087 *et seq.*

which have failed to be admitted in the thyroid and parathyroid) upon the test-organ and stimulation of the latter.* As this causes overactivity of the adrenals and a corresponding increase of adrenoxidase in the blood, general metabolism becomes more active. As a result, nutrition is improved, the processes of repair are hastened, and the bacteriolytic and anti-toxic powers of the blood are greatly enhanced.*

Therapeutic doses of iodine, or its salts, do not cause emaciation, and do not influence either the blood-pressure or the pulse.

The manner in which iodine is taken up by the leucocytes in the intestinal canal and the blood; the relationship between these cells and the thyroid apparatus, and, finally, the mode of action of the iodine-laden secretion of the latter on the test-organ, were treated in the preceding chapter.

As to the influence of iodine upon metabolism, Nothnagel and Rossbach,¹⁵⁵ alluding to the effects of the iodides on nutrition, write: "During a certain period the conviction that iodine and potassium iodide produced emaciation was such that all the theories on the mode of action of iodine were based on that idea. But this view has been actively combatted (Ricord, Boinet, Wunderlich), and it was finally concluded that K I not only did not cause emaciation, but that, conversely, it caused fattening." In truth, both views are sound. As stated by Manquat:¹⁵⁶ "Emaciation is an inconstant symptom, it is true, but it is often witnessed, especially with larger doses than 2 gms. (30 grains) daily. With very small doses (0.25 gm.—4 grains) it is not only not to be feared, but there occurs greater activity of the circulation, and secondarily of the nutrition, particularly of the myocardium." In other words, large doses produce emaciation and small doses enhance nutrition. This corresponds with the apparently contradictory results as to the excretion of nitrogenous and other wastes: While Rabuteau, Milanese and Bouchard,¹⁵⁷ Henrijean and Corin,¹⁵⁸ and others, noted an increase of nitrogen output, Handfield Jones,¹⁵⁹ in a series of six cases, noted an increase in only three patients, while the other three showed a decrease—all taking large doses of potassium iodide.

All these discordant observations assume a normal aspect in the light of my views: when the doses are small the test-organ is stimulated just enough to enhance nutrition, while large doses, by stimulating it too actively, excite hypermetabolism, *i.e.*, excessive consumption of tissue elements and wasting. That such is the case is further shown by the fact referred to by Wood¹⁶⁰ and Cushny,¹⁶¹ that iodine sometimes causes fever.

* Author's conclusion.

¹⁵⁵ Nothnagel and Rossbach: "Mat. médicale et thérap.," sixth edition, p. 270, 1889.

¹⁵⁶ Manquat: "Thérapeutique," vol. ii, p. 100, 1903.

¹⁵⁷ Bouchard: C. r. de la Soc. de biol., pp. 227, 237, 1873.

¹⁵⁸ Henrijean and Corin: Arch. de Pharmacodyn., T. ii, 1896.

¹⁵⁹ Handfield Jones: Beale's Arch., vol. i, cited by Wood: "Therapeutics," thirteenth edition, p. 502, 1906.

¹⁶⁰ Wood: "Therapeutics," thirteenth edition, p. 499, 1906.

¹⁶¹ Cushny: "Pharmacol. and Therap.," fourth edition, p. 514, 1906.

"Though we ascribe to it alterative virtues," says Griffin,¹⁶² "we are thereby not much nearer an understanding of its action, though some pronounced action over nutrition and its disorders it certainly does possess."

As hypermetabolism involves the presence in the blood of an excess of auto-antitoxin, the blood's bacteriolytic and antitoxic efficiency is increased in proportion. It is likewise richer in phagocytes, as shown by Heinz¹⁶³ and Schleich.¹⁶⁴ So active, in fact, can the blood become as an immunizing agent that excessive doses can provoke hæmolysis. Thus Henrijean and Corin found that 1 gm. (15 grains) of sodium iodide reduced the red corpuscles from 6,250,000 to 4,125,000 in the rabbit, in twenty-four hours. Heile also observed that iodoform caused autolysis.

Therapeutic doses of iodine or of its preparations do not influence the blood-pressure or the pulse. Stockman and Charteris¹⁶⁵ state that, although ordinary doses of sodium or potassium iodide cause no change in the strength or rapidity of the pulse, "reference to text-books on pharmacology and therapeutics shows that most authors attribute to the iodides a depressing effect on the circulation and blood-pressure, while only a minority hold that there is no adequate proof of this." Using von Basch's sphygmomanometer and Gärtner's tonometer, they studied the blood-tension and pulse-rate of numerous patients who, for one reason or another, were taking potassium or sodium iodide. Although the doses taken ranged from 15 to 180 grains (1 to 12 gms.)—one, in fact, 300 grains (20 gms.)—daily, "in no case did any fall in the blood-pressure occur, or any change in the rhythm of the heart." Similar researches were undertaken by James Burnet¹⁶⁶ in a variety of cases, including aneurism, arteriosclerosis, angina pectoris, asthma and tertiary syphilis, potassium iodide being given by the mouth. He observed "no effect whatever, either upon the pulse-rate or blood-pressure within the arteries." The hypodermic use of iodipin was also studied. "In no case," says the author, "was the blood-pressure altered; nor was the heart's rate or rhythm affected. Especially, I found that the heart's action was never increased nor depressed, and that the pressure within the radial artery, when markedly high to begin with, was never lowered, even after a prolonged use of the iodipin injections. Still, all the same, I had good results in nearly all my cases."

Iodine and its preparations not only do not, as shown above, cause vasodilation either in large or small doses, but they provoke constriction of all vessels, arteries and veins, because these vessels are supplied with a muscular coat, and owing to the excessive metabolism which they incite indirectly in this, the contractile layer of these vessels.* This morbid phenomenon is aggravated by another factor: the presence in the blood of sufficient iodine to irritate the intima, a feature which, in itself, tends to promote constriction in vessels supplied with vasomotor nerves. What has been mistaken for general vasodilation is dilation of the capillaries.* These

* Author's conclusion.

¹⁶² Griffin: Foster's "Therapeutics," vol. i, p. 535.

¹⁶³ Heinz: Virchow's Archiv, Bd. clv, S. 44, 1899.

¹⁶⁴ Schleich: Cited by Manquat: *Loc. cit.*, p. 101.

¹⁶⁵ Stockman and Charteris: Brit. Med. Jour., Nov. 23, 1901.

¹⁶⁶ James Burnet: Medical Mag., June, July, 1906.

delicate vessels not being supplied with a muscular coat or vasomotor nerves, are not morbidly influenced as are the others,* but they suffer indirectly: the arteries and veins, by contracting inordinately, drive the blood into them and cause passive dilation.* So great is the pressure in some cases, that the plasma is forced out of the capillary walls in relatively large quantities—sufficient, in fact, to cause œdema of the face, larynx, pleura, lungs, etc., and even to provoke their rupture, as shown by the ecchymosis, hæmorrhages, hæmaturia, purpura, menorrhagia, metrorrhagia, etc., witnessed.

E. Cyon¹⁶⁷ also lays stress on the fact that it is a grave error to consider iodine as a vasodepressor. The prevailing view that iodine and its preparations lower the blood-pressure is due to a deplorable habit (deplorable in the sense that it has contributed greatly to obscure our knowledge of the action of all drugs) into which experimenters have fallen, of taking as standard the poisonous effects of a remedy for its therapeutic action. Thus I have before me the protocol of experiments by an eminent therapist in which 0.25 gm. ($3\frac{3}{10}$ grains) per kilo of animal are administered to rabbits to illustrate the therapeutic action of potassium iodide. An equivalent dose to an average adult (70 kilos) would thus be 17.5 gms. (270 grains). Of course, he obtained vasodilation in five minutes—but dilation of the capillaries only, as we will see. Now, Sée and Lapique¹⁶⁸ found that certain proportions of the various iodides per kilo of animal were necessary to produce such vasodilator effects. Adapting their figures (the first column) to an adult of 70 kilos, the proportions used by the unnamed investigator to exemplify the therapeutic action of the drug, would be those given in the second column:—

	Example of experimental "therapeutic" dose in animals.	Equivalent of supposed "therapeutic" dose in adult man.
Iodide of Sodium	0.32 gm.	22.4 gms. = 346 grains
Iodide of Sodium	0.30 "	21. " = 321 "
Iodide of Strontium	0.32 "	22.4 " = 346 "
Iodide of Calcium	0.24 "	16.8 " = 259 "
Iodide of Potassium	0.27 "	18.9 " = 291 "
Iodide of Potassium	0.23 "	16.1 " = 248 "

Such a dose, suddenly thrown into the circulation, in no way illustrates the mode of action of iodine preparations used therapeutically, especially when administered orally—not even when large quantities are given. Prévost and Binet¹⁶⁹ and others who have observed "vasodilation" specify, moreover, that it was produced by large doses.

As to the irritating influence of iodine (accumulated in the blood) on living elements, it is not only exemplified by the irritating action of iodine on the skin and mucous membranes, but also by the irritation attending its elimination through the skin, kidneys, etc. As to its

* Author's conclusion.

¹⁶⁷ E. Cyon: "Les Nerfs du Cœur," Paris, 1905.

¹⁶⁸ Sée and Lapique: Bull. de l'Acad. de méd., T. xxii, p. 328, 1889.

¹⁶⁹ Prévost and Binet: Rev. méd. de la Suisse Romande, vol. x, p. 509, 1890.

influence on vessels, von Zeissl¹⁷⁰ found that when iodine was injected into the carotid of dogs, the blood-pressure rose intensely, producing œdema not only of the brain, but also of the lungs. This is ascribed to a direct action on the vessels. Although violent stimulation of the test-organ doubtless assisted in provoking such excessive vasoconstriction, the fact remains that the local irritation contributed materially as cause. The production of excessive vasoconstriction is well shown by a case of fatal poisoning following the injection into an ovarian cyst, reported by Rose.¹⁷¹ At the autopsy he found that even comparatively large arteries were completely occluded. Bogolopoff,¹⁷² on the other hand, observed microscopically that in frogs, into which a solution of potassium iodide had been injected, the capillaries were markedly dilated.

The production of œdema and interstitial hæmorrhage could be illustrated by a large number of cases on record. In a case reported by Milian,¹⁷³ for example, 6 gms. (90 grains) daily brought on at the end of six days, an ecchymosis and large submucous hæmorrhage of the palate. Wallace¹⁷⁴ observed pleural exudation and pulmonary œdema after prolonged treatment. œdema of the glottis may be brought on by 45-grain (3 gm.) doses (Fenwick), or much larger doses; but smaller doses have also caused it: 15 grains (1 gm.) in cases reported by Nélaton, Fournier, Huchard, Rosenberg; or small doses in cases reported by Fournier, La Barcerie and Guillemet. In all these cases, of course, the remedy had been used during a more or less prolonged period. The brain may also become hyperæmic. Sokolowski,¹⁷⁵ in animals trephined after the administration of large doses of potassium iodide, found the cerebrum gorged with blood. This accounts for the observation of Rilliet that iodine could cause a sort of drunkenness attended with excitement, tinnitus, palpitations and even convulsions, and for the cases of cerebral hæmorrhage reported by Hallopeau.¹⁷⁶ This excessive vasoconstriction may even entail death, as in a case observed by Franz,¹⁷⁷ in which 1 gm. (15 grains) doses led to acne, ulceration of the nares, abscesses, etc., and finally death by double hydrothorax and pulmonary œdema.

Iodism.—This condition is due to the presence of an excess of iodine in the blood over and above the aggregate of this halogen required by the body at large.* This aggregate is represented by the iodine contained in the thyroid and parathyroids, the red corpuscles (which take up their thyroidase) and what reserve the body fluids and the different organs can accommodate.

Although, on the whole, large quantities of iodine or its salts, whether given in one dose or in many small doses, are more likely to cause iodism than small quantities, the question

* Author's conclusion.

¹⁷⁰ von Zeissl: Zeit. f. klin. Med., Bd. xxvii, S. 363, 1895.

¹⁷¹ Rose: Virchow's Archiv, Bd. xxxv, S. 12, 1866.

¹⁷² Bogolopoff: Arbeit. a. d. pharm. Labor. z. Moskau, S. 125, 1876; Revue des Sci. méd., vol. x, p. 92, 1877.

¹⁷³ Milian: Presse méd., Sept. 30, 1899.

¹⁷⁴ Wallace: Cited by Nothnagel and Rossbach: Loc. cit., p. 270.

¹⁷⁵ Sokolowski: Ibid., p. 269.

¹⁷⁶ Hallopeau: Cited by Manquat: Loc. cit., vol. ii, p. 94.

¹⁷⁷ Franz: Wien. klin. Woch., Bd. xii, S. 643, 1899.

of dose is subsidiary to the condition of the patient. A very small quantity may thus produce iodism merely because the patient's asset in iodine is up to its maximum limit*—his supposed "idiosyncrasy."* This is particularly the case in subjects whose thyroid apparatus is only able, owing to local disorders (goiter, for example) or deficient development, to take up a small proportion of this halogen.* Any condition which inhibits more or less its excretion also predisposes a patient to iodism, by causing his asset to remain high.*

The two physiological effects of iodine on the test-organ (the direct action plus the sensitizing action of the thyroidase which acquires its *normal* (but not maximum) power during the use of iodine) causing it to react violently, the adrenals are stimulated with corresponding vigor and, the excess of iodine in the blood aiding, abnormal vasoconstriction, produced in the manner described, occurs. This abnormal vasoconstriction is the direct factor in the production of iodism, and may give rise to four classes of morbid phenomena: (1) passive engorgement or congestion of all capillaries; (2) œdema, when the engorgement becomes excessive; (3) ecchymoses and hæmorrhages when the walls of the capillaries are ruptured; and (4) arrest of function and nutrition when the vasoconstriction is such as to reduce or arrest the flow of blood to the tissues.

The group of morbid phenomena due to capillary engorgement includes:* in the respiratory tract, coryza, antral and frontal pain, pharyngitis, tonsillitis, cough, hoarseness, tracheo-bronchitis and pulmonary congestion; in the nervous system, headache, insomnia, delirium, neuralgia, neuritis, pleurodynia; in the muscular system, myalgia, tremor, twitching and spasm (the spinal centers being likewise hyperæmic); in the organs of special sense, conjunctivitis, dacryocystitis, tinnitus aurium, deafness, perversions of taste; in the digestive system, gastric irritation, vomiting and diarrhœa; in the skin, pruritus, erythema and dermatitis; in the urinary system, polyuria, albuminuria and nephritis; in the glandular organs, salivation, parotitis and hepatitis with icterus. Less frequently seen are the œdematous infiltrations: œdema of the larynx, palate, pleura and lungs, and of the lids, lips, neck, and even the entire sur-

* Author's conclusion.

face. Rupture of the capillaries under the stress of the blood-pressure is denoted by more or less extensive ecchymoses sometimes involving large areas, epistaxis, hæmoptysis, hæmaturia, menorrhagia and hæmorrhagic purpura.

The fourth group, due to excessive initial vasoconstriction, thus obliterating or reducing more or less local blood-supply and depressing functional activity,* includes as to the brain, somnolence, intellectual torpor, vertigo, loss of memory, hebetude, hypochondria, and melancholia; as to the spinal system and muscles, adynamia, muscular flaccidity, incoördination, paralyzes, a sensation of weight in the limbs; as to the alimentary canal, constipation; as to the skin, cyanosis, ulceration and necrosis. Nutrition may thus be impaired sufficiently under the prolonged use of iodides to produce atrophy, especially of the mammae and testicles.

Cutaneous eruptions of various kinds, papular, vesicular, eezematous, erysipelatous, pustular, etc., may appear during the administration of iodine or its salts, especially of the potassium iodide. The presence of several of these eruptions coincides with that of other symptoms of iodism and with abnormal vasoconstriction; they are due to the fact that the latter condition, by causing retention of the drug in the capillaries of the skin, promotes therein disorders similar to those produced by external applications of iodine. The multiplicity of cutaneous disorders is due to the presence in these capillaries of different kinds of wastes: alloxuric bases, hypocatabolized cellular débris, various acids, etc., each of which affects the cutaneous elements in its own way. The underlying cause of all these eruptions, therefore, is the same as in all phenomena witnessed in iodism, viz., abnormal vasoconstriction.*

All these phenomena, and the excessive constriction of the arteries, would not occur were iodine able to excite the thyro-pressor nerve.* But such is not the case. Even when taken in doses sufficient to produce acute poisoning, iodine and its preparations fail to increase the secretory activity of the thyroid.* Were it, in fact, otherwise, this organ would waste its product whenever its own pabulum, iodine, would enter the blood.*

* Author's conclusion.