is readily explained by the affinity of alcohol for oxygen. Fever being accompanied by a marked increase in the blood's oxygen ratio, the alcohol can be oxidized at the expense of the surplus of this gas and be itself consumed in the febrile process without appreciably modifying existing conditions. In the healthy individual, however, the conditions are reversed; there is no excess of oxygen in the blood, and the latter's oxygen being in part consumed by the alcohol, functional disturbances occur, *i.e.*, inadequate tissue metabolism, as shown by the reduced excretion of CO_2 and nitrogen, lowered heat-production and temperature and other morbid phenomena reviewed. As it is *only* in healthy individuals, therefore, that the variations of blood-pressure have been observed, and since these cannot be ascribed to a direct action of the alcohol upon the vasomotor center, they must be ascribed to a chemical process in the blood itself, *i.e.*, in the vessels.

This is further shown by the fact that alcohol so modifies the blood's physical properties that its access to the tissues is hampered. Thus, Bouchard[133] states that alcohol, owing to its feeble osmotic power, inhibits nutrition by delaying the penetration of plasma into the cellular elements. Burton-Opitz[134] found that it reduced the alkalinity of the blood, and rendered the latter abnormally viscid. Even the adrenoxidase, a globulin, must lose some of the fluidity so essential to its circulation in the cellular elements, since, as stated by Halliburton,[135] "it can be shown that the globulins require a lower percentage of alcohol to precipitate them than the albumins."

Cellular metabolism being now inhibited to a marked degree,* the sthenic symptoms are replaced by general asthenia and maudlin hebetude: the skeletal muscles become relaxed and unable to respond adequately to nervous impulses. The gait becomes staggering, the movements irregular and uncertain, the speech thick and difficult, and the eyes half closed owing to relaxation of the palpebral muscles.

Alcohol being converted by oxidation into water and carbonic acid and the excretion of the latter being interfered with through the increased viscosity of the plasma, an asphyxia-like condition, sometimes attended with beginning cyanosis, is initiated. This finally causes the patient to fall into a deep torpid slumber accompanied by stertorous breathing, due to relaxation of the palatal muscles.

The blood is depleted to such a degree of its oxygen in the larger vessels that it is practically venous on reaching the minute intercellular capillaries. The experiments of Warren P. Lombard,[136] Dastre,[137] Horsley,[138] Destrée,[139] Scheffer[140] and others have shown that alcohol

* *Author's conclusion.*

[133] Bouchard: *Loc. cit.*
[134] Burton-Opitz: Jour. of Physiol., vol. xxxii, p. 8, 1904.
[135] Halliburton: "Biochemistry of Muscle and Nerve," p. 22, 1904.
[136] Warren P. Lombard: Jour. of Physiol., vol. xiii, p. 1, 1892.
[137] Dastre: C. r. de la Soc. de biol., vol. ii, p. 798, 1895.
[138] Horsley: Lancet, May 5, 1900.
[139] Destrée: Quart. Jour. of Inebriety, Jan., 1899.
[140] Scheffer: Arch. f. exp. Path. u. Pharm., Bd. xliv, S. 24, 1900.

caused, at first, an exacerbation of strength, which was soon replaced by marked weakness if the dose was sufficient, and that large doses invariably reduced the muscular power. That the adynamia is not due to the direct action of the alcohol on the muscle fiber is shown by the statement of Cushny's[141] that "alcohol has no effect on muscle or on peripheral nerves when it is carried to them by the blood." The period of increased muscular power is due, we have seen, to passive hyperæmia of the muscular elements, a fact which indicates that it is fictitious. Indeed, as shown by Destrée and others, fatigue soon sets in and becomes marked. This accounts for the fact that troops deprived of alcohol stand long marches with much less fatigue than those supplied with it. This was emphasized anew recently by Beyer[142] and Fritig. The latter observer states that since Dutch officers and men were given, in 1898, the option of drawing the money value of their alcoholic ration, the many who ceased to use alcohol have shown a noticeable increase in their resistance to fatigue and disease. Conversely, those who consumed alcohol, while competent for duty during peace, quickly succumbed to these conditions during active service. Alcohol thus debilitates the muscular system even when not taken in toxic doses. Abel[143] states that "we have no experimental grounds for believing that small or even moderate quantities of alcohol exercise any beneficial direct action on the muscles of man and warm-blooded animals."

The third stage includes the symptoms witnessed in individuals said to be "dead drunk." Here an entirely different order of phenomena is observed. The patient is unconscious, pale or perhaps cyanotic, and his surface is insensible and cold. All the senses are in abeyance. The pulse is thin and compressible and the temperature sometimes extremely low. This condition may continue several hours—cases in which it lasts over twelve hours being usually fatal—and gradual recovery occur, or the respiration may become distant, feeble and shallow, and death ensue from arrest of this function.

This is due not only to the physical alterations and viscidity of the blood, but also to its accumulation in the large central trunks, especially those of the splanchnic area. The peripheral organs, including the brain, being partially depleted, their functions are almost in abeyance. When this reaches a certain limit the two lobes of the pituitary are themselves rendered sufficiently ischæmic to paralyze their functions, and death ensues.

A small quantity of alcohol added to sea-water containing very young fertilized sea-urchin eggs delays markedly cell-division and gastrulation, and so impedes the motility of the mesenchyma cells that the development of the skeleton is markedly impaired. This is due to the deprivation of what oxygen the alcohol consumes, metabolism in the

[141] Cushny: *Loc. cit.*, p. 139, third edition, 1899.
[142] Beyer: Boston Med. and Surg. Jour., Aug. 22, 1901.
[143] Abel: *Loc. cit.*

cellular elements being correspondingly slowed. The action of alcohol on the human tissue-cell differs in no way from that on the eggs of the sea-urchin. Possessed of a marked affinity for water, it is rapidly distributed throughout the blood-stream and at once enters upon its deadly work; the degree of harm done being commensurate with the quantity thus disseminated.

Another feature of the morbid process forcibly asserts itself at this stage of poisoning. As is well known and as recently emphasized by Hodge,[144] traces of alcohol suffice to inhibit the growth of yeast. Dastre,[145] on the other hand, found that while soluble ferments could exercise their specific action in relatively strong solutions of alcohol—15 to 20 per cent. in the case of trypsin—the blood's soluble ferments, including fibrin ferment, are but slightly soluble even in very weak solutions of alcohol, *i.e.*, 4 per cent. The fibrin ferment being, as I have shown, the *adrenoxidase*, it follows that the large quantity of alcohol ingested in the production of the third stage not only dispossesses this substance of the oxygen it should carry to the tissues, but that it actually paralyzes it.

It is when bereft of its vitalizing properties, therefore, that the blood reaches the nerve-centers. Indeed, that alcohol is a paralysant of the nervous system has been strongly urged by Bunge,[146] Schmiedeberg,[147] Ach and Kraepelin,[148] Crothers[149] and many other investigators, while Dogiel found that large doses depressed markedly not only the motor, but also the sensory nerve-centers. This necessarily applies to the most sensitive of them all, those of the pituitary body. The very source of the body's *pabulum vitæ* is thus rendered sterile, since the adrenals must soon cease to functionate as well as their center.

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

Therapeutics.—The present conception of the therapeutic value of ethyl alcohol in disease is based on a misinterpretation of the rôle of the kinetic energy yielded while this agent is being burnt in the body.* The claim that it is an albumin-saving food, the value of which corresponds with its dynamic equivalent of pure food hydrocarbon, falls, when the process through which it saves albumin is taken into consideration. To rob the blood of its oxygen is an albumin-saving process, but at the expense of cellular life;* to increase the viscidity and decrease the alkalinity of the blood is an albumin-saving process, but by inhibiting life.* On the other hand the kinetic energy it liberates in the form of heat contributes nothing to the vital process.* Alcohol, therefore, is valueless as a food.

Evidence to this effect has already been submitted. This view is further emphasized from another standpoint by Winfield S. Hall[150] in

* *Author's conclusion.*
[144] Hodge: "Physiol. Aspects of the Liquor Problem," June, 1903.
[145] Dastre: Arch. de Physiol., T. viii, p. 120, 1896.
[146] Bunge: "Die Alkoholfrage," Leipzig, 1885.
[147] Schmiedeberg: "Grundriss der Arzeneimittellehre," Leipzig, 1895.
[148] Kraepelin: Münch. med. Woch., Bd. xlvi, S. 1365, 1899.
[149] Crothers: Jour. Amer. Med. Assoc., Dec. 5, 1903.
[150] Winfield S. Hall: *Ibid.*, Feb. 2, 1907.

the following words: "Ethyl alcohol possesses several characteristics in common with the carbonaceous foods, *e.g.* (1) it is composed of C, H and O; (2) it is readily oxidized in the liver, yielding CO_2 and H_2O, which are excreted; (3) it yields heat incident to its oxidation, and this heat naturally augments the body income of heat; (4) ingestion of ethyl alcohol leads to a decrease in the catabolism of carbonaceous foods, and may even 'spare' proteins.

"In this connection, one must not lose sight of the following facts: (1) All vegetable toxins and alkaloids are composed of the same kind of chemical elements as enter into foodstuffs, viz., C, H, O and N. (2) Toxins and alkaloidal poisons in general are oxidized in the liver through the agency of oxidases, whose function is to oxidize, and thus to make harmless, substances which would act as protoplasmic poisons on all cells with which they come in contact. When moderate amounts of such toxins are taken the defences of the system are sufficient to reduce them to a harmless condition and no immediate injury results. If larger quantities are ingested the full drug effect (narcotic in the case of alcohol) is immediately experienced, the oxidases of the system being unable to defend it against a large dose. (3) All oxidation yields heat, whether it is a normal catabolism or a protective oxidation. That the heat from the oxidation of alcohol is not a normal catabolism for the purpose of heat liberation is evident from the fact that, notwithstanding the liberation of heat through oxidation of alcohol, the temperature of the body falls, because of increased loss of heat from the surface. This increased loss is due to dilatation of peripheral vessels. (4) Decreased catabolism of carbonaceous or nitrogenous foods following ingestion of a narcotic is a universal fact depending on the drug effect and giving to the oxidized narcotic no significance as a food. It may be said without reservation that ethyl alcohol is not a food in the scientific significance of the word."

In small doses, alcohol, by supplementing the heat energy normally produced (through the interaction of adrenoxidase and nucleo-proteid*) with the artificial energy liberated while it is being oxidized, augments momentarily the activity of metabolism* and the antitoxic activity of the blood. Its action, in this connection, becomes serviceable when, after exposure to cold and damp, the accumulation of toxic wastes under the skin (through the depressing effect of cold upon cutaneous metabolism*) and other conditions which render the body vulnerable to disease, a prophylactic is demanded; or to counteract promptly (especially if given in warm water) the toxic effects of *depressing poisons*, such as *ptomains, vemons, chloral, veratrum viride, mushroom poisoning, etc.*

As to the use of alcohol in febrile diseases, however, its physiological action is such as to interfere with the blood's defensive processes.* The belief of its advocates that it does good by lowering the temperature, the blood-pressure and the

* *Author's conclusion.*

pulse-rate, is based on the view that fever is a pathological phenomenon. In truth, fever is the expression of the body's power to defend itself; and if enough alcohol is given to lower the temperature, it can serve only to disarm Nature's own weapons.*

G. Rubin[151] found experimentally that alcohol decreased decidedly the resistance of animals to infection. No organic lesions were present, and it appeared to weaken directly the substance or substances that inhibited the growth and toxic action of bacteria, and which seemed to be derived from the leucocytes. These cells themselves appeared to be morbidly influenced. The two phases of the action of alcohol on the immunizing process—the primary ephemeral spurt of antitoxic activity, and the secondary and marked depressing influence—are well exemplified in the following quotation from H. C. Wood's treatise:[152] "Binz[153] found that alcohol increases the resistive power of the dog to septic material, but his experiments seem to have been too few to be of value. In an incomplete research, H. A. Hare and M. E. Pennington[154] found that alcohol increases the bactericidal property of the blood at least against some pathogenic organisms. Gruber[155] affirms, as the result of experimentation, that the frequent administration of small doses of alcohol to guinea pigs, injected with bacillus prodigiosus, prolonged life, and in some instances even brought about restoration. Opposed to these results are those of various investigators. Doyen[156] and Thomas[157] both found that alcohol increases the liability of animals to infection with cholera. Abbott,[158] using streptococcus pyogenes, bacillus coli, or staphylococcus pyogenes aureus, found that the alcoholized animals died with much more certainty than did those of the control experiments, in which no alcohol was given. Delèarde[159] reached the result that alcohol destroys the immunization of rabbits against tetanus and anthrax. Laitinen,[160] in a very elaborate research upon three hundred and forty-two animals, representing six species of mammals and birds, using anthrax, tubercle bacilli, and diphtheria toxin, arrived at the conclusion that alcohol diminishes very distinctly the resistance of the body towards infections. Pawlowsky[161] found that alcoholized animals reacted much more freely to staphylococcus citreus than did the normal animal. Kögler and Gruber[162] determined that alcoholization increases the mortality of animals infected with the pneumobacillus. Goldberg[163] came to a similar conclusion in regard to the influence of anthrax on pigeons. Ausems[164] found that the administration of alcohol in small doses to rabbits before infection diminished their resistance." Although the results of both sets of observers harmonize with my views, the fact remains that those who found that alcohol inhibited the protective functions are decidedly in the majority.

* *Author's conclusion.*

151 G. Rubin: Jour. Infect. Dis., May 30, 1904.
152 H. C. Wood: *Loc. cit.*, p. 305, thirteenth edition, 1906.
153 Binz: Verh. Congr. f. inn. Med., Bd. vii, S. 70, 1888.
154 H. A. Hare and M. E. Pennington: Therap. Gaz., May 15, 1903.
155 Gruber: Wiener klin. Woch., Bd. xiv, S. 479, 1901.
156 Doyen: Arch. de physiol., 3 série, T. vi, p. 179, 1885.
157 Thomas: Arch. f. exp. Path., Bd. xxxii, S. 38, 1893.
158 Abbott: Jour. of Exper. Med., vol. i, p. 447, 1896.
159 Delèarde: Arch. inter. pharmacodyn., vol. iv, 1897.
160 Laitinen: Zeit. f. Hygiene u. Infekts., Bd. xxxiv, S. 206, 1900.
161 Pawlowsky: *Ibid.*, Bd. xxxiii, S. 261, 1900.
162 Gruber: Wiener klin. Woch., Bd. xiv, S. 479, 1901.
163 Goldberg: Centralbl. f. Bakter., Bd. xxx, S. 696, 731, 1901.
164 Ausems: Diss. Utrecht, 1900; Centralbl. f. inn. Med., Bd. xxiii, S. 536, 1902.

BROMIDES.

(Bromides of Potassium, Sodium, Lithium, etc.)

Physiological Action.—The primary effect of potassium bromide is to depress the functional activity of the general vasomotor center and thus to cause relaxation of all vessels provided with a muscular coat.* The large central vascular trunks accommodating more blood, the capillaries of all organs, particularly those of brain and skin, are more or less depleted and their functional activity is correspondingly lowered.* Hence its quieting influence on cerebral excitement and its anæsthetizing effect upon the cutaneous sensory and end-organs, the main feature of its action as depresso-motor agent.*

The ephemeral tetanoid condition observed in frogs by Laborde,[165] Purser[166] and others, when even small doses are injected, is but a proof of the relaxation of the arteries. The peripheral arterioles being also relaxed, an influx of blood in the capillaries of the skin takes place and the sensory end-organs being suddenly stimulated, they incite reflex spasm. But this stage is temporary. As is well known, the spasms caused by strychnine in frogs can be prevented by anæsthetizing the skin. The depletion caused by the bromides produces a similar anæsthesia. During poisoning, this may become so marked that, as observed by Purser in frogs and Eulenberg and Guttmann[167] in rabbits, the animal, though able to jump, may be pricked, pinched or burned, and yet show no evidence of pain. The supply of blood to the peripheral capillaries is soon reduced and the true effects of the drug appear. "After a short time," writes Wood,[168] "this stage of muscular excitement gives way to one of great muscular relaxation and total abolition of reflex actions"—the capillaries of the contractile elements being themselves deprived more or less of blood.

The action on the brain is similar. The congestive stage due to relaxation of the terminal arteries is occasionally witnessed, the drug then causing headache, irritability and redness of tongue (Manquat), or what has been termed "bromomania," cases of which have been reported by Voisin, Stark, Kiernan, Moyer, Rockwell, Spitzka and others.[169] As a rule, however, the recession of blood occurs before excitation can take place. As shown by Albertoni[170] it so obtunds the sensitiveness of the cortex that its electrical excitation can no longer provoke epileptiform convulsions, while Sokolowsky[171] observed that "large doses of bromide cause *anæmia* of the brain." That this is due to recession of the blood, due, in turn, to general vasodilation, is shown by the fact that Schouten[172] found manometrically that even small doses of potassium bromide lowered the blood-pressure. De Fleury has also observed this phenomenon. A similar effect is caused, as is well known,

* *Author's conclusion.*
[165] Laborde: Arch. de physiol., T. i, p. 423, 1868.
[166] Purser: Dublin Jour. Med. Sci., vol. xlvii, p. 321, 1869.
[167] Eulenberg and Guttmann: Virchow's Archiv, Bd. xli, S. 91, 1867.
[168] Wood: *Loc. cit.*, p. 240, thirteenth edition, 1906.
[169] Cited by Stockwell: Sajous's "Cyclo. of Pract. Med.," vol. ii, p. 7, 1898.
[170] Albertoni: Arch. f. exp. Path. u. Pharm., Bd. xv, S. 256, 1882.
[171] Sokolowsky: Manquat: *Loc. cit.*, vol. ii, p. 739.
[172] Schouten: Arch. f. Heilkunde, Bd. xii, S. 97, 1871.

by dividing the upper part of the spinal cord, *i.e.*, the general vasomotor path, and by removal of the pituitary body, the seat of the general vasomotor center.

The diminution of blood in the capillaries of the various organs* impairs their functional activity. The temperature is lowered and the sensibility of the mucous membranes and the skin is more or less reduced. Mental torpor, defective memory, difficult enunciation, somnolence, depression of spirits (lapsing at times into melancholia) are also observed in some cases when the doses are frequently repeated. Digestion is impaired in some subjects, owing to deficient secretion of saliva and gastric juice. Sexual weakness is often produced, erethism of the sexual organs necessitating a marked degree of vascular engorgement. A similar deficiency of blood in the arterioles of the iris* may also cause dilation of the pupils. The circulatory torpor* in the skeletal muscles may entail muscular relaxation and weakness; but of all the muscular organs, the heart suffers most from the deficiency of blood,* and its contractile power is greatly diminished. This constitutes an additional factor in the morbid process, since it tends further to reduce both the vascular pressure and the speed of the blood-current in the capillary system.

As shown below, the temperature of the surface is reduced by bromides—a phenomenon partly due to the recession of blood to the deeper vessels. Quite familiar to all laryngologists is the diminution of sensibility of the mucous membrane of the pharynx and larynx, which is quite perceptible after a single dose of 30 grains (2 gms.). The cerebral phenomena are also of common observation. Gubler[174] found that 2 to 4 gms. (30 to 60 grains) daily sufficed in some cases to induce melancholia, even in maniacal subjects. Weir Mitchell[175] and others have reported similar instances. Diminution of the salivary secretion was observed by Gubler, Rabuteau[176] and other clinicians. As to the influence of vascular depletion on the pupil, Landois[177] states, referring to the blood-vessels of the iris, that "everything that diminishes the amount of blood dilates the pupil." As to the rôle of the heart in the morbid process Wood[178] concludes that "the fall of the arterial pressure is certainly largely of cardiac origin," though he considers it probable that "the vasomotor system also shares the paralyzing influence of the drug."

Bromism.—When large doses are administered during a prolonged period, the oxygenizing power of the blood becomes

* *Author's conclusion.*
[174] Gubler: Manquat: *Loc. cit.*, vol. ii, p. 738.
[175] Weir Mitchell: Trans. Assoc. of Amer. Phys., vol. xi, p. 195, 1896.
[176] Rabuteau: Gaz. hebdom., 2 série, vol. vi, p. 177, 1869.
[177] Landois: "Physiology," tenth edition, p. 842, 1905.
[178] Wood: *Loc. cit.*, p. 244, thirteenth edition, 1906.

inadequate.* This is due to the fact that, as is the case with all organs that are remote from the splanchnic area (in which the blood accumulates when the vessels are dilated), the pituitary body also becomes ischæmic, and the adrenals are inadequately stimulated.* Their secretion being materially reduced, the proportion of adrenoxidase formed is insufficient to satisfy the needs of the organism at large, *i.e.*, to sustain nutrition.*

The condition known as "bromism" appears when this condition is added to the primary vasomotor paresis caused by the drug.* It is mainly due to the fact that, owing to the impaired catabolism and to the resulting torpor of the eliminatory functions of the skin, kidneys, intestinal and respiratory tracts, the drug and imperfectly catabolized wastes accumulate in the system at large. Hence the marked cutaneous disorders observed in this condition, the latter varying from an erythematous and rubeoliform blush to acne, pustules, furuncular swellings, more or less extensive ulcerations and even gangrene—all aggravated by the cutaneous denutrition. A typical sign of adrenal insufficiency* is frequently observed in these cases, viz., copper-colored blotches.

The other symptoms of bromism are but exaggerations of those produced by smaller quantities of the drug.* Mental torpor lapses into stupidity, the facial expression recalling that of an idiot. The senses are also greatly weakened. The eyes lose their lustre, and are surrounded by dark rings, and the pupils are more or less widely dilated. Hallucinations, visions, utter listlessness or melancholia with outbursts of mania, may precede the ultimate issue, cerebral paralysis. The muscular weakness gradually becomes complete adynamia. The temperature is greatly reduced, the heart's action is hardly perceptible and the respiration becomes correspondingly feeble and shallow. The patient gradually sinks into a condition of general impotence, hardly able even to ingest his food, liable at any moment to be carried off by some intercurrent disease, especially pneumonia, or to lapse suddenly into coma, the precursor of death.

The action on the adrenal center is but a counterpart of that on other organs. The inhibition of the functions of the salivary glands observed by Gubler, Rabuteau and others, illustrates the action of the drug on secretory organs in general. The diminution of saliva merely

* *Author's conclusion.*

typifies, therefore, the corresponding effect on the adrenals, *i.e.*, a diminution of secretion. The deficiency of adrenoxidase in the blood normally causes a reduction of the temperature. Martin-Damourette and Pelvet[179] found that the entire surface was hypothermic. Wood[180] also states that in warm-blooded animals, toxic doses of potassium bromide lower very decidedly the temperature. This is, in part, due to the recession of blood from the surface; but actual reduction of activity of all oxidation processes is shown by the fact observed by H. Bill,[181] that the elimination of carbon dioxide from the lungs is markedly decreased by large doses. The excretion of urea has been studied by various investigators, but with contradictory results—a fact explained by the renal irritation, which, according to Pletzer,[182] large doses provoke. Skoog,[183] who reported several cases of bromism, including some presenting mental disturbances, noted that "after a few weeks cellular resistance is lowered, the degree depending on the individual susceptibility and amount of drugging."

The torpor of the blood-stream in the capillaries, coupled with the lowered oxidizing efficiency of the blood itself, favors the accumulation of the drug in the system. Wood states that it is undoubtedly to be found in every tissue of the body, and refers to the labors of Doyon and Cazeneuve,[184] confirmed by those of Féré and Herbert,[185] as showing that bromide of potassium "is stored up in the nerve-centers much more largely than elsewhere." The elimination occurs, in part, through the skin as shown by eruptions, pustules having been found by Guttmann[186] and others to contain the drug. The violet areola observed around the cutaneous lesions is characteristic of bromism, according to Féré.[187] It is doubtless partly due to the deficient local oxygenation, and the precursor of the gangrenous plaques observed by Malherbe,[188] Darnall[189] and others. That the salt is also eliminated in the perspiration, the urine, and the fæces is well known.

The predilection of cases of bromism to pneumonia has been emphasized by Féré. Baker[190] ascribes the predisposition of epileptics to phthisis to the excessive use of bromides. Cushny[191] states that the patient "is, of course, liable to fall a victim to infectious disease," and that "in a number of cases of chronic bromide poisoning, the immediate cause of death has been an attack of bronchitis or pneumonia."

Acute Poisoning.—Acute intoxication in abnormal subjects who had not previously taken the drug is seldom, if ever, witnessed. An ounce (30 grammes) has been ingested without causing more than a temporary attack of bromism. A sensation of heat in the mouth, œsophagus and stomach, fœtid breath, intense headache (due to hyperæmia of the cerebral

179 Martin-Damourette and Pelvet: Bull. gén. therap., med. et chir., vol. lxxiii, p. 241, 1867.
180 Wood: *Loc. cit.*, p. 244, thirteenth edition, 1906.
181 H. Bill: Amer. Jour. Med. Sci., July, 1868.
182 Pletzer: Manquat: *Loc. cit.*, p. 741.
183 Skoog: Jour. Amer. Med. Assoc., Dec. 1, 1906.
184 Doyon and Cazeneuve: Lycn méd., vol. lx, p. 479, 1889.
185 Féré and Herbert: C. r. de la Soc. de biol., 9 série, vol. iii, pp. 670, 769, 807, 1891.
186 Guttmann: Virchow's Archiv, Bd. lxxiv, S. 541, 1878.
187 Féré: C. r. de la Soc. de biol., 9 série, vol. iii, pp. 670, 769, 807, 1891.
188 Malherbe: Presse méd., vol. vi, p. 243, 1899.
189 Darnall: Med. Record, Sept. 7, 1901.
190 Baker: Med. Register, Dec. 8, 1888.
191 Cushny: *Loc. cit.*, p. 501, fourth edition, 1906.

capillaries owing to relaxation of their arterioles*) difficult ideation and perhaps aphasia, hypothermia, cutaneous anæsthesia, weakness and irregularity of the pulse with concomitant or subsequent drowsiness which may persist several days, and be followed by slow recovery.

In mammals, as well as in frogs, toxic doses cause death by provoking, as shown by Eulenburg and Guttman,[192] symptoms similar to those observed in man, *i.e.*, general paralysis of all functions. Prominent among these are the evidence of impaired oxygenation, *i.e.*, lowering of the temperature and gradual respiratory failure, the animal dying of asphyxia. The heart is invariably arrested in diastole.

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

Therapeutics.—The action of the bromides thus interpreted, accounts readily for their beneficial effects in the various conditions in which they are generally employed. Though their use is to be deprecated* in *epilepsy* as curative agents, since they aggravate the disease by inhibiting catabolism and therefore the destruction of the spasmogenic wastes,* the fact that the accesses are partly due, as will be shown, to excessive vascular tension* (caused by these wastes) renders their employment permissible to ward off the attacks. This applies as well to *tetanus,* puerperal *eclampsia* and kindred disorders.* The value of the bromides in the various forms of *nervous* and *mental excitement* is likewise explained, since all nervous structures are channels for adrenoxidase.* Excitement being due to hyperæmia of nervous elements, the depletion of these elements that general vasodilation insures, affords the required relief. The same physiological process accounts* for the value of the bromides in abnormal sexual excitement, *nymphomania* for example, in *uterine disorders* due to local hyperæmia, in *seminal emissions* due to a similar condition of the spinal cord, in various subacute inflammatory disorders.

VERATRUM VIRIDE.

Physiological Action.—The action of veratrum viride has in recent years been said to resemble that of aconite, but this certainly is not the case. The symptoms ascribed by the authors of certain text-books are those of veratrine, an alkaloid

* *Author's conclusion.*
[192] Eulenburg and Guttmann: *Loc. cit.*

derived from *Veratrum Sebadilla,* and which occurs only in traces in suitable preparations of veratrum viride and whose effects do not appear even in cases of poisoning by the latter drug. Veratrine is an unreliable agent and should not be used internally.

Veratrum viride, on the other hand, is a valuable remedy when judiciously employed. By depressing directly the general* vasomotor center, it enables us to lower excessive arterial tension and to relieve an overburdened heart. It does this by causing the blood to accumulate in the splanchnic area and other great vessels of the trunk.

The most valuable observations upon the action of veratrum viride *per se* are those of H. C. Wood,[193] who found experimentally that one of the effects of the main active principle of veratrum viride, *jervine,* was a "depressing action" upon "the vasomotor centers." "The circulatory phenomena," says this author, "were primary slowing of the pulse with later rapid pulse and a progressive falling of the arterial pressure from the beginning to the end." While it is probable that the "primary slowing" was due to a slight preliminary stimulation of the general vasomotor center, the subsequent fall of blood-pressure could not be ascribed to inhibition of the heart, since Wood also says: "The slowing of the pulse was not due to any effect on the pneumogastric nerves, the jervine acting as usual after section of these nerves." The central action of the drug is emphasized by the statement that: "As, however, asphyxia, not galvanization of a sensory nerve, produces rise of pressure in the poisoned animal, it is evident that jervine depresses the vasomotor centers." Pesci[194] confirmed these observations clinically in 19 cases, all of which showed reduction of exaggerated arterial tension. Similar observations have been recorded by others.

But this applies only to experimental (and, therefore, relatively large) doses of jervine; as shown below, veratrum viride contains also a small proportion of another alkaloid, *veratroidine,* the effects of which only become manifest when large doses of veratrum viride are administered.

The vasodilation produced being commensurate with the size of the (therapeutic) dose given, we can at will regulate the vascular tension when this becomes excessive; again, as a given dose repeated at appropriate intervals sustains the effect, we can hold the blood-pressure in check until the danger is past. Finally, as the general vasomotor center recuperates promptly when the use of the drug is not too prolonged, the depression induced is readily recovered from—which is not the case when bleeding, employed with the same ends in view, is resorted to.

* *Author's conclusion.*
[193] H. C. Wood: *Loc. cit.*, p. 367, thirteenth edition, 1906.
[194] Pesci: Gazzetta degli osped., vol. xxvii, p. 630, 1906.

H. C. Wood has long maintained that veratrum viride replaces bleeding advantageously, and that "the patient is bled into his own circulation" by it. In pneumonia, for instance, he deems it the best remedy at our disposal. This view is sustained by considerable clinical evidence. Gilardoni,[195] in an exhaustive experimental and clinical research, reached a similar conclusion. He found that the effect increased with the dose, but that it was more marked when the drug was given hypodermically. No other drug decreased the arterial tension with safety to such an extent. In one case, the patient took at one dose the entire quantity intended for twenty-four hours, and only showed as morbid symptoms vomiting and diarrhœa. J. B. Tuttle[196] also witnessed a case in which a man took by mistake, in the course of an hour, four teaspoonfuls of Norwood's tincture of veratrum viride instead of four drops. Some vomiting, slight pallor and marked weakness were the only symptoms observed.

Untoward Effects.—A large dose of veratrum viride brings out the physiological effects of veratroidine, an alkaloid present in too small a proportion in a therapeutic dose to provoke morbid effects. These occur in addition to a further depressing action upon the general vasomotor center and the resulting decline of arterial pressure, vomiting, diarrhœa, some hypothermia and cold sweating, all with feeble pulse and respiration.

These are the cases usually met with in practice. Besides the instances witnessed by Gilardoni and Tuttle, referred to above, cases have been reported in which the foregoing symptoms were present, by Pedigo,[197] Brothers,[198] and others. Wood[199] alludes to several instances in which teaspoonful doses of the fluid extract were followed by recovery. The other cases mentioned also recovered under appropriate treatment. In an experimental research, veratroidine was found by Wood[200] "to be more irritant than jervine, producing usually vomiting and some purging."

Acute Poisoning.—A poisonous dose of veratrum viride introduces new factors in the morbid process. By lowering the blood-pressure to an excessive degree, the blood is caused to accumulate in the large central vascular trunks, now widely dilated. This entails lowered oxygenation in all peripheral tissues,* as shown by the marked hypothermia present, and slowing of the blood-current in all organs. The functions of the pituitary body, including the adrenal center, being depressed from the same cause, less adrenoxidase is supplied to the blood —another feature that entails lowered oxygenation.* As a

* *Author's conclusion.*
[195] Gilardoni: Gaz. Med. Italiana, Nos. 10, 11, 12, 1902.
[196] J. B. Tuttle: N. Y. Med. Jour., June 18, 1892.
[197] Pedigo: Va. Med. Mthly., Sept., 1889.
[198] Brothers: Mittheilungen des Vereins der Aerzte in Medicin, Oct., 1889.
[199] Wood: *Loc. cit.*, p. 370, thirteenth edition, 1906.
[200] Wood: Phila. Med. Times, Aug. 22, Sept. 12, 1874.

result of this, toxic waste-products gradually accumulate in the blood, and as such wastes violently stimulate the general vasomotor center, causing general vasoconstriction, the specific effects of the drug, vasodilation, suddenly disappear. These are soon replaced, however, by another cause of general vasodilation, *i. e., inhibition* of the functions of the pituitary body and heart, due, as we have seen,[201] to excessive constriction of the arteries that supply these organs.*

The transition stage from the legitimate effects of the drug to the phase of inhibition is marked by a clearly-defined sign: the pulse, previously soft and large and somewhat more frequent, now begins to drop steadily, until from perhaps 90, it falls to 50, 40, and even 30 per minute. This is due to the increasing pressure exerted by the blood-stream upon the heart.* Another result of the increasing vascular tension is violent retching and vomiting, due to the onslaught of blood in the gastric vessels, and the resulting reflex (vagal) action.*

The heart, whose work is markedly increased while its nutrition is reduced* (the ischæmia of the pituitary aiding the latter by depriving the blood of adrenoxidase*), soon begins to yield. While the period of inhibition is only in its incipiency, *i.e.*, while the heart's action is not very slow, its action may suddenly be rendered rapid, weak, and perhaps irregular by a physical exertion. Even in the absence of such an exciting cause, the organ soon assumes this gait—that of impending arrest. Relaxation of the vessels, due to loss of the propulsive power of the heart, now recurs. The blood once more receding to the deeper trunks,* the skin becomes cold, clammy, and bedewed with cold sweat, and the prostration is extreme. The brain likewise being deprived of much of its blood, vertigo, loss of vision, and unconsciousness occur in rapid succession. Finally, the pituitary and heart-muscle receiving an insufficient amount of blood to subsist,* the pulse becomes thready and then imperceptible, the heart ceasing its work in diastole. This is preceded, however, by arrest of the respiration, owing mainly to the fact that the venous blood is no longer projected with sufficient vigor to the pulmonary alveoli to be exposed to the air.*

Briefly, we have (1) recession of blood to the deep chan-

* *Author's conclusion.*
[201] *Cf.* this volume, p. 1185 *et seq.*