skin, starting in the rete Malpighii, resemble to some extent the cell arrangements observed in the case under consideration. In the epidermic cancer, however, the cells are larger, and do not rest upon a distinct basement membrane, as in this case. Furthermore, the epithelial bands or tubules starting from the rete have no distinct calibre, and do not reproduce so perfectly the glandular structure.

ETIOLOGY.—The development of cancer of the skin is favored by a number of antecedent conditions to which reference has been made under Symptomatology. In a general way the statement is true that chronic irritation of slight intensity is one of the most potent factors which precede the malignant change in epithelial growths. The origin of highly malignant tumors from certain congenital moles has given some support to Cohnheim's theory of latent embryonic "remains." In xeroderma pigmentosum a congenital weakness of the skin is present which strongly predisposes to malignant growths. Heredity probably has some influence in favoring the evolution of some forms of malignant disease.

Inflammatory changes in the papillary region of the derma, by impairing the integrity of the basement membrane, favors the downward growth of epithelium. Atrophic changes in the connective tissue in advanced life exercise a similar influence.

The advocates of the parasitic origin of cancer consider the association of the malignant affection with pre-existing lesions as accidental. According to them the changes in syphilis and other chronic skin diseases merely furnish a favorable soil for the superadded infectious agent.

Cancer of the skin is more frequent after the age of forty, though no time of life is exempt. Kaposi has observed it a number of times between the ages of eight and eighteen. Rodent ulcer begins, as a rule, about the age of forty, but it may make little or no progress for several years.

DIAGNOSIS.—Superficial cancer of the skin is frequently mistaken for late syphilitic infiltration and ulceration or for lupus. These late nodular and ulcerative syphilitic lesions are usually more rapid in their evolution and involution, are frequently multiple, and lack the characteristic elevated and waxy border which distinguishes malignant ulceration. When syphilitic ulcers or those of lupus are complicated with epithelioma the diagnosis is more difficult. Lupus generally develops early in life, pursues a chronic course, and spreads on the margins of the patch by brownish-red nodules deeply embedded in the skin. These nodules or tubercles are as characteristic of lupus as the waxy margin is of superficial epithelioma.

Tuberculosis verrucosa cutis might be mistaken for papillary cancer of the fingers or hands. Induration about the base of a wart or cutaneous horn should excite suspicion of a malignant change.

In case of doubtful diagnosis resort should always be made to the microscope.

PROGNOSIS.—In superficial cancer of the skin the prognosis is more favorable than in any other form of the disease, as the progress is slow and the lymphatic system seldom implicated. If the growth is radically removed in its early stages there is little tendency to recur.

Cancers from moles are decidedly malignant, as they early involve the lymphatics and may soon be followed by a general metastasis. Papillary cancers are usually rapidly growing, and when they infiltrate the deeper parts, if not removed, lead to a fatal issue within from one to three years.

Rodent ulcer in its later stages almost invariably returns after removal, though preserving its local seat.

It is well to bear in mind that a superficial growth may become deep-seated and pursue a rapidly fatal course, as in the galloping or phagedenic epithelioma described by Besnier.

TREATMENT.—Early and complete extirpation with the knife is the only method of treatment that should be employed in cancer of the mucous membrane of the mouth, or of the lip.

On other parts of the body, as the neck, scrotum, etc., when the skin is freely movable and union by first intention can be secured, an excision offers the most rapid, painless, and satisfactory method of cure. If the operation is resorted to before the lymph nodes are invaded and if the incisions are made at a sufficient distance from the morbid growth, a cure may be looked for in the majority of cases.

Associated lymph nodes when invaded should be removed in as thorough a manner as possible.

Partial removal of cancer of the skin, even the most superficial, by the knife, curette, or caustics, accomplishes no good result and frequently stimulates these new growths to increased activity.

Superficial cancers of the skin are sometimes so situated that a cutting operation is followed by more deformity than after the employment of curettage and caustics. Many patients are so prejudiced against any cutting operation that they will endure the more prolonged and painful action of caustics rather than submit to the use of the knife. Under these circumstances the diseased tissue may be scraped away with the dermal curette and some suitable caustic applied to the resulting ulcer.

Numerous cures of cancer of the face have been obtained in this way by the writer, the caustics employed, as a rule, having been arsenic, in the form of Marsden's or Bougard's paste, or pure chloride of zinc. Arsenic is perhaps the best of all caustics as it is more certain in its action and presumably has a selective action on the morbid tissue. Marsden's paste is made by mixing two parts of arsenious acid with one part of powdered gum acacia and sufficient water to make the mixture of a firm consistence.

Robinson, who has devoted much time and consideration to the use of caustics in the treatment of cancer, prefers to vary the strength and duration of the application according to the cancer to be treated. He uses the paste in the strength recommended by Marsden and somewhat weaker, but never uses less than equal parts of arsenic and gum acacia. The paste is applied somewhat beyond the diseased area and is left on for from eight to twenty hours (Robinson). If the desired destruction of tissue is not obtained within the shorter limit a second but weaker application should at once be made until the necessary necrosis is accomplished.

The advantages claimed for the caustic treatment of cancer are the lesser degree of deformity which results and the greater certainty of reaching foci of diseased cells in the lymph vessels outside of the parent growth. It is, however, painful, and the separation of the resulting slough is somewhat slow.

Pain during the action of the caustic may be controlled by morphine, and the after-treatment should be conducted on the usual lines.

Before scraping away the morbid tissue as preliminary to the use of the caustic agent, the parts may be rendered anæsthetic by a spray of chloride of ethyl. If this is followed by the application of tampons saturated in a five or ten per cent. solution of cocaine the slight surgical procedure may be rendered absolutely painless.

Instead of employing destructive chemical caustics like arsenic and chloride of zinc the Paquelin or galvanocautery may be used to complete the treatment. The actual cautery is, however, not so certain to reach all the diseased cells as is the arsenical paste.

Patients who have been operated on for cancer should remain under observation for one or two years or longer, and the slightest recurrence should immediately be removed.

The internal use of arsenic for several months after the removal of malignant tumors has, perhaps, some influence in preventing or limiting recurrences.

John A. Fordyce.

CARDAMOM.—CARDAMOMUM. The fruit of *Elettaria repens* (Sonnerat) Baillou (fam. *Zingiberaceæ*). Since the seed is the only active part, the above definition should be so restricted. The cardamom plant is a tall, reed-like, perennial herb, from six to twelve feet high. The flowers and fruits are borne upon special short, scaly stems, partly prostrate among the bases of the leafy culms.

The plant is a native of Southern India, where also it has been long in cultivation. It has been introduced into other tropical countries. The cardamoms of commerce are mostly the product of cultivated plants, which are grown in the moist shade, either in clearings of the natural forests or in plantations of betel palms. The fruits are gathered before they are quite ripe. They are thoroughly washed, partly with soap and partly with a solution of a saponaceous fruit, and then bleached for some hours. They are frequently rubbed between the hands with a mixture of starch and buttermilk. They are ovoid or oblong, pointed, rounded-triangular, three-valved, and three-celled capsules. The husk, when dried, is of a pale yellowish-gray or brown, flexible, and tough. Those which have been starched have a white and almost chalky surface. The seeds, five or six in each cell, are irregularly compressed, brown, and spicy. The fruits of the best varieties are usually short, about once and a half or twice as long as broad (1 to 1.5 cm. = $\frac{1}{16}$ to $\frac{6}{16}$ in.), very plump and full. They are commercially called "shorts." Others, longer and more angular, are denominated "short-longs" and "longs." The larger and longer cardamoms are mostly the produce of other species of Elettaria, and are therefore unofficial. Their odor and taste are not so pleasant. In selecting cardamoms, the point of chief importance is to see that they are short, plump, and well-filled, as otherwise the proportion of husk is too great, and the strength is thus weakened through the diminution of the active portion. This difficulty can be avoided by specifying the amount of the seeds instead of the fruits. The seeds from unfilled fruits are themselves defective, however.

FIG. 1140.—Malabar Cardamom. (Natural size.)

Cardamoms are also distinguished, according to the countries or ports from which they are exported, as Malabar, Aleppo, Madras, etc. The former are the most esteemed.

The seeds contain about five per cent. of a pale yellow aromatic oil, of complex composition, which represents them in odor and taste. The ash of cardamom is rich in manganese. Cardamom is a typical aromatic, and is useful in all the conditions which call for articles of that class. As an agreeable flavor and appetizer, as a stimulant to digestion, and as a carminative in flatulence and in simple colic, it is sometimes, but not often, given alone. In combinations, as a pleasant and useful adjuvant and corrective, it is in more frequent use, acting favorably with cathartics, bitter tonics, stimulants, etc. But the principal use of cardamom is as a condiment or household flavor, for which purpose, especially on the continent of Europe and in the East, it is extensively employed. It is also used in flavoring liqueurs, and in curry-powder, etc. It is less irritating than the spices proper, and more so than anise and the milder carminatives. The dose of cardamom as an aromatic by itself would be from .5 to 1 gm. (gr. viij ad xv.). There is a ten-per-cent. official tincture which represents it completely. The compound tincture contains two per cent. each of cardamom and cinnammon, one of caraway, five of glycerin, and one-half per cent. of cochineal, in diluted alcohol, and is given in doses of 8 to 15 c.c. (2 to 4 fl. ʒ). It also enters into the aromatic powder and the aromatic fluid extract. *W. P. Bolles.*

CARDAMOM, OIL OF.—This term is understood as applying to the volatile oil, and not to the ten per cent. of fixed oil which the seeds yield. It is yielded to the extent of five or six per cent. It is of a pale yellow color, highly aromatic, has a specific gravity of about .900 and a rotation of +13°. Its important constituent is *terpinene* ($C_{10}H_{16}$). Its properties are identical with those of cardamom. It is, however, chiefly used for flavoring, especially liqueurs. *Henry H. Rusby.*

CARDIAC DEPRESSANTS AND CARDIAC STIMULANTS.—I. CARDIAC DEPRESSANTS.—The term cardiac depressant is applied to drugs which lessen the force and frequency of the heart's action and are employed for this purpose in therapeutics. Since all classes of vertebrates and many invertebrates are provided with a nervous mechanism (the cardio-inhibitory apparatus) through which such changes in the heart are brought about in the normal animal, we should expect to find that those drugs which experience has shown to have the power of reducing the heart's action would exert their influence through this mechanism. As a matter of fact, the two drugs which are most used for their depressing influence upon the heart, aconite and veratrum viride, do exert their influence through the cardio-inhibitory nerves. It is conceivable that the part affected by these drugs might be any point in this mechanism—the nerve centres in the medulla, the nerve fibres, which in the higher animals are contained in the vagi trunks, or that which is rather vaguely (since the exact anatomical elements are not well known) termed the endings of the nerves in the heart. As is well known, nerve fibres are, as a rule, less easily affected by drugs than are nerve cells or the terminations of nerve fibres; and no drug is known which is able to exert a special influence upon the cardio-inhibitory nerve fibres, although there are many which stimulate the nerve cells in which these fibres originate and also their terminations in the heart. There are, moreover, drugs which seem to increase simply the sensitiveness of the vagus terminations without actually stimulating them, or at least without stimulating them sufficiently to slow the heart; the increased sensitiveness may, however, cause them to respond to a slighter stimulus than usual or with greater energy to a normal stimulus.

Another class of drugs, of which tartar emetic is a good example, depress the action of the cardiac muscle directly and so have been used as cardiac depressants; but such drugs are not considered as safe as those which work through, so to speak, more physiological channels. In fact, the depression brought about by a direct action upon the cardiac muscle is often associated with the condition known as collapse.

For the sake of completeness it may be added that the heart's action may be depressed by drugs acting in ways other than those just mentioned. Thus, if a drug causes a great fall of blood pressure the heart may be imperfectly supplied with blood and beat very feebly and slowly. If the blood pressure be much increased by a drug causing contraction of the arterioles, the high blood pressure may act as a stimulus to the vagus centre and so depress the action of the heart. The vagus centre may be stimulated reflexly by drugs having a powerful local action; it may also be stimulated by the accumulation of carbon dioxide in the blood if some drug which interferes with the respiration has been given. Again, it is probable that there are drugs which can slow the heart by depressing the accelerator nerves. Since these nerves are in a condition of tonic activity, any interference with their activity would lead to a slower rate.

While the most typical cardiac depressants exert their influence through the cardio-inhibitory mechanism, their action upon the organism is not by any means confined to this apparatus. Not only may many other functions—as, for instance, those of the central nervous system, the respiration, secretion, etc.—be influenced, but other parts of the vascular mechanism (the vaso-motor centres and nerves, the blood-vessels, the accelerator nerves of the heart, the cardiac muscle, etc.) may undergo changes which exert a profound influence on their action as cardiac depressants. In fact, a drug may stimulate the vagus and thus slow the heart and at the same time stimulate the cardiac muscle and in this way antagonize the effect of the vagus; sometimes one and sometimes the other effect will predominate. The condition becomes much more complicated when the preparation used contains several active principles, each with its peculiar action. For this reason it is desirable to use simple preparations and to determine as accurately as

possible all their effects; in this way reasons can sometimes be found for the failure of the drugs to produce the desired effects under certain circumstances.

The three drugs which have been used most extensively as cardiac depressants are aconite, veratrum viride, and tartar emetic.

Aconite.—The action of aconite as employed in medicine is almost identical with that of its chief alkaloid, aconitine. As most of the physiological experiments have been made with the alkaloid, its action will be considered first, and then the manner in which the other substances present in the ordinary preparations of aconite influence its action will be discussed.

Aconitine affects the circulation in three ways: it has a direct action upon the heart muscle, it stimulates the centre of the cardio-inhibitory nerves, and it influences the vaso-motor centre. With medicinal doses the second of these effects, the stimulation of the cardio-inhibitory nerves, is the most prominent and important and is the one desired in therapeutics.

When aconitine is administered to man or to one of the other mammals the first effect upon the circulation is usually a slight acceleration of the heart. This is usually attributed to a direct action upon the cardiac muscles, although it is not improbable that in some cases the effect may be brought about reflexly through the local irritant action which the drug is well known to have upon the terminations of sensory nerves. This slight acceleration may be accompanied by a small increase in arterial pressure. The acceleration of the heart, which with mammals is never marked and does not always occur, is followed by a remarkable slowing and weakening of the heart beat. In man a pulse rate of 36 to 40 not uncommonly follows a moderate dose of aconite. In cases of poisoning a still slower rate is occasionally seen; it is said to have been reduced to 10 per minute in one case. At the same time the pulse is much weakened. Sudden exertion at this stage may lead to a very rapid, irregular heart action and fatal syncope has occurred. Achscharumow (*Archiv für Anat. und Physiol.*, 1866, p. 255) showed that this slowing of the heart is due almost entirely to a powerful stimulation of the centre of the cardio-inhibitory nerves in the medulla oblongata. Section of the vagi prevents the slowing in nearly every case. At times, however, there seems to be a slight stimulation of the peripheral endings of the vagi, for some slowing may be observed when the drug is administered after section of the vagi; this slowing is abolished by atropine. This action upon the vagus terminals is of very slight importance in comparison with that upon the medullary centres; in fact, there is probably no drug which stimulates these centres as powerfully as does aconitine and has at the same time so little action, in small doses, upon other parts of the vascular mechanism. The amount of blood expelled by the heart under the influence of aconitine is much reduced and the blood pressure falls markedly. Some of the general symptoms of aconite poisoning are attributed to this fall of blood pressure. Thus there is a marked lowering of the body temperature, and this is usually ascribed to the depression of the circulation which leads to lessened oxidation and to an increased loss of heat from the surface of the body. Experiments of Brunton and Cash, however, indicate that there is also some action upon the nerve centres regulating the temperature of the body. The convulsions which frequently occur in cases of severe poisoning by aconite have been ascribed by some to the low blood pressure. While it is very probable that the latter is one factor in causing the convulsions, these seem to be due to a greater degree to a direct action upon some of the nerve centres, for convulsions occur in animals in which the fall of blood pressure is prevented by paralyzing the vagi with atropine. Moreover, there is ample evidence that several other parts of the medulla oblongata—the cardio-inhibitory, the vaso-motor, and the vomiting centres—are stimulated by aconite, and it is very probable that the nerve cells causing convulsions are similarly stimulated. The severe dyspnœa which is one of the first symptoms of aconite poisoning seems to be dependent to some extent upon the low blood pressure, for von Anrep (*Archiv für Anat. und Physiol.*, 1880, Supple. Bd., p. 180) found that if the blood pressure was raised by compressing the abdominal aorta the first symptoms of dyspnœa disappeared. Later there is a direct action upon the respiratory centre. The great muscular weakness so often observed seems to be due to anæmia of the spinal cord.

The details of the action of aconitine upon the mammalian heart have been recently studied by Matthews (*Journal of Experimental Medicine*, ii., p. 593) and Cash and Dunstan (Phil. Trans. of Roy. Soc., London, cxc., p. 248). By the use of a modified form of the Roy-Adami myocardiograph (an instrument by which the rate and force of the contraction of the cardiac muscle can be recorded) Matthews found that during the above, or first, stage of its action aconitine causes the following changes: the diastolic pauses of the ventricle are prolonged, the systolic contractions are weakened, while the relaxations of the ventricle are little changed or are a little increased. The relaxations of the auricle are little affected, but the diastolic pauses are much longer than in the ventricle. The auricular systolic contractions are greatly weakened and in some experiments are entirely suppressed, the auricle remaining in diastole; in such cases the ventricle assumes a slow, spontaneous rhythm. If the drug be administered in small doses, the rhythm can be reduced to one-half or to one-third of its original rate and the blood pressure lowered to a corresponding degree.

If the administration of aconitine be continued the heart beat becomes irregular and extremely rapid. Sometimes this effect is the first one seen in man, even after a moderate dose of the drug; it would seem that in such cases the cardio-inhibitory centre is not very irritable. The cause of this acceleration is frequently said to be the paralysis of the vagus terminations, but direct stimulation of the cardiac muscle seems to be a much more important factor. In fact, the effect of aconitine upon the peripheral endings of the vagi in the later stages of the intoxication has been a matter of considerable dispute. Some writers state that these structures are paralyzed, others that they remain intact, while a third group state that they may seem paralyzed at one instant and not at the next. Matthews has observed that sometimes stimulation of the vagus in the later stages of poisoning causes a change in the form of the contraction but no diminution in the rate. The explanation of the above results is probably that while the irritability of the vagus terminations is depressed that of the heart muscle is greatly increased so that inhibition is much more difficult. One reason why stimulation of the vagi causes slowing of the ventricle at one instant and not at the next may be found in the varying irritability of the muscle fibres connecting auricle and ventricle; these may be in a condition to transmit impulses from the auricle to the ventricle at one time but not at another.

Simultaneously with this acceleration, and often preceding it, there appear marked irregularities in the rhythm of the heart. These irregularities affect both the strength and the rate of the heart beat; they will be discussed somewhat fully here as similar irregularities occur after poisonous doses of many of the drugs acting upon the heart. At first, certain ventricular beats seem "missed"; when the number of such beats increases, the rate may seem but half as fast as before; but closer examination usually shows that there is an alternation of large and small beats and that only the former are distinctly recorded. The blood pressure falls during these imperfect systoles. This period of alternate large and small beats may be followed by a very rapid but regular rhythm during which the extent of the contractions is very limited. The auricle departs but little from the position of diastole and the ventricle from that of systole. Then periods of rapid beats may alternate with periods of slow beats. So far the auriculo-ventricular rhythm may have remained unaltered, each beat of the auricle being followed by one of the ventricle; but this rhythm is soon disturbed and contractions of the ventricle may occur independently of the auricle. The ventricular beat may dissociate itself entirely from that of the auricle and the two chambers beat independently of each other. At the same time there seems to be an effort on the part of the heart to maintain a simple ratio between the beats of the auricle and the ventricle; frequently this ratio is two to one or one to two—*i.e.*, the ventricle beats one-half or twice as fast as the auricle. Sometimes, when no such simple ratio exists, if one chamber becomes accelerated the other may become slowed until such a ratio is established. Many varieties of pulse may develop during this stage; but they may at any time yield to a regular one for a brief period, and stimulation of the vagi or accelerators will usually bring about the same result. The chief cause of this irregularity seems to be an increase of the irritability of the cardiac muscle which enables the ventricle to beat independently of the impulses received from the auricle. Two rhythms (one ventricular, the other auricular) are thus established, and they may interfere with each other. The extent of this interference is determined by the condition of the muscle fibres connecting auricle and ventricle and which transmit the impulses from one chamber to the other. As the intoxication continues the irritability of the cardiac muscle becomes greater and greater, and the ventricle contracts exceedingly rapidly and imperfectly and finally passes into delirium. These cardiac irregularities caused by aconite are antagonized to a considerable extent by atropine. The latter does not prevent the acceleration, but it reduces the tendency to arhythmia and tends to approximate the speed of the ventricle to that of the auricle when the auriculo-ventricular rhythm is disordered, and it averts or delays the very rapid and feeble action of the systole which is the precursor of death. In fact, atropine often enables the heart to stand several times the fatal dose of aconitine. Although the usual cause of death in aconite poisoning is failure of the respiration, it is necessary to pay attention to the condition of the heart, and probably as much good is to be expected from atropine as from any drug.

The blood pressure is extremely irregular during the second stage of the action of aconitine. When the heart is very irregular the pressure falls to nearly zero, but it rises again during the periods in which the heart beats more regularly. It is also fairly high when some simple ratio is maintained between the rate of the auricular and ventricular beats and is lowest when the asequence of the two chambers is most marked. These sudden changes in the blood pressure are undoubtedly due largely to changes in the heart beat, but there is evidence that the vaso-motor centre is also affected. If atropine be administered to an animal in quantity sufficient to paralyze the vagus terminations, aconitine causes a rise instead of a fall of blood pressure. The cause of this rise of pressure is usually considered to be a stimulation of the vaso-motor centre, but it is also stated that there is a constriction of peripheral vessels due to a direct action of the drug upon their walls. In the second stage of poisoning the vaso-motor centre is depressed; asphyxia now causes but a slight rise of blood pressure, and the same is true of a stimulation of a sensory nerve (although in this case the possibility of the paralysis of the sensory nerve itself must be considered). The peripheral vaso-motor nerves remain intact, as is shown by the fact that stimulation of the medulla or of the splanchnic nerves causes a rise of blood pressure even late in the intoxication.

Most preparations of aconite contain besides aconitine certain of its decomposition products, especially benzaconine and aconine. Benzaconine, which differs from aconitine only in that one acetyl group has been removed, has an action upon the heart having little resemblance to that of aconitine; in fact, it acts to some extent as an antagonist of aconitine. Instead of causing a great acceleration of the heart as do large doses of aconitine, it slows the heart, especially the ventricles, and if incoordination between auricle and ventricle is produced the latter beats more slowly than the former; with aconitine the opposite is usually the case. The slowing of the heart is due largely to a direct depression of this organ. It is not due to a stimulation of the inhibitory nerves, either centrally or peripherally, as it occurs after atropine.

Aconine, which differs from benzaconine in that a benzoyl group has been removed, has an action just the reverse of aconitine. Instead of being a cardiac depressant it is a cardiac stimulant and strengthens the heart beat; the blood pressure rises and no disturbances of the rhythm are produced. In fact, it is an antagonist of aconitine and tends to prevent asequence of the auricle and ventricle by facilitating the transmission of impulses from one chamber to the other. It also opposes the tendency of the ventricle to go into delirium.

The action of benzaconine and aconine is, however, so feeble in comparison with that of aconitine that it is improbable that they do more than simply to weaken the action of the latter. It is due largely to these decomposition products that the preparations of aconite vary so much in strength.

A number of other alkaloids derived from the Aconitum genus have been isolated, but they have at present little interest and their action upon the heart is not well known. Among these are pseudaconitine (the alkaloid of Aconitum ferox); lappaconitine, septentrionaline, and cynoctonine—all derived from Aconitum septentrionale; and lycaconitine and myoctonine from Aconitum lycoctonum. In addition to these certain artificial derivatives of aconitine have been prepared recently and studied by Cash and Dunstan.

Another alkaloid closely resembling aconitine, but one which is little known, is delphinine. It is found in Delphinium staphisagria, or stavesacre, along with a number of other bases which may be products of its decomposition.

Veratrum viride. Several species of the genus Veratrum have been found to contain alkaloids which resemble aconitine in their action upon the heart.[1] The only preparations in use as cardiac depressants are derived from the rhizome and roots of the American or green hellebore, veratrum viride. After the administration of veratrum viride to man the first effect upon the circulatory system is a reduction of the force of the pulse; the rate is not at first influenced. A little later the pulse rate is much reduced; in exceptional cases it may fall to 35 or even 30 beats per minute, any alarming symptoms which may arise passing away when the administration of the drug is discontinued. The pulse may be moderately full, but it is soft and compressible. If any exertion be made at this stage the pulse becomes very rapid and may become almost imperceptible. The slowing is especially marked during sleep, the patients thus exhibiting an intensification of the ordinary physiological law in virtue of which the pulse falls during sleep. The reduction in pulse rate is often accompanied or followed by nausea and vomiting; there seems, however, to be no connection between these, for if the drug is administered with care a very marked reduction of the pulse rate may occur without any nausea being produced. Decided muscular weakness accompanies the depression of the pulse. Profuse perspiration also occurs; this is frequently attributed to the low blood pressure, but as the drug stimulates the cutaneous glands of frogs it is not improbable that it has some direct action upon the terminations of the sweat glands. After toxic doses there are also a fall of temperature and convulsions as in aconite poisoning and a running, almost imperceptible pulse.

Efforts have been made to analyze the action of the veratrum alkaloids by experiments upon animals, but these have not as yet been entirely satisfactory. This result is due largely to the confusion which has prevailed as to the chemistry of these bodies, so that it is not always certain with what substances the various investigators have worked. According to Wright and Luff the following alkaloids occur in veratrum viride: jervine, pseudojervine, cevadine, very little rubijervine

and traces of veratrine and veratralbine. The alkaloid called by Wright and Luff "cevadine" has the empirical formula $C_{32}H_{49}NO_9$; this is usually called "veratrine" or the "crystalized veratrine of Merck," and will be so designated here. There are three modifications of this veratrine, one crystalline and two amorphous; they all have the same physiological action. The alkaloid called by Wright and Luff "veratrine" has the formula $C_{37}H_{53}NO_{11}$; its physiological action is not well known. Bullock discovered an alkaloid in veratrum viride which he named veratroidine; this seems to have been a mixture of rubijervine and an almost inert resin. Wood studied the physiological action of jervine and the so-called veratroidine. The alkaloids the physiological action of which have been most studied in Europe have been derived from veratrum sabadilla (Asagræa officinalis) and V. album. The seeds of the former contain veratrine ($C_{32}H_{49}NO_9$), the veratrine of Wright ($C_{37}H_{53}NO_{11}$), and cevadine. A mixture of these alkaloids constitutes the Veratrina of the United States Pharmacopœia. Of these alkaloids only veratrine has been carefully studied, but it is not certain that the earlier investigators worked with pure preparations. Veratrum album contains protoveratrine, jervine, pseudojervine, rubijervine, protoveratridine, and others; of these the physiological action of protoveratrine is best known.

Thus the alkaloids of veratrum viride the physiological action of which is known are jervine, veratrine, and rubijervine. The effects produced by preparations of the entire drug are doubtless due largely to these three bodies, and a brief résumé of their action will be given.

The principal investigation of the physiological action of jervine has been made by Wood (*Amer. Jour. of the Med. Sciences*, 1870, and Philadelphia *Medical Times*, iv., 1874), and the following account is taken from his papers. After the administration of jervine to an animal the pulse is generally, if not invariably, lessened in frequency, provided the animal is quiet. When there are convulsions or even marked tremors the pulse becomes very rapid. The arterial pressure is greatly lowered, falling progressively from the beginning to the end of the experiment. The force of the individual beats appears not to be much altered at first. According to Wood these effects are not due to a stimulation of the cardio-inhibitory nerves, for they occur after section of these nerves.

Stimulation of the peripheral ends of the vagi in animals under the influence of jervine caused the usual cardiac results. The alkaloid lessens the arterial pressure after division of the spinal cord—*i.e.*, after vaso-motor paralysis; it also paralyzes the heart of the frog or turtle when placed directly upon it. From these experiments Wood concludes that jervine lowers the force and frequency of the cardiac beats by a direct action upon the cardiac muscle or its contained ganglia. Apparently, however, Wood did not exclude the possibility of the slow heart being due to a stimulation of the vagus endings. Stimulation of sensory nerves or asphyxia caused little or no rise of arterial pressure, indicating a paralysis of the vaso-motor centre.

Wood also studied the action of an alkaloid which he called veratroidine; this, as has been already noted, seems to be a mixture of rubijervine and a resin. This substance caused at first a slowing of the heart and a fall of arterial pressure. After a time, the pulse still remaining very slow, the individual beats became unusually powerful and the blood pressure became normal; then suddenly the pulse rate became very rapid, the individual heart beats losing much of their extraordinary vigor, but the arterial pressure rising nearly fifty per cent. beyond its original position. If the alkaloid was thrown directly into a vein there was a very rapid fall, and then a remarkable rise of blood pressure; the latter is due to asphxyia and did not occur if artificial respiration was maintained. The slowing of the heart was due to stimulation of the cardio-inhibitory centres in the medulla; it did not occur if the vagi had been divided. If, moreover, marked slowing had occurred with intact vagi, section of these nerves was followed by a great acceleration. The slowing was especially marked when the spinal cord had been cut so as to paralyze the accelerators; under these circumstances Wood saw gr. $\frac{1}{10}$ of the alkaloid completely stop the heart, which however commenced to beat again when the vagi were divided. After large doses the slow pulse was replaced by a very rapid one; that this was due, at least in part, to paralysis of the vagus termination was shown by the fact that stimulation of the vagus now had no effect upon the heart. Enormous doses thrown directly into the circulation killed the cardiac muscle directly. Veratroidine (rubijervine) had little or no effect upon the vaso-motor system. Asphyxia or stimulation of a sensory nerve caused a great rise of arterial pressure just as in normal animals.

The action of veratrine upon the mammalian heart resembles in general that of aconitine, except that the stimulation of the cardiac muscle is not so marked. Bezold and Hirt ("Untersuchungen aus dem physiolog. Laboratorium in Würzburg," 1867, p. 95) describe the effect upon the circulation in mammals as follows: The first effect of a small dose is a slight acceleration of the heart, probably due to direct stimulation to the cardiac muscle; then comes a slowing of the heart. With a large dose the latter is the first effect; the pulse rate may be reduced to one-half or one-third the previous rate. Section of the vagi now is followed by an acceleration of the heart; this shows that the medullary centres of the cardio-inhibitory nerves are stimulated just as in aconite poisoning. At the same time there is an increase in the irritability of the vagus endings in the heart, for electric stimulation of the peripheral end of this nerve, which in the unpoisoned animal had no effect, produces a marked slowing after the administration of the drug. If the vagi be divided before the administration of the alkaloid, then this causes an acceleration of the heart, showing that the cardiac muscle is affected directly. This acceleration is followed by a slowing of the heart; this seems to be due to a direct poisoning of the heart muscle. With larger doses the heart is slowed still more, and now the strongest stimulation of the vagi has no effect upon the heart, showing that the vagus endings are paralyzed. These facts indicate that large doses reduce the irritability of the cardiac muscle and paralyze the terminations of the vagi, whereas small doses increase the irritability of both.

After a very large amount of veratrine the heart becomes irregular; unlike the heart in aconitine poisoning, however, it remains slow. The irregularity consists chiefly in the ventricle assuming a rhythm slower than that of the auricle; the ventricular beats then become weak and of a peristaltic character. Little blood is expelled, and the ventricle becomes widely distended and finally stops in diastole; even electrical stimulation does not cause a contraction—indicating a profound poisoning of the cardiac muscle.

Small amounts of veratrine stimulate the vaso-motor centre; this and the slight stimulation of the cardiac muscle cause a rise of blood pressure. After larger amounts the vaso-motor centre is depressed; this increases the fall of blood pressure caused by the slow heart. Bezold and Hirt ascribed the fall of pressure in part to a stimulation of the depressor nerve, but later investigators have failed to confirm this view. Lissauer (*Archiv für experiment. Path. und Pharmakol.*, xxiii., p. 36, 1887) has obtained results slightly different from those of Bezold and Hirt. Thus, he thinks the chief action of veratrine is upon the vaso-motor system and that the heart is not as much depressed as was thought to be the case by Bezold and Hirt. Lissauer found no paralysis of the vagus endings.

Hedbom (*Skand. Archiv für Physiologie*, viii., p. 197, 1898) has recently contributed a very interesting article on the action of veratrine upon the isolated mammalian heart. The heart (of the rabbit) was kept alive by the circulation of a mixture of blood and normal saline solution through the coronary arteries—*i.e.*, by a modification of Newell Martin's method. The contractions were

recorded by a thread attached to the ventricle and moving a small lever. When a very small amount of veratrine was mixed with the circulating blood there was first a sudden and very considerable (up to forty per cent.) increase in the amplitude of the contractions. This increase in the amplitude was due to a more complete systole, *i.e.*, to a greater shortening of the muscle fibres. Soon the relaxation became less complete and so the amplitude decreased again. There was usually a slight acceleration of the heart (as described by Bezold and Hirt); this was followed by a marked slowing. During these slow, large heart beats the individual contractions were much prolonged—up to three and a half seconds. As is well known, one of the most characteristic of the physiological actions of veratrine is the peculiar effect it exerts on ordinary striated muscle: the contraction is increased and enormously prolonged. Bezold and Hirt, Böhm, and others have shown that the ventricle of the frog's heart is affected in a way similar to that of the skeletal muscle. The experiments of Hedbom show that veratrine has a similar action upon the mammalian heart. The slight acceleration of the heart seen immediately after the injection of the drug seems to be due to a direct stimulation of the cardiac muscle; the more marked slowing which follows is probably due to a stimulation of the vagus terminations in the heart, as it is often removed by the administration of atropine. A secondary acceleration follows this slowing of the heart. This appears to be due in part to a paralysis of the vagus terminations, in part to a stimulation of the cardiac muscle. This secondary acceleration is often accompanied or preceded by marked irregularities, resembling those seen in digitalis poisoning. This irregularity is marked by the formation of groups and by the appearance of "missed" beats—*i.e.* strong contractions are followed by very weak, almost imperceptible ones. Finally, the heart muscle is paralyzed.

Thus the action of three of the alkaloids of veratrum viride upon the heart is tolerably well known; that of the others is very imperfectly known, but they seem to resemble those already described. No complete experiments seem to have been made with any of the ordinary preparations of veratrum viride in which all of the alkaloids are present, and it is not altogether easy to form a clear idea of the details of the action of such preparation from what is known concerning these three alkaloids. While chemical analyses show the proportion in which the various alkaloids occur in veratrum viride, we have few data as to the comparative toxicity of the individual alkaloids. It seems, however, that veratrine is more powerful than most of the others, and since, according to Wright and Luff, it is the most abundant alkaloid in veratrum viride, it probably plays a much more important part in the action of the preparations of the crude drug than has been generally recognized. Rubijervine is also very poisonous, but it occurs in small quantities.

From the various experiments described above, assuming that all are trustworthy, we may perhaps draw the following conclusions as to the action of veratrum viride upon the circulation: The slowing and weakening of the heart are due to the stimulation of the medullary centres of the cardio-inhibitory nerves by the veratrine and rubijervine (veratroidine). This slowing may be increased by the stimulation of the vagus terminations by the action of the veratrine. The slowing may be due in part to the direct action upon the cardiac muscle by the jervine, but this effect is doubtless antagonized to some extent by the stimulating action of the veratrine described by Hedbom. In therapeutics this slowing of the heart is the only effect desired, and it will be seen that it is produced to a large extent in the same way as when aconite is used—*i.e.*, by a stimulation of the vagus centre in the medulla. With veratrum viride there is another action, however, which is scarcely shown at all by aconite, viz., a stimulation of the vagus terminations in the heart, and it is possible that veratrum viride may thus cause slowing in some cases in which aconite would fail. The rapid pulse after large doses of the drug is due to a paralysis of the vagus terminations by veratrine and rubijervine and perhaps to some stimulation of the cardiac muscle. At the same time jervine and larger amounts of veratrine weaken the heart by a direct action upon the cardiac muscle. Veratrum viride in large amounts does not tend to produce as rapid a pulse as does aconite, probably partly because all the alkaloids have a less stimulating action on the cardiac muscle and partly on account of the peculiar action of veratrine upon all kinds of striped muscle. The fall of blood pressure caused by veratrum viride is due largely to the slowing of the heart; at the same time the vaso-motor centre is depressed by the jervine and when larger amounts are given, by the veratrine.

The physiological action of protoveratrine, the chief alkaloid of veratrum album, has been studied by Eden (*Archiv für exper. Path. und Pharmakol.*, xxix., p. 440, 1892). As far as its action upon the circulation is concerned this alkaloid does not differ very much from veratrine.

Tartar Emetic.—Tartar emetic is classed with the cardiac depressants for clinical and not for pharmacological reasons. Although it depresses the circulation to a marked degree, it has no such special action upon the heart as have aconite and veratrum viride; in fact its action does not differ greatly from that of several other drugs which, since they have never been used clinically for this purpose, are never thought of as cardiac depressants.

The action of tartar emetic upon the pulse in small doses is closely connected with, and to a considerable extent dependent upon, its action as an emetic, for ordinarily it is absorbed very slowly and in very small amounts. The effect upon the circulation of man is described by Ackermann (*Virchow's Archiv*, xxv., p. 531, 1862) as follows: After a small dose the pulse becomes accelerated as feelings of nausea arise and reaches its maximum rate just before the act of vomiting. Thus in one case the normal pulse rate was 71 per minute; during the period of nausea it rose to 110. The strength of the pulse decreases with the increase in rate, and vice versa. It is not necessary for vomiting to occur; the mere sensation of nausea is sufficient to cause an acceleration of the heart. Any drug (such as apomorphine) or any condition (as sea-sickness, swinging, etc.) which causes feelings of nausea is accompanied by a similar acceleration of the pulse. This acceleration is sometimes attributed to a reflex stimulation of the accelerator nerves, but it is more probable that it is due to a reflex diminution of the tonus of the cardio-inhibitory nerves. Accompanying this change in the pulse rate and probably dependent upon it there is a fall of temperature of the extremities and other symptoms of mild collapse. Thus Ackermann found the temperature of the hands to fall .2 to 3.5° C. during the period of nausea; the temperature under the tongue did not vary. After large doses the pulse becomes very feeble, then slow, intermittent, and irregular and the other symptoms of collapse are very marked. The depression of the central nervous system and of the respiration is doubtless due in part to the circulatory disturbances. These more pronounced effects upon the circulation are probably due in part to a direct action of the poison upon the heart. That antimony does exert a depressing action upon the heart is shown by experiments upon the lower animals; the action is most marked in the case of the frog's heart.

Soloweitschyk (*Archiv für exper. Path. und Pharmakol.*, xii., p. 441, 1880) found that for some time after the administration of antimony (in the form of the antimony-sodium tartrate) to a frog the heart continued to beat regularly; the contractions were at times unusually vigorous and the rate was slightly increased. Then the contractions became irregular and peristaltic; arhythmia of auricle and ventricle soon developed, the latter beating but one-half, then one-third, one-fourth, etc., as rapidly as the former. Finally the ventricle stopped in diastole while the auricles continued to beat feebly. The cardiac muscle does not seem to be paralyzed, for a little helleborein will cause it to commence beating again; only the