fangs deeply implanted, or was the skin merely scratched? How old and in what condition of health was the bitten individual? India, as is generally known, has the largest mortality from snake-bites—a fact easily explained by the enormous number of snakes, and these the most deadly of all, the cobras. Nevertheless, indolence and superstition of the population may increase the number of fatal accidents considerably. Those may be right who consider the smaller number of deaths in America and Australia as due to the greater intelligence of the people, because a rational treatment, especially the early application of a ligature, is instituted in time.* In default of reliable analyses, the only way to decide this point has been shown by Calmette to be that of comparative experiments. After carefully graded hypodermic injections, to determine how much poison may kill a kilogram of animals (mostly rabbits), the following table has been worked out:

1 gm. of cobra and aspis kills	4,000 kgm. of rabbit.
1 gm. of hoplocephalus kills	3,450 kgm. of rabbit.
1 gm. of fer de lance and pseudechis kills	800 kgm. of rabbit.
1 gm. of Crotalus horridus kills	600 kgm. of rabbit.
1 gm. of Pelias berus kills	250 kgm. of rabbit.

But even this method has not yet yielded undisputed results, for Martin claims for hoplocephalus 4,000 and for pseudechis 2,000 kgm. At any rate the toxicity of snake venom is exceedingly high. A comparison with the toxins of infectious diseases shows that only that of diphtheria comes up to 4,000 kgm., toxopeptone to 3 kgm., and the albumose of anthrax to not more than 80 gm. Besides the high toxicity it is also the extremely rapid absorption and consequent early appearance of grave symptoms which distinguish snake venom from other toxins.

If the most serious cases (*e.g.*, when both fangs, and especially those of a large tropical snake, have thrown their full dose of poison into the tissues) are left out of consideration the prognosis is not so bad as is generally believed. Weir Mitchell gives the mortality of crotalus bites in one place as 25 per cent., in another as not more than 12 per cent.; that of the Australian snakes is said to be only 7 per cent.; but for India Fayrer states it at from 25 to 35 per cent. It has been mentioned how quickly an amelioration may set in, even after the most serious nervous symptoms have preceded. This is undoubtedly a reason why so many remedies have gained the undeserved reputation of being a sure cure. Most of the patients would have recovered without them. Comparing these conditions with the results obtained in experimental bacteriology, we should say that in most cases of snake-bite the minimum lethal dose of toxin is seldom injected, so that the body cells are still able to combine with and fix the toxin, in consequence of which they not only speedily recover, but also, as we shall see later on, develop a certain immunity by casting off antitoxin.

TREATMENT.—The proof of the utter helplessness of therapeutics of past years is the long array of remedies recommended and used at all times for snake-bite. The object of treatment is threefold: first, to prevent absorption of the poison; second, to accelerate its elimination; third, to destroy or neutralize it, and to treat symptoms of imminent danger. If the wounded limb, *e.g.*, a finger, cannot be amputated quickly, at least the circulation should be checked or retarded by a ligature, as practised since time immemorial. A ligature is applied as tightly as possible, not only at one, but at two or three places—*e.g.*, when a finger has been bitten, round the finger itself, at the wrist and at the elbow. The experienced Wall is so convinced of the advantages of Esmarch's rubber band that he not only recommends every physician in India to have one in readiness, but wants to see it in every well-regulated household. The ligature is relaxed at intervals of some hours to prevent gangrene, but is applied again as soon as practicable.

It has been an often recommended custom to suck the wound with the lips or to apply cups. The result of such a measure is at least doubtful, because of the finely punctured bites; the sucking ought to be preceded by a long scarification into the deeper tissues. It is still safer to excise a large area of these tissues or to destroy them with the actual cautery. Wall, taught by long experience, recommends proceeding in the most ruthless manner. By these means the absorption of poison can be limited to a possible minimum, so that the system shall gain time to overcome the whole quantity at intervals.

How can we hasten the elimination of the injurious substance? The kidneys are attacked to a greater or lesser degree by the poison, especially that of vipers; hence it is doubtful whether we should be permitted to increase their activity. The vicarious excretion by perspiration, stimulated by diaphoretics (*e.g.*, jaborandi) has had dubious results. It has been demonstrated, however, that part of the poison is excreted by the stomach. Alt found that alkaloids, chiefly morphine, after hypodermic use were excreted by the stomach almost to one-half of their amount. When he tried the same method for snake venom, it was discovered that the animals whose stomachs were washed out were saved, whereas the controls died; at the same time, the washed-out fluid was again poisonous to other animals. Hence it is probable that the use of the stomach pump may be of good service. Those who have read a minute description of, or have personally witnessed, the snake dance of the Moki and Zuñi Indians of Arizona will remember that after the performance the dancers, who are sometimes bitten by the snakes, receive a potion prepared by the priests which contains an emetic. The whole crowd stand around a certain part of the parapet to empty their stomachs freely. This custom has undoubtedly been justified by long experience.

The question then remains, Are we able to render innocuous the poison in the tissues surrounding the bite? This efficacy has been claimed for a whole series of specifics, which owe their reputation partly to old traditions, partly to experiments in the test tube. The majority of these specifics, which it is true neutralize the poison *in vitro* after a shorter or longer period (carbolic acid, *e.g.*, only after twenty-four hours), destroy all tissues to such an extent that it seems preferable to apply the cautery. Even the much-praised permanganate of potassium, recommended especially by Lacerda, of Rio, Brazil, has not fulfilled the high expectations, for neither locally applied in a one-per-cent. solution nor injected intravenously has it the elective faculty to single out snake venom for oxidation in presence of other proteids. One per cent. of chromic acid has gained somewhat of a reputation; it does not destroy the tissues simultaneously with the poison, but it merely makes them shrink. Calmette has frequently tested hypochlorite of lime in a solution of 1 to 60.* He found both its local and repeated hypodermic application near the bite as well as its internal administration of good effect; not less so a one-per-cent. solution of chloride of gold as a local remedy.

Ammonia, extensively used internally and externally, is nothing but a stimulant. Feoktistow actually advises against it, because he thinks he has seen after its use increasing hemorrhages, caused by higher blood pressure. Wall also cautions against exciting the circulation by stimulants; he advises to keep the victim as quiet as possible and to husband his strength. Neither has alcohol any local effect as a coagulating medium; it is to be rated also as a mere stimulant. It has always met with appreciation on the part of the real or, more so, of the alleged victim. Indeed, the use of this infallible specific has often been carried to such an extent that it was impossible to decide whether the patient succumbed to snake venom or to an acute alcoholism. In one case,

*The statistics of the Indian Government have given for years an average annual mortality of 20,000 persons. Recent advices, however, have called this number again into doubt, as has been done before. It seems to be the practice of officials in remote, isolated districts to ascribe in their reports any case of death to snake-bite, whenever it is thought desirable to cover a crime or even a neglect of duty on the part of the official.

* He advises against the employment of more concentrated solutions which are less active and produce eschars.

e.g., the use of five quarts of whiskey is recorded. It is, moreover, a fact that intoxicated persons, when bitten in this state, have not proved to be better protected against snake-bites than sober people; and the enormous doses which we often hear of as having been administered deserve nothing but condemnation.

As to a rational treatment, it is necessary to inquire first as to the prominent morbid changes which threaten life. Are they irremediable or are they transient? That they are transient is proved by the many individuals who survive a snake-bite in spite of the gravest symptoms. We have seen that the poison exerts, first, a hæmolytic action; second, a destructive influence upon the cells of the medulla. We know at present of no pharmaceutical remedy which will arrest either the escape of the hæmoglobin into the plasma or the rupture of the capillaries, nor is any drug known that will check the influence of toxin upon the nerve cells. The changes in the ganglion cells, the dissemination and disappearance of the Nissl granules, whatever this may mean, must be fully reparable, since, as we have seen, rehabilitation takes place rather suddenly without leaving any sequelæ. If we are not able, *e.g.*, to re-establish the function of the respiratory centre immediately, could we not at least tide over the dangerous period of deep depression? One method suggests itself to a medical mind, *i.e.*, artificial respiration. The heart beat ceases several minutes later than respiration, and in one experiment Fayrer succeeded in keeping up the circulation for eight hours longer by artificial respiration. Fayrer and Lauder Brunton strenuously recommend that it be continued not only for hours but for days, with or without a tracheal cannula. This advice seems to have fallen somewhat into disuse, especially since Martin claims that in poisoning by Australian snakes he saw no good results from artificial respiration, death occurring in spite of it in fifteen minutes after the heart stopped. Notwithstanding some failures, we are justified in trying it for an extended time, always keeping in mind that an abrupt change may set in in the most desperate cases.

In this connection we have to consider a remedy which even recently has been praised with a certain persistency as a specific, *i.e.*, strychnine. First used by Pringle in Australia, it was tested in India, and in spite of the little encouraging reports was enthusiastically championed by Dr. Muller, of Sydney. He declared that the failures were due to insufficient doses, and he began with a dose of at least 0.01 gm., repeated several times until slight tetanic symptoms appeared.*

Many cases in Australia have been treated with strychnine, and upon the advice of the Government Indian surgeons have also used it quite extensively. Nevertheless, the results are not so convincing that we could rely upon this drug as a specific. The experiments of Kanthack and Feoktistow were negative. Interesting, however, is the latter's positive experiment that artificial tetanus, brought on by strychnine, was arrested by snake venom. Roux states that tetanus antitoxin has a certain influence upon snake poison, but not inversely. Atropine has been recommended as a stimulant for the respiratory centre. Not many instances of its use are recorded, but there is no reason why it should not be resorted to as well as strychnine.

It may be appropriate to relate the few instances in which snake poison has been used therapeutically. Dr. Amaden, of Glens Falls, near Lake George, a country abounding in rattlers, cured a man, aged twenty-five years, with unmistakable tetanus by two injections of one drop of fresh rattlesnake poison. It should be mentioned that snake venom has been used in an unsystematic way for several other diseases (*e.g.*, yellow fever), of course without success. Recently it has been asserted that during the plague in India some successful inoculations of cobra poison (gtt. $\frac{1}{20}$ and $\frac{1}{25}$) were made, and that some similar experiments in monkeys gave equally good results. Later correspondence, however, is silent regarding these experiments. The treatment of lepra with snake venom has been without any result.

Antivenomous Serum.—The therapeutics of snake-bite were in this state of hopelessness when in 1895 Calmette, and almost simultaneously Fraser, surprised both the scientific and the lay world with an antivenomous serum. It is to serum therapy and immunization, as we shall presently see, that we have to look for the successful treatment of snake-bites.

Regarding this topic the question first arises: Are there animals, as often asserted, which are immune to snake poison? In East India the mongoose, a kind of weasel, the deadly enemy of the cobra, has the reputation of immunity; and in Europe the droll, bristled hedgehog (Erinaceus europæus) is considered as the natural destroyer of vipers because of its reputed invulnerability. More accurate observers have shown that the mongoose owes its apparent safety to a low susceptibility (from ten to twenty-five times less than rabbits, Elliot) against both cobra and viper venom, but more to its agility, and that the hedgehog is partly protected by its spinous coat. It possesses, however, a higher resistance to snake poison than other animals, and from my own investigations I might figure a resistance of about four times that of a rabbit of equal weight. A relative immunity toward various toxins is well known to exist in different animals. The poisonous snakes themselves possess a perfect immunity against their own poison, the species with weaker poison a relative immunity toward those with stronger venom, and even the non-poisonous snakes enjoy a certain security against the bites of the poisonous ones. The king-snakes of our Southern States, which are the enemies and destroyers of our poisonous serpents, seem to enjoy a perfect immunity.* Although Weir Mitchell finds that, at least in some cases, crotalus is not immune against its own poison, it is a common occurrence among venomous snakes in captivity that they bite each other furiously without any evil effect. One of Cunningham's cobras resisted inoculation with an amount of cobra venom sufficient to kill one thousand fowls. This faculty is ascribed to inner secretion, to the incessant influx of toxin into the circulation. The discovery of Blanchard, that the extract of the yellow part of the supralabial gland of Tropidonotus natrix, and even its blood serum, kills small animals with distinct symptoms of poisoning, seems to corroborate this theory. Cunningham, however, finding after many experiments with cobras that their serum has no antitoxic action, comes to the conclusion "that the natural immunity of cobras is perfectly distinct in its nature from the artificial immunity, which is established in other animals as the result of continued treatment with cobra venom, and that it is unconnected with any material of the nature of an antitoxin in the blood."

The idea of immunization is by no means a modern one. Even in antiquity we hear of it, and among savage tribes of ancient and modern times, wherever poisonous snakes abound, attempts at protection against snake venom are made under various forms, sometimes associated with mystic ceremonies. The poison is rubbed into the skin, as is done in Bengal, or it is taken internally in the fresh state, or parts of the dried poison glands are eaten (as practised by the savages of South Africa). A shepherd, immunized in this way, admitted that the dried gland of the cobra had an intoxicating effect, which he compared to that of Indian hemp, except that, whereas the latter lost its effect gradually, the action of the first was not impaired by habit. Or it is used as an inocula-

*The tolerance toward strychnine seems to be quite extraordinary in these cases: thus 0.035 gm. was used in the case of a boy thirteen years of age within three and three-quarter hours, 0.05 gm. in five and one-half hours, 0.05 gm. in four and one-half hours, 0.066 gm. in seven hours, 0.25 gm. in six days.

* I have injected a king-snake (*Ophibolus getulus*) of Florida of 700 gm. weight, with 1 gm. of fresh moccasin poison, a quantity which can never be injected by a single bite of the largest venomous snake. With the exception of a pronounced local swelling and some apparent sick feeling for a few days, the snake survived this experiment well. A crotalus of three feet in length and about 500 gm. weight received four drops of cobra venom: it sickened within half an hour and was found dead the next morning.

tion in the interior of Africa (Serpa Pinto). Sometimes one of the reputed antidotes is employed for an extended time, as, *e.g.*, the *curados de culebras* of Mexico use a composite plant, Micania guacho.*

Sewall, of Ann Arbor, Mich., was the first to introduce methodical inoculation of snake venom with the idea of immunization. His experiments, in which, by gradually increased doses, he made his pigeons secure against seven times the lethal dose of massasauga poison, were published in 1887. Calmette, director of the Pasteur Institute of Lille, France, after a number of failures succeeded in securing immunity, and at the same time in elaborating a protective antivenomous serum which, in spite of some weighty opposition, must be considered today the only reliable antidote to the deadly action of snake poison. Fraser, who worked independently of Calmette for six years on the same subject, has produced a similar serum, called by him antivenene. It is dried, in which state it is said to keep indefinitely. Calmette manufactures his serum by inoculating with cobra venom or with a mixture of cobra, crotalus, viper, and hoplocephalus venoms, in both of which the hæmolytic agent has first been eliminated by heating to 80° C. The inoculation of horses has been carried on in some instances for three successive years, so that these animals, which succumb to a dose of 15 mgm. of cobra poison, finally tolerate a dose of 2 gm. A prolonged feeding also imparts immunity, but requires larger doses and induces less protective power. Antivenomous serum is put up and sold in vials of 10 c.c. each. Its protective value is calculated by Calmette in the following way: If 1 c.c., injected into the ear vein, is found to protect a rabbit of 2,000 gm. (2 kgm.) against a dose of venom, fatal within fifteen to twenty minutes, it is said to contain 2,000 antivenomous units, and a vial of 10 c.c. consequently 20,000 units. No serum is sent out without possessing a strength of at least 10,000 units; and for the tropical countries serum of as high as 40,000 units is manufactured.

It has been shown by experiment (Myers, Martin, Semple, Flexner) that 0.1 cgm. of Calmette's serum neutralizes 0.1 mgm. of dried cobra poison, both *in vitro* and *in corpore*. This proportion holds good for the hæmolytic and antibacteriolytic and the inhibitory action of venom upon clotting of the blood. Of rattlesnake venom even 3 mgm. are neutralized by 1 c.c. of the serum. For the counteraction of the neurotoxic principle of the venom, somewhat larger doses of antivenomous serum are required. For practical purposes it may be stated that it acts as a full protective in a dose of from 5 to 20 c.c.; and the 10 c.c. contained in Calmette's vial are therefore amply sufficient for the average case of snake-bite when injected even one and a half hours after the introduction of venom. If more time has elapsed, or graver symptoms have set in—as may occur after the bite of a large tropical snake—it is advisable to inject 20 or even 30 c.c. simultaneously. Fraser recommends injections into the injured limb rather than into distant parts, and the administration of repeated smaller doses instead of one large dose; but Calmette thinks they are best made into the lax skin of the hypochondrium. Although antivenomous serum is absorbed rapidly from the subcutaneous tissue, it may not be quick enough in severe and belated cases; then it is advisable to resort to direct intravenous injection. Immunity thus conferred by antivenomous serum acts very rapidly and energetically, but disappears very soon again, inside of from two to four days, while immunity, created by gradually increased inoculations of venom, lasts for months (five to eight), the longer the larger doses were finally employed (active immunity). Even the young guinea-pigs of a mother thus immunized acquire immunity for several months.

Calmette's statements have not been accepted without contradiction. Fraser does not agree with him on all points, nor did the experiments and practical experience of the Indian surgeons and of Martin thoroughly confirm his premises and predictions. Not only has controversy arisen as to the curative value of antivenomous serum, but also other questions have been stirred up in relation to the chemical and physiological action of toxin and antitoxin, questions which promise to be of the greatest importance in settling this vital problem of therapeutics. The interest of the subject warrants us going into some details as regards the controversy.

First, it was objected that Calmette asserted his antivenomous serum to be equally effective against all kinds of venom, in direct opposition to Behring's law that every toxin requires a specific antitoxin. It should be borne in mind that Calmette's horses are immunized with a venom in which the hæmolytic element has been destroyed. Hence while he may work out an antitoxin to the more important constituent, the nerve poison, he neglects the other agent entirely. And indeed Cunningham declares an antivenomous serum which is efficient against cobra venom entirely valueless against Daboia venom and inversely, while Martin claims that Calmette's serum has a slight but distinct protective effect against one of the constituents of Australian snake venom; but, on account of its present slight antitoxic strength, it is practically valueless in Australia. Calmette, after having elucidated experimentally all these points of objection, comes to the conclusion "that his antivenomous serum acts as a perfect preventive against the venom of any species of snake." He admits that in a case of viper poisoning some local disturbances may persist, even with consequent suppuration, but that fatal exitus is at all events prevented. Other experiments seem to prove that also the hæmolytic agent in venom as well is decidedly influenced by antivenomous serum (Stephen and Myers). Furthermore, we must consider that a dose of venom may not be sufficient to kill, even though only one of its constituents has been neutralized. And as a most decisive proof, a number of reports from different parts of the globe leave no doubt of the curative value of Calmette's serum. It has been used with beneficial effect in East India, in Egypt, Africa, and the West Indies, against the different serpents of those countries. Some of the failures reported by the Indian surgeons may be accounted for by the deterioration and consequent diminution of power, to which antivenomous serum is subject in a hot climate. Notwithstanding this impairment, however, there are even reports of the effective application of such weakened samples of antivenene.

Another objection was made that the curative power was entirely overrated, since Calmette used as a test for estimating its value only one minimum lethal dose of poison. Fraser thus calculates that for a man weighing 60 kgm. a dose of 330 c.c. of antivenene would be required,* an amount which because of its bulk and price would preclude its practical employment. Statistics and calculations do not, however, bear out this objection, for, with rare exceptions, not much more than the lethal dose is injected by the snake in the average instance.

More theoretical, but not less interesting, is the question of action of the antivenene, whether it is chemical or physiological. Whereas Calmette with Roux and Buchner insists that antitoxin elicits or stimulates the resistance of tissues, Fraser and Martin assert with Behring that the action can be only chemical. The experiments with snake poison and its antidote conducted by Martin and others point positively to a chemical action.

Observations of great interest were reported by Phisalix. While experimenting with viper venom exclusively he found many substances which exhibited apparently a decided antitoxic effect—*e.g.*, cholesterin, separated from biliary calculi and from carrots, or tyrosin, obtained from the bulbs of the well-known flower Dahlia, and from mushrooms.* All these bodies, some of vegetable origin and the highest final products of proteid metabolism, had a decided immunizing effect against viper venom, as had also the serum of the animals treated with these substances. They were capable, however, of raising the resisting power of the organism but little above the minimum lethal dose of venom; and, moreover, to be at all efficacious, they had to be injected at least twenty-four hours previous to the administration of the venom.† A similar antitoxic influence is exerted by the cortical substance of the suprarenal glands.

Calmette, after repeating the above experiments, has extended them by using bouillon, bile, normal and antitetanic serum, etc., with the same apparent antitoxic effect, which is little pronounced and transient. He claims that all these substances act only as cell stimulants, to counteract the deleterious influence of the venom. Advocates of Ehrlich's theory would as well say that they stimulate the cell to the overproduction of a toxophil side chain, which as antitoxin is received and kept ready for use by the blood plasma. It is immaterial which theory we may apply. The observations of Phisalix are still in an experimental stage, and, though they may result in very practical conclusions, they may in the mean time serve to unravel the mysteries of the relation between toxins and antitoxins. And to investigations of this nature snake poisons, as Martin has pointed out, are particularly well adapted. They have the advantage of being less sensitive than other toxins to light and heat, and of being comparatively easy to obtain in a form which preserves a remarkably constant composition.

To sum up, the most commendable treatment would be:

One or several tight ligatures should be made above the wound, followed perhaps by deep scarifications; then injection of antivenomous serum, if at hand. If the latter cannot be had, injections should be made of 20 to 50 c.c. of a solution of hypochlorite of lime, 1 to 60, at several points near the bite and elsewhere. Stimulation, if necessary, by either strychnine or atropine (or alcohol?); lavage of the stomach; artificial respiration for hours; and, not least of all, continuous encouragement of the victim, for a deep mental prostration goes together with the physical depression of the nervous centres.

HELODERMA.—It remains now to consider the only poisonous reptile not belonging to the snake group, the lizard heloderma, which is represented by two species.

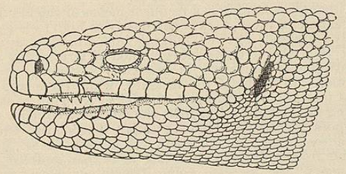

FIG. 3871.—Head of Heloderma. Side view.

The habitat of one of them, Heloderma suspectum Cope, is in the southwest of the United States, in New Mexico and Arizona, around the Gila River, while its somewhat larger congener, Heloderma horridum, lives in Central America. Its popular name, "Gila monster," denotes the awe and fear with which the animal is regarded by the native population, but the same is hardly justified by its exterior nor by its habits. The length attained by the adult animal varies from eighteen to twenty-two inches. Its skin, which is studded with innumerable horny elevations, like small, round nail-heads, exhibits a salmon or orange color, interrupted by black rings and irregular figures; the slow and sluggish, dragging gait does not enable it to make an attack or onslaught. The breath is said to be offensive and to issue from the mouth in puffs of black vapor; but only the black tongue is sometimes thrust out, and the exhalations and saliva have the pleasant odor of fresh calamus or sweetflag. Its reputation as a monster seems to be founded upon the fact that the natives have occasionally observed grave consequences following its bite. It undoubtedly bites very rarely, and then only when it is teased or cornered. When pursued it throws itself upon its back and bites in this position, holding on as tightly as a bulldog.

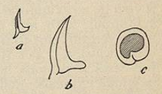

FIG. 3872.—Teeth of Heloderma. *a*, Natural size (3 mm. in length); *b*, enlarged (3 diam.); *c*, cross section.

The fact that but occasionally grave sequelæ follow the bite of a Gila monster accounts for the many discrepancies that have prevailed as to its toxicity until very recently, not only among the natives, but also among the best scientific observers. The first confirmation of its poisonous nature seemed to be established by the discovery of grooved teeth, about 3–4 mm. long, four on either branch of both maxilla and mandibula, in shape similar to those in the snakes Opisthoglypha or "suspecti."* The mandibula appears somewhat swollen, owing to the projection of its disproportionately large, elongated submaxillary glands, whose four separate ducts lead to the base of the above-described grooved teeth. The buccal secretion is whitish, transparent, slightly turbid, somewhat viscid, alkaline, mostly contaminated with traces of blood; it has the fragrant odor of calamus and shows some scaly epithelia, salivary corpuscles, and some amorphous granules. A hanging drop soon swarms with bacteria. Gelatin is liquefied with lemon-colored colonies. When biting on a rubber cord an animal yields on the average five to six drops; a large animal once gave twenty-two drops. The saliva dries in grayish-white scales to one-eighth or one-tenth of its original weight.

The arrangement of the teeth and of the glands makes us understand why opinions as to the poisonous nature of heloderma have differed so widely. When an animal seizes its victim only with the front teeth, or does not lie on its back while biting, none or very little of the buccal secretion may enter the wound. When, however, a vigorous bite has been inflicted, the consequent phenomena have proven the venomous character beyond any doubt, and the hypodermic application of the pure saliva in sufficient doses has invariably proved fatal to the animals experimented upon—rabbits, mice, and frogs.

The first effect of the injection—an inability to sit or stand—is manifested after a short time, about ten to fifteen minutes in frogs, thirty minutes in rabbits. A certain drowsiness, similar to a narcosis, overpowers the animal; paralysis and insensibility seem to proceed from behind forward. The respiration is not labored, but becomes gradually slower and superficial until the animal expires after a few hours with some hardly noticeable twitchings. The heart has first a period of increased activity, which is followed by gradual paralysis and a great fall of arterial pressure, due to vascular dilatation. While these symptoms prevail after a small dose of ven-

* From facts to be reported later on, it seems not at all improbable that certain herbs may contain substances which are capable of reducing the toxicity of venom.

* The logic of this argumentation is not quite obvious. Assuming that more or less power of natural immunity is dormant in every animal which enables it to overcome a subminimal lethal dose of poison, we ought to expect that this power increases in the same ratio as the size of the animal, no matter whether the power is ascribed to the whole system or to one or several separate organs. The average dose of poison in a snake-bite will remain the same in the large as in the small victim; part of it is immunized by the injured organism itself, and only the surplus remains for the action of the antivenene. Consequently, the larger animal stands a better chance and requires comparatively less antivenene. Calmette and others have already expressed this opinion by formulating a law that the quantity of antivenomous serum required is not only in inverse ratio to the susceptibility of an animal, but also to its weight. Man shows more power of resistance than the animals experimented upon.

* There are, no doubt, many other substances of similar action, and it is not improbable that some of the popular antidotes to snake venom, like the plant mentioned before, Micania, owe their partly deserved reputation to an influence similar to that stated above as exerted by cholesterin, etc.

† Possibly in these cases the presence of a large amount of cholesterin in the blood serum acts in the same way as it does with other protoplasma poisons, *e.g.*, saponin; it combines directly with the toxic substance, thus preventing the cholesterin of the blood cells themselves from doing so, and from being destroyed. (Ransom.)

* There is possibly another poisonous lizard in East India, Lanthanotus Borneensis, which differs considerably from Heloderma, but which is provided with shallow grooved teeth. As to its toxicity nothing is known (Steindachner).

om, large doses seem to act directly upon the heart muscle, the animals dying within ten to twenty minutes with dyspnœa and convulsions. Some investigators explain these symptoms as the consequence of general muscular paralysis (Santesson); others, as a paralysis of the central nervous organs (Van Denburgh). A faint hæmolysis is noticed *in vitro*, but in the body no effect upon the blood is visible, no exudation or hemorrhage appears. The local symptoms, with rare exceptions, are entirely wanting; it is even difficult to find the spot where the venom has been injected. Yet it ought not to be forgotten that a few cases of persons bitten by a heloderma are on record in which extensive and painful local swelling is noted.

The autopsy shows nothing but a very much dilated heart and an enormous venous congestion of all internal organs. The microscopical examination of the spinal cord, however, reveals extensive changes in the ganglion cells of the anterior horns; in fact, Bailey found the changes almost identical with those described as due to the action of snake venom. It is not hard to believe, therefore, that snake venom and the saliva of heloderma are almost identical in chemical composition. Santesson has demonstrated that this saliva contains albumoses as well as some nuclein bodies, the latter perhaps responsible for the slight action upon the blood.

Treatment.—It is to be expected that the persons bitten by a heloderma will seldom exhibit grave symptoms, except when accidentally a blood-vessel has been struck directly. A treatment after general surgical principles will suffice to subdue the local phenomena, while the organism has time to overcome the effects of the injected toxin. Yet a ligature ought not to be omitted, and otherwise the use of antivenomous serum should be resorted to as well. The similarity of the toxins of snake venom and the saliva of heloderma justifies the administration of the same antidote. Calmette even claims for his antivenomous serum the same success in stings of scorpions as for snake-bite. *Gustav Langmann.*

BIBLIOGRAPHY.

Alt: Münch. med. Woch., 1892.
Amaden: Med. News, 1883.
Auché: Journ. de Méd. de Bordeaux, 1902.
Bailey, in Langmann's "Poison Snakes," Medical Record, 1900, ii.
Blanchard: Compt. rend. de la Soc. de Biolog., 1894.
Calmette: Annal. de l'Instit. Pasteur, 1894, 1897, 1898.—Le venin des serpents, Paris, 1895.
Cunningham: Report, Calcutta, 1895–96, in Nature, 1896, December 10th.
Delezenne: Arch. de Physiol., x.
Eliot: Brit. Med. Journ., 1900, 1900, i., ii.
Ewing: Medical Record, 1894, i.
Ewing, J. in Langmann's, "Poison Snakes," Medical Record, 1900, ii.
Fayrer: Thanatophidia of India, London, 1872.
Fayrer and Lauder Brunton: Proc. Roy. Soc., 1872, 1873, 1875.
Feoktistow: Inaug. Dissert., Dorpat, 1888.
Flexner and Noguchi: Journ. of Exper. Med., vi.
Fraser: Brit. Med. Journ., 1895, i., 96, i.
Kanthack: Journ. of Physiol., xiii.
Leydig: Arch. f. mikr. Anat., ix.
Martin, C. J.: Proc. Roy. Soc. N. S. W., 1895.—Also in Allbutt's System of Medicine, iii.
Mitchell, W.: Smithsonian Contrib., xii.
Mitchell, W., and Reichert: Smithsonian Contrib., xxvi.
Müller: Snake Poison, Sydney, 1893.
Myers: Trans. Pathol. Soc., 51; Lancet, 1900, i.; Journ. of Pathol., 1901.
Nowak: Ann. de l'Inst. Pasteur, 1898.
Phisalix: Compt. rend. de la Soc. Biol., 1896, 1897, 1898.
Ransom: Deuts. med. Woch., 1901.
Semple: Brit. Med. Journ., 1899, i.
Sewall: Journ. of Physiol., viii.
Stephen and Myers: Journ. of Pathol., 1900.
Stejneger: The Poison Snakes of North Amer., Washington, 1895.
Wall: Indian Snake Poisons, 1883.
Wehrmann: Annal de l'Inst. Pasteur, 1898.
Wolfenden: Journ. of Physiol., vii.
Yarrow: Amer. Journ. of Med. Sciences, 1884, i.

Heloderma.

Bailey, in Langmann's "Poison Snakes" Medical Record, 1900, ii.
Mitchell, W.: Medical News, 1883, i.
Santesson: Nord. Med. Ark., Key Festband, 1897.
Shufeldt: Nature, London, 1891.—N. Y. Med. Journ., 1891, i.
Steindachner: Denks. d. k. Akad., Wien, 1878.
Van Denburgh and Wight: Amer. Journ. of Physiol., iv.
Yarrow, Forest and Stream, 1888.

POISONS.—A concise definition of the term poison, which will satisfy the medical, the legal, and the popular acceptations, is a practical impossibility. To the layman a poison is any substance which, when administered in small doses, causes disturbance to health or destruction of life; in a legal sense it is any substance of a destructive or noxious character, whatsoever its nature or mode of operation, which, taken into the system, produces injurious or fatal effects. The popular definition excludes many well-recognized poisons which act injuriously only in large doses; the legal includes, or may be made to include, many substances not strictly poisonous, such as powdered glass, iron filings, and other things of a similar character, which are merely mechanical irritants. To the physician and toxicologist the term means any substance of inherent deleterious character, either organic or inorganic, and incapable of self-reproduction, which, acting chemically upon the tissues or fluids of the body, may, by causing alteration or destruction of the same, or disturbance of function, seriously affect the health or destroy life. This definition excludes mechanical agencies, direct thermal changes, electricity, bacteria, and the low forms of animal life.

The published statistics of poisoning are very meagre, but the few tables which we have are interesting in several ways, indicating the classes of substances and special substances most frequently selected or accidentally administered, at different times and in different countries, and showing the proportion of accidental, suicidal, and criminal deaths due to poisoning.

The returns made by the English coroners of the inquests held during 1837 and 1838 showed the whole number of deaths by poisoning to be 541. Of this number opium was the cause in 196 cases, the majority of which were accidental or suicidal. Arsenic stood next in order, with 185 cases, the majority of which were criminal. Thirty-two cases were due to sulphuric acid, 27 to prussic acid, 19 to oxalic acid, and 15 to corrosive sublimate and other preparations of mercury.

During the years 1863 to 1867 there occurred in England and Wales 2,097 deaths from poison. Of this number no less than 628 were due to opium and its preparations, 151 to prussic acid and potassic cyanide, 83 to arsenic, 77 to mineral acids, 66 to oxalic acid, 61 to strychnine, 58 to compounds of mercury, 15 to phosphorus, and 11 to ammonia.

In France, during the years 1851 to 1871, out of 873 cases, 287 were due to arsenic, 267 to phosphorus, 159 to copper, 36 to sulphuric acid, 35 to cantharides, while opium and its preparations were responsible for but 6.

In Finland, of 30 fatal cases occurring between 1860 and 1866, arsenic caused 7, phosphorus 5, and strychnine 4.

Out of 45 cases reported in Massachusetts during the period 1878 to 1881, opium was responsible for 18, arsenic for 13, and all others for 14.

Although poisoning is a frequent means of suicide, the percentage of these cases is not nearly so high as is generally supposed; but yet, judging from what figures we have been able to obtain, this method of terminating an unsatisfactory existence is gradually becoming more popular. In Prussia, for instance, while there was a great increase in the number of suicides from all causes during the period 1871 to 1876, the relative frequency of self-poisoning was very much greater. The increase from all causes over preceding years was 43.60 per cent., but suicide from poisoning alone had more than doubled in frequency, the increase being 126.10 per cent.; but, even then, poisoning was the means employed by but a fraction over three per cent. of the whole number of suicides. During the eight years ending with 1876, the whole number of these cases was 24,918, and of this number 786 were by poisoning (3.15 per cent.). Solid or liquid poisons were elected by 707 persons, and gaseous by 79. It is interesting to note further that, while by far the greater number of suicides were men, the proportion being 80.50 against 19.50, or more than 4 to 1, the 786 suicides by poisons were nearly evenly divided between the two sexes, the proportion being 52.9 men to 47.1 women.

Of the whole number of suicides reported in Bavaria

during the fourteen years ending with 1870, 2 per cent. were due to poisoning. In 1871 the percentage increased to 3.2; during 1872 it was 3.00; in 1873 it fell to 2.20; increased again in 1874 to 2.70, and fell off again slightly in 1875 to 2.50. The popularity of poisoning as a means of suicide varies greatly in different countries. In Sweden, from 1843 to 1855, nearly a fourth of the suicides chose this means (21.7 per cent.); in England, in 1858 and 1859, 9.10 per cent.; and in other countries as follows: France, 1835–44, 2.48 per cent.; 1848–57, 1.80 per cent.; Belgium, 1840–49, 1.80 per cent.; Denmark, 1840–56, 1.50 per cent.; Würtemberg, 1857–70, 1.20 per cent.; Geneva, 1838–55, 4.90 per cent.

Of the accidental deaths occurring in Prussia during the years 1869–76, 54,363 in number, 2,448, or 4.50 per cent., were due to poison. This number includes 1,873 men and 575 women; 348 of the victims were under and 2,100 over fifteen years of age. During the fifteen years ending with 1877 there were 77 cases of criminal poisoning in Prussia, or 0.056 per cent. of all crimes. In France, during 1826–29, out of 2,663 capital offences, 150, or 5.63 per cent., were for poisoning. In England and Wales, during 1840, there occurred 349 deaths from poisoning (181 men, 168 women); 161 cases were suicidal (74 men, 87 women); and 188 were accidental and homicidal (107 men, 81 women). Among the latter, opium caused the death in 42 children under five years of age.

CLASSIFICATION.—Various methods of classification of poisons have from time to time been recommended; but no system has as yet proved wholly satisfactory. The old classifications, according to source or chemical properties, such as: (1) animal; (2) mineral; (3) vegetable; or, (1) organic; (2) inorganic; or (1) acids; (2) alkalies; (3) salts, are of no value, since they convey no idea regarding the properties of a poison or its mode of action. Orfila's division into (1) irritants; (2) narcotics, and (3) narcotico-irritants; Tardieu's into (1) irritants and corrosives; (2) hypostheniants; (3) stupefacients; (4) narcotics, and (5) tetanics; and Taylor's into (1) irritants, and (2) neurotics, are all good; but each has its defective points. Taylor's is, perhaps, the best. The irritants are derived from the animal, vegetable, and mineral kingdoms; those from the latter source may be further subdivided into acid, alkaline, non-metallic, and metallic. The neurotics are subdivided into (1) cerebral; (2) spinal; (3) cerebro-spinal, and (4) cerebro-cardiac.

The irritant poisons include many which are also corrosive in their action, causing disintegration of the parts with which they come in contact. The pure irritants exert no such chemical action, and are much slower in the development of symptoms. They cause irritation and inflammation of the parts to which they are applied, with violent vomiting and purging, intense pain, and well-marked effects on the nervous system. These symptoms occur after a greater or lesser interval, according to the nature of the particular poison. The pain, which is usually of an intense burning character, is, unlike that due to colic, much increased by pressure. Septic irritants produce additional symptoms of a character formerly known as typhoidal.

The neurotic poisons act chiefly on the brain, cord, and nerves; occasionally, the symptoms manifested partake more or less of the character of irritant poisoning. Those acting chiefly on the brain, producing stupor and insensibility, preceded by fulness in the head, vertigo, impaired vision, delirium, etc., belong to the cerebral; those affecting chiefly the cord, producing tetanic or clonic convulsions, to the spinal; those producing symptoms referable to the brain and cord, to the cerebro-spinal; and those affecting the brain and heart, to the cerebro-cardiac class.

ACTION.—The action of poisons may be local, remote, or both. Local action is physical and chemical, and is manifested by inflammation, corrosion, and direct effect upon the nerves, whereby the functions of organs are impaired or destroyed. If the chemical affinity of the poison for the tissues at the point of application be not great, the result is irritation and inflammation; if, however, the affinity be great, the action is most intense, and we have actual corrosion. Remote action depends upon absorption into, and transportation by, the blood to the various organs which may be affected. Thus, for instance, digitalis affects the heart, strychnine the cord, and opium the brain. In any case of acute fatal poisoning, death is the result of the remote action of the poison, which may or may not have a local action.

The ordinary action of poisons may be modified by the size of the dose, by the chemical combination of the substance, by the state of aggregation or admixture, by the condition or absorptive power of the part or membrane to which it is applied, by the condition of the patient, by habit, and by idiosyncrasy. The young and old are more susceptible, as a rule, than the middle-aged; women more than men; and fasting more than well-fed persons. Disease also may render the subject less susceptible, or, on the other hand, may facilitate the action of the poison. Habit diminishes the effect of many poisons, so that a much larger dose is required for the manifestation of symptoms than would be for persons not so habituated. Idiosyncrasy is a peculiar condition of the system which enables harmless substances to produce violent symptoms similar to those of irritant poisons. Thus many persons are unable to eat certain articles of food, even unknowingly—such as shell-fish, fish, strawberries, some kinds of meat, butter, honey, and other things. In the same way, many persons are seriously affected by small medicinal doses of opium, strychnine, arsenic, and other pharmaceutical preparations. A second form of idiosyncrasy is a tolerance for exceptionally large doses of poison by persons in no way protected by the influence of habit.

ABSORPTION.—In order to produce poisonous symptoms, the presence of a certain amount of poison in the blood is usually necessary, and the amount required depends upon rapidity of absorption and of elimination. A certain amount of any poison in the blood is incapable of producing any symptoms. Beyond this is that amount which is capable of producing characteristic symptoms—the poisonous dose; then that amount capable of destroying life—the minimum fatal dose; and beyond this up to a certain point, the action is increased in violence and rapidity. The poisonous and minimum fatal doses are relatively large if absorption is slow and elimination rapid, and small if the latter conditions are reversed. The rapidity of absorption depends greatly upon the physical properties of the poison; liquids are more rapidly absorbable than solids, soluble solids more than insoluble, and gases more than liquids or solids. Some insoluble solids may be rendered soluble, and hence more absorbable, by the action of the juices of the stomach and intestines.

Poisons may be taken into the system directly through the blood, as in absorption from wounds or injection into blood-vessels; they may be absorbed through the skin or from the cellular membrane, from inflamed serous surfaces, and from all mucous membranes. Absorption directly into the blood from wounds occurs with great rapidity. Through healthy skin covered with cuticle, absorption is very slow and in small amount. It is increased by rubbing and by the addition of fatty substances or solvents of the poisons. Gaseous substances are more absorbable than watery solutions, particularly if the latter are warm or hot. On the other hand, absorption from a diseased skin is very rapid, and many fatal cases have been noted from the application of washes, ointments, and dressings to diseased surfaces.

Mucous surfaces absorb poisons in the following order of rapidity: (1) lungs; (2) stomach; (3) intestines; (4) mouth; (5) nose; (6) eyes; (7) tear passages; (8) rectum; (9) vagina; (10) uterus; (11) bladder; (12) prepuce. The mucous surfaces of the lungs and the air passages absorb poisons with great rapidity, and particularly those in the form of gas or dust. The lining membrane of the stomach and intestines is usually the absorbent surface in ordinary cases of poisoning. Fulness of these organs retards, and emptiness favors, absorption. Certain poi-