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ON THE PHYSIOLOGICAL ACTION OF THE KENYAH DART POISON AND ITS ACTIVE PRINCIPLE ANTIARIN.

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[ABSTRACT.]

WHILE in Sarawak in 1899 I obtained from the Kenyahs of the Baram district a quantity of the poison made from the crude sap of *Antiaris toxicaria*, which when inspissated is used to poison their blowpipe darts. Passing over a larger amount of the earlier work done on this, the poison of the much fabled upas tree, two recent papers must be briefly considered. One of these, by Hedbom, which deals only with the physiological action of the poison, will be immediately referred to. The other, by Kiliani, contains that author's account of the chemical composition of the juice of several large upas trees sent home from the Malay Peninsula in tins preserved by admixture with methylated spirit. From this, besides other bodies, he isolated antiarin as a crystalline nitrogen-free glucoside, having the formula $C_{27}H_{42}O_{10}$. The physiological effect of this preparation has been carefully studied by Hedbom, who states that in cats spasms, and even opisthotonos, occurred shortly before death; in rabbits and frogs convulsions also occurred.

Separation of Antiarin, the Poisonous Principle in the Juice of Antiaris Toxicaria.

By treating ipoh with boiling benzene for two days, and extracting the dried residue in water, I was enabled to obtain a dark-brown fluid almost free from resins which was physiologically extremely active. The pigment was then precipitated with basic lead acetate, and excess of lead removed from the clear filtrate by sulphuretted hydrogen, after which the resultant slightly-acid liquid neutralized with chalk was evaporated to dryness. The residue was extracted with alcohol from which crystals of antiarin, subsequently purified by recrystallization from water and alcohol, were obtained in the form of needle-shaped crystals or sometimes flat plates with a not quite sharp melting point between 208° and 215° C. The substance so obtained was found to be a nitrogen-free glucoside which on hydrolysis split into a reducing sugar and a yellowish body, which, unlike the products of the hydrolysis of other poisons of the digitalis group, was quite inert.

Upon analysis, the preparation gave results which agree best with the formula $C_{27}H_{42}O_{10}$, the average carbon and hydrogen percentages of three analyses being C 61.26 H 7.24.

The above analytical results are at variance with those of Kiliani, who found C 61.46, H 8.05.

My figures for carbon show no divergence from these, but for H (7.24) I find a lower percentage. That this divergence from Kiliani's analytical results is not to be attributed to accident seems to be borne out by physiological differences between the two preparations immediately to be described.

Physiological Action of Ipoh.

1. Fish and small fresh water crustacea were left in a watery solution of ipoh for some hours without any effect being produced.

2. Frogs into which ipoh had been injected subcutaneously showed well-marked symptoms. Inco-ordination, with inability to maintain their position on an inclined plane, was first noticed, often accompanied by passing clonic spasms, especially of the hind legs, and occasional gaping movements of the lower jaw. Respiration became slower, usually with apnoeic intervals, but the latter was not a constant effect. Meanwhile, paresis passing into paralysis appeared; before the latter was complete a limb when stimulated was not always withdrawn, though it generally was. Complete paralysis of the limbs and trunk preceded the cessation of the reflex movement of the third eyelid obtained by stimulating the cornea. Not infrequently a short period of excitation was noted immediately after ipoh was injected.

A cardiograph taken after ipoh has been applied to an exposed frog's heart shows that the beats become slower and more forcible, then the ventricular beats became smaller, the auricles usually beating slowly and firmly till the ventricle stops in systole; the auricular beats then become

slower, slighter, and more irregular until the auricles stop in diastole.

The action of ipoh on frogs, therefore, is to produce (1) clonic spasms of the muscles, (2) paralysis, (3) systolic arrest of the ventricle.

When in place of the crude poison a solution of antiarin was injected, the same results were obtained, with the exception that the clonic spasms were not elicited. Death resulted from systolic arrest of the ventricle, and was preceded by paralytic symptoms. As to the part of the neuro-muscular system, the affection of which caused the paralysis, a large number of experiments showed this to be the nerve centres. Whether these are affected directly by the poison, or secondarily owing to circulatory failure, does not seem quite clear. In mammals the former is undoubtedly the case, in frogs the heart is, as a rule, arrested before paralysis is complete. I was quite unable with the Kenyah ipoh or with antiarin prepared from it to obtain any evidence that nerve or muscle was directly affected by the poison. It was necessary to determine this point precisely, and a large number of experiments were performed with this end in view, since other observers, notably Hedbom, who worked with Kiliani's antiarin, have come to the conclusion that the poison acts on the muscles themselves. As has been already pointed out, the analyses of my preparations and of Kiliani's show that the substances we respectively obtained were not identical; the results of physiological tests also point to their being different.

As regards dosage, it was found that for pithed frogs the minimum dose required to produce the full physiological effect on the heart lies between 0.01 and 0.05 mg. of ipoh, while as little as 0.001 mg. of antiarin produced a typical effect.

3. In mammals the short convulsive movements seen after administering ipoh to frogs become one of the chief features of the action of the poison, and, in addition to the other effects seen in frogs, gastro-intestinal symptoms are conspicuous. Repeated acts of defaecation are common; often the stools are loose and watery; this character was never present in guinea-pigs, but appeared to be fairly constant in carnivora, in whom salivation and vomiting are usually well marked. Convulsions do not, however, invariably occur, and are usually absent when large and rapidly fatal doses are given.

Post mortem the heart is found arrested in diastole (very rarely the ventricles are in systole) and distended with blood. Often by a single stimulus applied to the distended ventricle, or even without this, a very slow contraction of the ventricular wall takes place, so that without any definite beats the ventricles may be found extremely contracted a quarter of an hour after the chest is opened; the lungs may show a few small subpleural (probably agony) haemorrhages and are generally congested. The liver and large veins of the chest and abdomen contain much blood. The lethal dose of ipoh for guinea-pigs was found to be about 0.2 mg. per 100 grams, while the lethal dose of antiarin was about 0.05 mg. per 100 grams.

If blood-pressure curves be taken in a mammal (cats and rabbits were investigated, under anaesthetics), the first effect observed is a steady rise of blood pressure, with usually a slowing of the pulse. This occurs even with quite small doses. If the dose is larger, the steady rise of pressure is succeeded by a period in which, with the pressure still high, the inhibitory mechanisms are excited, dropped beats occur or longer pauses causing irregularities of various degrees (Fig. 1, p. 1131). Death is usually caused by sudden extreme inhibition in this stage.

It is much less usual for the inhibitory apparatus to become suddenly paralysed after the preliminary stage of excitation, and without any inhibition occurring in which recovery does not take place. In these instances the curve is commonly maintained for some time at a high pressure with a very rapidly-beating heart, and death results from a gradual failure of the heart, the blood-pressure curve slowly falling.

More rarely still, this result is brought about without any preliminary rise of blood pressure, the curves simply showing increased frequency of heart rhythm coming on almost immediately after injection of the drug (Fig. 2, p. 1131).

4. Birds with the exceptions to be immediately noted are susceptible to ipoh, death being as a rule very sudden, a comparatively slight paresis rapidly becoming complete paralysis, when the animal falls down and after a few convulsive (? asphyxial) struggles and expires. In fact, the suddenness with which the poison acts on pigeons, for

Fig. 3.—Result of repeated injections of antiaridin into femoral vein of fowl; first dose, 0.5 mg.; subsequent doses, 0.025 mg. ($\times$ about $\frac{1}{2}$).

instance, probably accounts for the stories of the upas tree told by early travellers in Malaysia. Fowls, and to a less extent pheasants, possess a high degree of immunity to the poison when this is injected subcutaneously; but, although usually very large doses produced little effect in the former, smaller doses occasionally produce transient paresis and repeated watery evacuations, and it was evident that individual fowls varied in their susceptibility to ipoh.

Blood-pressure tracings taken from fowls show that, though these birds resist enormously large doses given subcutaneously, the action of the drug on the circulatory system when it is injected intravenously is essentially the same as in mammals, although weight for weight the fowl will survive a larger amount of the poison given intravenously in successive doses, and recover from a degree of inhibition which, judged by the fall in blood pressure, would have been fatal in mammals. Fig. 3 illustrates these points.

Immunity.

An attempt was made to determine the proximate cause of the difference in the effects produced by the subcutaneous injection of ipoh into mammals and fowls. The frequent occurrence of diarrhoea soon after injection, even when paresis was absent, seems to point to their immunity not being due to slow or incomplete absorption. It was not possible to obtain *in vitro* evidence of a difference in the action of the poison on the heart muscle of immune and susceptible animals. A number of experiments, in which minimum lethal doses of ipoh were treated with heart extract of fowls and susceptible animals and then injected into guinea-pigs, uniformly failed to show that these extracts had in any way altered or weakened the action of the poison. On the other hand, it was not difficult to demonstrate by the physiological test the presence of ipoh in the heart muscle of frogs and guinea-pigs which had been killed by ipoh when the test animal was sensitive enough. The only animals which fulfilled this condition were very small frogs, not more than 5 to 6 cm. long. These, when left in a moist chamber for an hour after their brain had been destroyed, became extremely efficient reflex machines. The following experiment illustrates the method employed:

A guinea-pig weighing 512 grams was given 1.4 mg. of ipoh subcutaneously at 5.30. Paresis soon came on, and the animal died at 6.15, after a few convulsions. Its head was cut off, and as much blood as possible allowed to drain away, the heart removed, opened, and quickly washed in normal saline, then minced and ground in a cooled mortar, with a further small quantity of normal saline, and placed in an ice chest. At 9.30 a few drops of turbid pink solution which resulted were injected at room temperature under the skin of a small frog prepared as described, whose heart was beating 45 per minute. At 10.15 the heart beat 30, at 10.45 the ventricular beats were few and intermittent, auricular beats were also irregular, but about twice as frequent as those of the ventricle. A small frog similarly prepared, into which a few drops of normal saline were injected, was used as a control, and showed no such alteration in rhythm.

Similarly conducted experiments with the freshly-prepared heart extract of healthy unpoisoned guinea-pigs killed by decapitation showed that such a result was not given by the extract of the normal tissue. When a few drops of the heart extract of two large frogs killed by ipoh were employed, typical results were obtained in each of two small frogs injected.

These experiments seem to show that in frogs and susceptible mammals into which the poison is injected subcutaneously the latter acts on the heart by entering into combination with its muscle substance, and preventing the execution of its normal rhythmic function. Probably this effect is always absent in fowls, and has not time to occur to a full extent in susceptible mammals when these are submitted to the effects of large suddenly-acting doses as the result of intravenous injection, stimulation of inhibitory mechanisms here causing death. As has been already seen, under these circumstances fowls and mammals are similarly affected, so that the immunity of the former to subcutaneous injections is probably an expression of a power of resistance of their heart muscle. Their respiratory and spinal centres, too, are probably less readily affected than those of mammals or pigeons. That their immunity is not due to slowness of absorption seems proved by the constancy of diarrhoea after subcutaneous injections.

CONCLUSIONS.

The action of Kenyah ipoh when frogs were used for the experiments is as follows:

1. It acts on the ventricle of the heart as a poison of the digitalin group; this has been noted by all observers working with the juice of *Antiaris toxicaria*.
2. It causes paralysis of the central nervous system.

Fig. 1.—Cat; ipoh, about 2 mg., injected into jugular vein.

Fig. 2.—Gradual fall in blood pressure and late arrest of respiration brought about by the second of two injections of ipoh, each of 1 mg.

3. It causes passing clonic spasms of the voluntary muscles. When mammals or birds are subjected to its action marked gastro-intestinal symptoms are usually added to the above effects. Certain birds are, however, comparatively immune. My preparations of antiarin, a crystalline glucoside, the active principle of ipoh, lacked the convulsive effect of the crude substance, thus differing physiologically as well as chemically from Kiliani's antiarin, investigated by Hedbom, although in its purely cardiac toxicity it was at least as active as Kiliani's.

In conclusion, I wish to express my thanks to Dr. J. B. Leathes for much kind help and advice throughout this investigation.

CENTENARIANS IN THE UNITED STATES.—According to the United States census for 1900 there are 3,536 persons in the United States who are 100 or more years of age. The value of these figures is, however, somewhat discounted by the fact that 72.8 per cent. of the whole number are negroes; many are very hazy as to the date of their birth. It is improbable, as pointed out by the *Journal of the American Medical Association*, that the United States should have over 3,500 centenarians, when Germany, with a population of nearly 55,000,000, has only 778; and England, with 32,000,000, only 146; and France, with 40,000,000, has only 213.

DRUG ERUPTIONS.

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THE number of medical remedies which may give rise to rashes is a large and increasing one. Scarcely a week passes but some new synthetic product is placed upon the market, usually accompanied by an assurance that it has no drawback in the way of causing ill-effects. As a rule one has not to wait long before cases crop up which show that the new remedy is not so innocent as was at first supposed. Now many of these products are useful, but what I desire to emphasize is that they should be employed with care. Rather than give you a long list of drugs, with details of the cutaneous manifestations they may occasion, I propose to take the various eruptions as they come before you clinically. This arrangement will be more practically useful, although it will necessitate some repetitions and cross-references owing to the overlapping of the morbid phenomena. It is the eruption we see, but the drug which caused it we have to find out. I shall adopt the following rough classification of the rashes: