ON THE

ACTIVE PRINCIPLE OF CASTOR OIL.

BY

THOMAS DIXSON,

LECTURER ON MATERIA MEDICA IN THE UNIVERSITY OF SYDNEY.

(COMMUNICATED BY DR. LAUDER BRUNTON, F.R.S.)

Received June 7th—Read November 23rd, 1886.

IT has long been known that the seeds of castor oil are exceedingly active, but the active principle has never been isolated. The object of the following paper is to try and throw some light upon the connection between the activity of the seeds and that of the oil. Previous observers having either obtained no definite result or contradictory results, the further investigation of the subject was suggested to me by Professor Schmiedeberg, of Strasburg. The last investigation previous to mine was that of Bubnow, who found that by extracting the seeds with acid, filtering the solution, and then precipitating with an alkali, a precipitate was obtained which was active when dried. This young investigator having been unfortunately removed by death, without publishing his method, I had to recommence afresh. After removing the oil from

the powdered and shelled seeds by alcohol and ether, a process which required eight days, I extracted with acid; but Bubnow having left no details I was obliged to make a number of experiments in order to ascertain the proper strength of acid. These experiments showed that hydrochloric acid containing 1 per cent. of absolute acid yielded a precipitate with carbonate of soda which was inactive, and so was that obtained with any stronger acid. An acid containing 4 per 1000 of HCl was found serviceable, as it yielded an active precipitate, although it did not appear to remove the whole of the active principles from the seeds, inasmuch as the residue still remained active after being treated with acid for twelve hours. When the acid was weaker than 1 per 1000 no precipitate was obtained. When the precipitate was treated with sulphate of copper and caustic soda it gave the reaction characteristic of albumen very strongly, so that it evidently contained an albuminous substance. I next tried to make a watery extract of the powdered seeds, but as it could not be got clear by filtration I obtained from Italy some of the seed cake, that is, seed from which the oil had been expressed. This seed cake and the active seeds I had experimented upon were obtained from the same source. Numerous observations have already shown that the symptoms of poisoning by castor-oil seeds are vomiting, purging, and collapse, occasionally with a subsequent febrile condition, and sometimes albuminuria. In some experiments I found that if 5 grammes of the shelled seeds in the natural state were given to a rabbit, nothing was to be noticed within the first few hours; for example, if given at 4 p.m. nothing would be observed that evening, but next morning the animal would suffer from violent diarrhœa and would die any time after 7 p.m. on the second day. The only abnormal post-mortem appearances were in the intestine, with the exception that as a rule the stomach was slightly inflamed at the pylorus. Close to the pylorus the intestine was red with scattered extravasations, the glands were swollen, and though not much

reddened towards the mucous surface they were reddened towards their subserous aspect. At the end of the small intestine there was usually a dark purple patch, and this often occurred also at the entrance of the bile-duct into the pylorus. The whole of the small intestine was full of a greenish-yellow fluid with greenish flakes floating in it; the mesenteric glands were swollen and dark red. The two thirds of the cæcum nearest the small intestine were reddened. All the other organs appeared to be normal with the exception of a few small scattered extravasations in the lung.

The effects of the powdered seed deprived of oil, and also of the cake, were the same as those just described; but it was noticed that sometimes subserous extravasations were present upon the peritoneal surface of the intestine and in the mesentery, and these were also seen after the administration of Bubnow's extract. A quarter of a gramme of this extract injected subcutaneously had a very remarkable action, for the next day the animal would have slight diarrhœa and die on the second day. On post-mortem examination the only differences observed between the effect of the extract when administered subcutaneously and by the mouth were that after subcutaneous administration the purple extravasated patches at the beginning and end of the intestines were absent, while subserous and mesenteric extravasations were invariably present. There was no inflammation at the site of injection. Sometimes the lower part of the large intestine contained stiff gelatinous masses, and the lymphatics of the neck, axilla, &c., were congested. Bubnow's extract appears from the facts already mentioned to be a substance which is precipitated along with albumen either as a compound with it or mechanically by it. I therefore thought that it might be possible to get an active solution from the cake by extracting it with water, and this idea proved to be correct. I bruised the oil cake with about twice its weight of water, pressed out the liquid, and after allowing it to stand for twenty-four hours so as to clear, I filtered

it. I thus obtained a clear yellow, transparent, semi-syrupy solution of extreme activity. On adding four times its bulk of alcohol to this, and letting it stand, a precipitate was formed which was not increased by the further addition of alcohol. This precipitate when dried proved to be extremely active. I invariably obtained the reaction of a glucoside whenever the substance was active. All attempts to obtain an active principle without albumen failed, and an albuminous body was always present in the solution when it was physiologically active. The same was the case when attempts were made to purify Bubnow's extract. Amongst the means used for this purpose were precipitation with acetate of lead and ammonia, fractional precipitation with alcohol and dialysis. After this active substance had been extracted from the castor-oil seeds the residue was no longer active. This active substance keeps well when dried, but if the first precipitate thrown down by alcohol from the aqueous extract of the seeds be again treated with water, it does not redissolve completely as one would expect, but only partially. The filtrate is exceedingly active and the residue is also active, but its activity appears to depend upon the difficulty of washing out the active principle completely. But if the process of precipitation by alcohol and re-solution be continued we at last get a small quantity of an insoluble residue, which is inactive; a soluble residue, which is also inactive, would be obtained as well. In other words, the mere action of alcohol is sufficient to render the active principle inert. Mere contact with chloroform for a few days has the same effect. Many attempts to obtain the substance pure by the use of various chemical reagents ended in yielding an inert substance.

Considering that a glucoside reaction was always present, and that the active substance always became inert under chemical treatment, it is possible that some light may be thrown upon the nature of this active principle by the following fact. If the slightly acid aqueous solution of castor-oil cake be precipitated by adding

chloride of calcium and afterwards soda, a precipitate of hydrate of lime falls, and along with this there is also precipitated a compound of lime with a physiologically inert glucoside. By continued washing with water, rendered alkaline by soda, the albumen present can be almost entirely removed, leaving the hydrate of lime and the compound of calcium with the glucoside behind. By now adding oxalic acid the glucoside can be set free, and as it is insoluble in alcohol and ether it can be precipitated by the addition of two parts of alcohol or of ether to one of the solution. The glucoside then falls as a flaky substance, very like the active substance containing albumen obtained from the seeds. This fact, which was discovered by Professor Schmiedeberg, would seem to indicate that we are here dealing with an anhydride of a glucosidic acid, which becomes inert whenever it is altered from its anhydrous condition, and becomes either hydrated or combined with a base. In this character it appears to resemble other bodies of a similar nature, such as euphorbin and other substances of the acrid group, or cathartic acid, which was lately shown by Stockman to be an insoluble, non-nitrogenous glucoside of this kind. Although the glucoside has been prepared, I have not further examined its composition.

Referring to the crude but active substance, I may state that, when injected hypodermically, it is excessively active, causing the usual congestion of the intestine with small extravasations over all the serous membranes. Thus after ·0059 gramme injected hypodermically there were extravasations into the wall of the intestine on its subserous aspect, into the mesentery, into the pericardium (visceral), slightly into the lungs, into the fold between the cerebrum and cerebellum, and into the dura mater of the spinal cord. Large doses of the substance or of the seeds taken by the mouth cause similar effects.

The active body obtained by Bubnow is the same as that which I have obtained, and he supposes it to be the active principle of castor oil.

But there are certain remarkable differences between castor oil and this active body. The reputation of castor oil as an aperient is a well-justified one, but that of the seeds is so far questionable that it seems by no means a true aperient, and acts as such only by producing an effect upon the vessels, which in cases of poisoning is not confined to those of the intestine. The points of difference are as follows:

1st. It was found by Bubnow that boiling the seeds for a short time was enough to render them inert. This I found to be invariably the case; even exposure to heat below boiling point, *e. g.* mere boiling in absolute alcohol (98 per cent.), was enough to destroy the activity. But castor oil may be boiled hours, till, indeed, it evidently is decomposing without losing its activity.

2nd. This substance is soluble in water, not in alcohol; but castor oil never yields any precipitate, no matter how much alcohol or ether be added to it. Hence this substance cannot be present in the oil. But what is still more striking is the fact that if a rabbit be poisoned by castor oil in such a dose as to cause death, diarrhœa invariably occurs, but death never occurs before the second day, and the intestine never shows anything beyond a muco-purulent appearance, and not a trace of congestion or inflammation is to be seen anywhere. In other words, the action of the oil seems to consist only in a stimulation of the intestinal secretion, death being due to exhaustion from the great drain. But with the seeds death may occur in about twelve hours, without positive diarrhœa, and the intestine always shows excessive vascular engorgement, even when the dose of the seeds given is so small that the animal does not die. I performed this experiment several times, and always with the same result. Last summer I found thirty grammes of oil sufficient to kill small rabbits in two days; this winter, for large rabbits, sixty grammes were necessary, but the result was the same, and in both cases there was no inflammation. Moreover, it is impossible to get water to take up any

active principles from castor oil, when shaken up with it for a long time. Again, I never found the oil prepared by me, nor that left by Bubnow, stronger than the ordinary commercial oil; and I can only say that it seems as if the statement made by Parola and repeated in various books (*e. g.* Flückiger and Hanbury), to the effect that oil extracted from the seeds by alcohol keeps better, does not cause nausea or vomiting, and is four times as strong as ordinary oil, is based upon an error of observation. It does not seem that they ever filtered their oil (extracted by alcohol) through paper, but this I always did. In fact on one occasion where I had filtered only through cloth as they did, the solution showed only a very slight cloudiness indeed, but was much more energetic than usual. It was not until I refiltered through paper that I found that it was this mere trace of impurity which made the difference in activity. It is evident that if further proof be required it is only necessary to take the oil cake, and as it has lost its milder oil by pressure, to extract it by alcohol. One thus gets almost 20 per cent. of the weight of cake of oil of a rather mawkish almondy smell, but it is not one whit more active than the usual oil.

Ricinoleic acid I found, like others, to be perfectly inert in a fifteen-gramme dose, which would be a powerful dose were it like castor oil in activity. Olive oil soaked on the castor-seed powder did not take up any active principle. Some of the substances which give rise to the characteristic disagreeable flavour of castor oil can be got during saponification of it, but they are inactive. The taste of ricinoleic acid is quite different, though also nauseous. As many experimenters have tried to get the active principle of castor oil by saponification, and it was evident that it disappeared *en route*, I tried all the different bodies left in the solutions, but found none active. It is thus evident that it is destroyed by saponification, and I therefore tried, but in vain, to see if it were possible to get a substance differing in activity and in solubility in diluted alcohol. Thus absolute alcohol mixes in any quantity

with castor oil; if one add 25 parts of water to, say, 200 alcohol and 100 of oil, the whole becomes cloudy, but on heating to boiling point it clears up, again becoming cloudy on cooling, and an alcoholic layer rising to the surface. No matter how I varied the proportion of water I never found any difference in the activity of the body dissolved in this alcoholic layer. Now, is it possible that after all there is a *tertium quid* besides the ricinoleic acid and seeds, or is it the glycerine which causes the aperient effect, the castor oil simply decomposing with sufficient readiness to allow the glycerine time to act? It is perfectly possible, I fancy, but I did not unfortunately think of this till it was too late for me to carry out the experiment, but I hope to do so soon. If it be so it is evident that there is no need of seeking for a resin, as one will never find it. Certainly the appearance of the bowel is such as one would expect from glycerine. There is one thing against this theory, viz. the fact that castor oil injected into the bowel is said to be aperient. This statement is, however, not a very easy one to prove, seeing that the physical nature of the castor oil would cause aperiency. Of course ricinoleate of magnesia would cause aperiency due only to the magnesia, an experiment of no value as regards this question. Seventeen grammes of ricinoleic acid given to a rabbit caused but a very slight aperient effect, corresponding to about eight grammes of the oil itself.

Before concluding this I may state that it seemed to me that the castor-oil cake, although a deadly poison, might be made to subserve beneficent purposes. Thus in Italy there remains about one fifth part of the oil in the seeds, in India, where the mode of extraction is cruder, there remains more. It appears to me that if greater heat were used, that is, 212° or even much less, the oil could be better extracted, and as the oil is not always for internal use, this would in general do no harm to the oil, while much of the above waste would be avoided. The heat would render the oil cake harmless. Now, as the cake has rather a pleasant smell and taste, and is full of

albumen, we have before us what might become an article of diet.[1] As an example of the similar transformation by heat of a poisonous substance into an article of diet we may cite cassava. The only difficulty that I see here is the husks of the seeds; these would be very indigestible and nauseous, but I fancy could be easily removed before the expression of the oil. As regards the possible importance of this body I may mention that there are some 700,000 gallons of castor oil exported from India, which would mean some 3000 tons of castor-oil cake, and as this is highly albuminous, and by the mere cooking becomes harmless, it simply implies that there are so many tons of highly nutritious food thrown away. The value of this in India is inestimable, because it would be much more valuable than so much rice, and would help to eke out the rice. The importance of a nitrogenous food, where religious superstitions forbid the use of animal food, is self-evident. I suggest this as worthy of consideration by those who could investigate the matter further. In times of famine what a blessing it would be, and, so far as I can see, it would keep exceedingly well in a very dry climate.

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[1] I may state that for comparison, and with the hope of obtaining the substance free from albumen, I examined some leaves fresh from Italy, but obtained no active substance; there seemed to be a substance like the altered glycoside present. The so-called ricinin of Tuson, &c., is probably not originally present in the seeds, but is a product of decomposition. The statement made by Power in the 'American Journal of Pharmacy,' xxxvi (1854), p. 207, that the seeds have a protein substance and a body like amygdalin may be true; but though I had not any description of the experimental grounds for this, I can only say that if we make a watery extract after an alcoholic one, and add the products to each other, the result is nothing physiologically.

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