POISONING BY CANTHARIDIN

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Cantharidin is the active principle of a species of beetle of which the Spanish fly, *Cantharis vesicatoria*, is probably the best known. The Russian and Chinese species, *Mylabris cichorii* and *M. phalerata*, contain the same principle. Cantharidin is the anhydride of the unstable cantharidic acid and has the formula $C_{10}H_{12}O_4$; it occurs as colourless, odourless, glistening crystals (Martindale, 1952). It is a comparatively simple compound, giving no colour reactions or other simple tests. Bamford (1951) describes a colour test with Mecke's reagent which is useless in practice, since the presence of minute amounts of organic impurities causes charring which obscures the colour produced by the cantharidin.

It was found that only three tests could be relied on for identifying cantharidin: (1) melting point; (2) production of characteristic pain and blistering when the material was applied to the arm by the method described in Taylor (1948)—only the production of a blister was regarded as a positive identification; (3) *x*-ray diffraction pattern of the crystalline material. The identification is therefore much more difficult than that of powdered cantharides with its characteristic insect fragments.

The principle of the *x*-ray diffraction method of identification depends upon the fact that *x* rays are diffracted by crystals and the angles of diffraction are characteristic of the interatomic distances in the crystal, so that a series of diffraction lines are produced peculiar to a particular crystalline structure. These diffraction patterns can therefore be used to identify crystalline substances even when crushed to a fine powder and in small amount.

Cantharides has been known as a drug for over 2,000 years and was described in the treatment of dropsy by Hippocrates (Gathercoal and Wirth, 1936). Preparations of cantharides and cantharidin were used years ago as blistering agents in the treatment of pleurisy and pericarditis (Avery, 1908), and cantharidin, being of more certain composition than the various preparations of cantharides, at one time became the more popular. There still remain several recognized preparations of these drugs: cantharidis pulvis, emplastrum cantharidini in massa, liquor cantharidini, liquor epispasticus (Martindale, 1952); and a blistering liquid is also officially described in the *British Veterinary Codex*.

Spanish fly has also held the reputation for many years of being an aphrodisiac. This reputation was apparently known to the Count de Sade in the early eighteenth century, when he poisoned the inhabitants of a brothel with this drug, and many of the girls were killed when they flung themselves from windows in the agony so caused (Dühren, 1906). Stary (1936) reported an incident in a Slovakian village when some young men offered the guests at a dance chocolate containing cantharides, in the hope of seeing a sexual orgy, for which purpose they had rented a large room next to the ballroom. Twenty-five persons were poisoned.

Cases of homicidal cantharides poisoning are also reported by Taylor (1948), and of accidental poisoning by Avery (1908) and Womack (1911). The latter author described two cases of abortion which have some of the characteristics of *Cl. welchii* infections, but claimed to have recovered a blistering agent from chloroform extracts of the urine.

The earliest record of cantharidin poisoning is probably that of Andrewes (1921), who describes the illness of a medical student following the ingestion of cantharidin. This student, imbued with curiosity, placed a crystal of cantharidin, which he described as being the size of a pin's head, on his tongue—it probably was no more than 1/50 gr. (1.3 mg.). He experienced no immediate sensation and ate a large tea. He was seized with pain in the lumbar regions the same evening, passed small quantities of urine associated with strangury hourly, developed severe haematuria, but had no oral vesication or aphrodisiac symptoms: he was completely recovered in a fortnight.

Gormsen (1945) described a fatal case of cantharidin poisoning, and gives an extensive review of the literature. At that time he could find in an extensive literature only four cases which had been the subject of necropsy. Gormsen's case was that of a man who had been given 1 g. of cantharidin by a dentist as an aphrodisiac. Half this dose had been taken and the man was found dead in bed, having had time to write a note explaining what had happened and naming the dentist, who was subsequently charged with manslaughter, sentenced to 30 days' imprisonment, and fined 7 Danish kroner. The post-mortem examination showed vesicles in the mouth and pharynx, oedema and haemorrhage of the gastric and intestinal mucosa, and haemorrhages in the kidneys and throughout the urinary tract.

A further case was recorded in the *Pharmaceutical Journal* (1953).* A man of 43 died two days after the onset of gastric symptoms. He was a keen fisherman and had been told that fish could be attracted by ground bait that contained something "sexy." He obtained 1 gr. (65 mg.) of cantharidin from a chemist and was told to add it to a bottle of water in which he soaked his ground bait. His thumb became contaminated while shaking the bottle, and when a little later he pricked his thumb on a hook he sucked it. The records in this case show that the pathological symptoms found at necropsy were similar to those described in our cases. An analysis of certain organs was made but cantharidin was not detected. It was stated that the probable amount of cantharidin ingested was between ½ and 1 gr. (32 to 65 mg.).

Case Histories

On April 26, 1954, two female clerks, aged 19 and 27, shortly after lunch, at about 2.30 p.m., ate some coconut ice offered to one of them by a male employee (Mr. X), working in the same firm of chemists. A few minutes later, variously estimated at 5 to 15 minutes, both girls complained of feeling ill and vomited. They were taken to the firm's first-aid room, where Case A decided to take a taxi to her home, which she reached at 6 p.m. in a state of collapse, having vomited repeatedly in the taxi. Her local doctor saw her at 7.15 p.m. and arranged for her admission to St. James's Hospital, Balham, with a diagnosis of haematemesis. She reached this hospital at 9.30 p.m. and was still vomiting almost pure blood.

*This case is described in detail on p. 1399 of this issue of the *Journal*.

On admission she was pale and collapsed. Her blood pressure was 90/70. Her stomach was washed out and morphine given, and an improvement in her condition enabled her to be admitted to the ward. Shortly after that she vomited about half a pint (280 ml.) of fresh blood and her pulse became thready. At 6 a.m. the following day she is said to have become stiff, then relaxed, and finally unconscious. The doctor who was called found her to be in

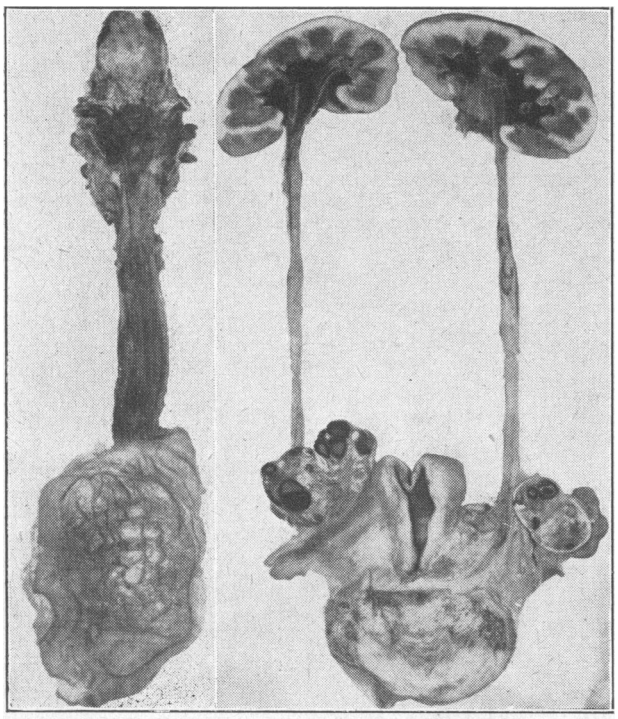

FIG. 1 FIG. 2

FIG. 1.—Upper intestinal tract, showing destruction of the mucosa. FIG. 2.—Genito-urinary system, showing haemorrhage around the pelves of the kidneys and into the uterine walls, the ovaries, and the bladder.

peripheral failure with a pulse rate of 140, deeply unconscious, and her blood pressure was unrecordable. She died one hour later.

Case B was admitted to University College Hospital at 5 p.m. in a collapsed and distressed state, and died at 4.40 p.m. the following day. Her clinical course is described by Craven and Polak elsewhere in this issue (p. 1386).

Figs. 1 and 2 illustrate the upper part of the intestinal tract and the genito-urinary tract in Case B. Apart from a white patch on the tip of the tongue there was actually no normal mucosa left between the lips and the pylorus. The lips showed an excoriation similar to that visible on the tongue. The most severe damage appeared to be in the pyriform fossae and in the lower two-thirds of the oesophagus.

As this poison had been taken on top of a heavy meal it is not surprising that the stomach did not show such severe changes as the oesophagus. There was intense engorgement of the whole of the genito-urinary tract with frank blood in the renal pelves, ureters, bladder, and ovaries. There was also much peripelvic and periuteric haemorrhage.

Numerous haemorrhages up to 2 mm. in diameter were seen on the surface of the heart and there was one linear haemorrhage, 1.5 cm. long. Subendocardial haemorrhages were present on the interventricular septum, but no haemorrhages were seen in the brain. There was intense injection of the whole of the bronchial tree, with fine frothy blood-stained mucus in the air passages. The lungs were grossly oedematous. Slight fatty changes were seen in the liver.

Microscopical examination of the kidney showed gross haemorrhage into the tubules, with some damage to the tubular epithelium. Sections of liver showed early fatty changes. The condition of the ovaries requires, in our view, some more dramatic explanation than mere pelvic congestion, and it would appear that cantharidin has some specific stimulating effect on the ovarian stroma just as it has on the bone marrow (Lipsitz and Cross, 1917; Craven and Polak, 1954).

Post-mortem examination in Case A showed an almost identical picture, except for the fact that there was no excoriation of the lips or anterior part of the tongue. The fauces were extremely haemorrhagic, and the brunt of the vesication was seen in the lower half of the oesophagus, where, from the level of the bifurcation of the trachea, the mucosa lay in haemorrhagic tags, which could be eased off with the most gentle pressure of the fingers. The oesophagus contained frank blood clot and the stomach almost a pint (570 ml.) of very heavily blood-stained fluid.

Haemorrhages in this case were found on the surfaces of the heart and lungs, but, apart from intense congestion and some oedema, the respiratory system was not seriously damaged.

A tentative diagnosis of poisoning by cantharidin had been made at University College Hospital, and this was supported by the post-mortem examination on Case A, which was performed five hours after her death, and before the death of the other girl. Mr. X had also been admitted to University College Hospital on the afternoon of April 26, with some peculiar blisters on his face but no signs of general poisoning.

There were recovered from the offices where the three employees worked some minute crystals from the surface of the desk and a pair of scissors bearing smears of material on the tips. There were also sent to the laboratory: vomit of Cases A and B and organs removed at post-mortem examination in both cases.

The crystals were identified as being cantharidin. The smears on the scissors were shown to be a mixture of cantharidin crystals and coconut ice (Fig. 3). Attempts were therefore made to extract crystalline cantharidin from the vomit of both cases and the organs removed at necropsy. It was found that the method of Bamford (1951) was unsatisfactory and gave a recovery of only about 30% of added cantharidin. A modification of the method described by Autenrieth (1928) was finally adopted as follows.

The macerated organs were acidified and heated to 75° C. in a water-bath with excess of solid ammonium sulphate, some of the solid remaining undissolved, and the material was filtered on a Buchner funnel under reduced pressure. The granular solid was extracted three times with chloro-

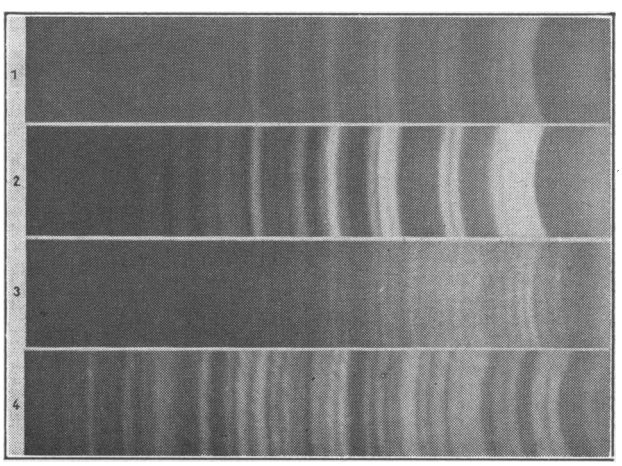

FIG. 3.—*X*-ray diffraction patterns. (1) Crystalline material from desk. (2) Pure cantharidin crystals. (3) Material from end of scissors. (4) Coconut-ice control.

form and the extracts were used to extract the clear filtrate. The combined chloroform extracts were evaporated to dryness under reduced pressure, leaving an oily residue. This residue was boiled with water and rendered alkaline with potassium hydroxide. Excess of calcium chloride was added and the calcium soaps were removed by filtration. The clear filtrate was acidified and extracted with chloroform.

In the case of the vomits, micro-sublimation of the residue yielded characteristic rectangular plates of cantharidin. In the case of the organs, no method of purification would give a crystalline residue free from fatty acids. By the blister method, it was found that, using our particular technique, approximately 0.5 mg. of cantharidin produced a standard blister (Fig. 4). Varying proportions of the

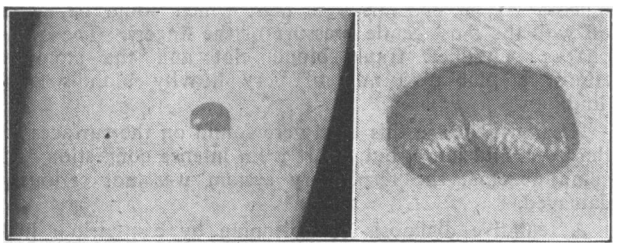

FIG. 4.—Blister produced by extract from vomit of Case A.

residues were tested under uniform conditions, and from the blistering an approximation of the amount of cantharidin circulating in the body was calculated. It was found that there was circulating in the organs of Case A between 1 and 2 gr. (65 and 130 mg.) of cantharidin and in the organs of Case B somewhat less.

As the result of the post-mortem examinations and chemical findings, Mr. X was interviewed by the police and made a statement, much of which was confirmed by persons mentioned therein. He had read a little about cantharidin, but was not a qualified chemist. On the morning of April 26 he went to one of the chemists in the firm and said that he wanted some cantharidin for a neighbour who was having difficulty in getting his domestic rabbits to breed. The chemist showed Mr. X the stock of cantharidin, but refused to part with any, pointing out that it was a Schedule I poison. During the chemist's absence at lunch, Mr. X, now knowing where the cantharidin was stored, stole a quantity and put it in an empty pay envelope. It was probably during this operation that his hands became soiled with cantharidin, which was transferred to his face, causing blistering. He then went out and bought ¼ lb. (110 g.) of coconut ice, which consisted of eight pieces. Into two of these pieces he introduced, by means of a pair of scissors, a small quantity of cantharidin, one of which he offered to Case A, who ate it. Four other girls in the office ate untreated pieces, and Case B picked up the second treated portion and ate it. There is little doubt that this was not intended for her; and later the Lord Chief Justice described the incident as an "incredible piece of carelessness" on the part of Mr. X.

Mr. X was charged with the manslaughter of both these girls, charges to which he pleaded guilty and for which he was sentenced to five years' imprisonment.

Fatal Dose

It would appear that there is no minimum toxic dose for solid cantharidin. A minute crystal of cantharidin weighing not more than 0.5 mg. lodging in the mucosa will produce a blister which could prove fatal. After absorption the cantharidin will produce the secondary effects in the excretory organs already described, since it does not seem to be decomposed in the body. The fatal dose would appear, from this case, to be certainly less than 1 gr. (65 mg.) of crystalline material. If the substance is ingested in solution the fatal dose is probably greater than that of the solid cantharidin.

Summary

The post-mortem findings in two cases of cantharidin poisoning are given, together with short clinical histories and a brief description of the circumstances leading up to them.

The difficulties of identifying this drug are pointed out and a method of isolation is described. The final identification still depends chiefly on the physiological "blister" reaction and the *x*-ray diffraction spectrum.

The probable fatal dose of cantharidin has been estimated.

We wish to record our thanks to Mr. W. Bentley Purchase, H.M. Coroner for the Northern District of London, for permission to publish these cases, and to Dr. J. D. Craven, of University College Hospital, and to Dr. P. Watts, of St. James' Hospital, Balham, for the synopses of the clinical histories.

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CANTHARIDIN POISONING

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In the nineteenth century, when the use of cantharides preparations was still popular, descriptions of their toxic effects were not uncommon. We have, however, been able to find only twenty clinical accounts of cantharides poisoning published since 1900, three of them in this country. Gordon (1943), however, states that in the Union of South Africa 15 fatal cases occurred in 1939, and 23 in 1942.

Case Report

A girl aged 19 was admitted to University College Hospital at 5 p.m. on April 26, 1954, in a state of collapse. At about 2.30 p.m. she had accepted a "coconut ice" sweet from a man in the office. She ate it, and noticed no unpleasant taste. About ten minutes later she felt abdominal pains and nausea. She was given about a teaspoonful of sodium bicarbonate in a tumbler of water, and immediately after this the abdominal pain became worse and she noticed an intolerable burning sensation in the mouth and throat which made speaking very painful and swallowing impossible. Another girl who had eaten some of the coco-