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

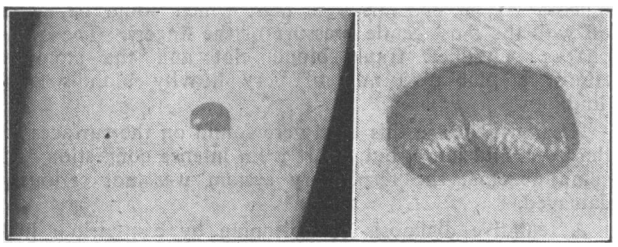

FIG. 4.—Blister produced by extract from vomit of Case A.

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

BY

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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-

nut ice was taken ill a little later. Several others had had some without being affected. There was no other relevant history.

Physical Findings.—On admission she was vomiting blood-stained mucus and had diarrhoea which contained no frank blood. She also passed about 4 oz. (114 ml.) of urine which was normal in appearance. She was in great pain and her general condition was poor. Her temperature was 97.4° F. (36.3° C.) in the axilla, pulse 100, respirations 20, and blood pressure 108/65. There was no dyspnoea or cyanosis. The extremities were warm and she was perspiring slightly. A small blister was present at the left angle of her mouth. Her tongue was swollen, and white epithelium was peeling from the whole of its dorsal surface. The fauces and soft palate were peeling similarly. The throat contained blood-stained mucus. In the abdomen there was generalized slight tenderness, maximal in the epigastrium and flanks, but none in the loins. There was no rigidity. Bowel sounds were present. No free fluid was detected. The heart was not enlarged, the sounds were normal, and there was no evidence of congestive failure. Abnormal signs were not found in the lungs, but mucus was present in the upper respiratory passages and tenderness over the trachea at the root of the neck. The skin showed no erythema, blistering, or petechiae.

Progress.—She was given morphine, ¼ gr. (16 mg.), and an intravenous infusion of 5% dextrose in normal saline was set up. In view of the excoriation of the mucosa in the mouth and pharynx, no attempt was made to pass a stomach tube. Her general condition remained unaltered until about fourteen hours after swallowing the poison, when it rapidly deteriorated. She became shocked and comatose, the pulse rate rose, and the blood pressure fell. The abdominal signs were unchanged. As no urine had been passed for sixteen hours, she was catheterized at 9 a.m. on April 27 and a few ounces of deeply blood-stained urine was obtained. Intravenous dextran was now substituted for the dextrose saline. Dimercaprol, 200 mg. intramuscularly four-hourly, and nikethamide, 2 ml. intravenously hourly, were given. Her condition was still deteriorating, and it became necessary to pass a tracheal tube. Her blood pressure continued to fall, although intravenous noradrenaline was given at a rate of 80 µg. a minute. She died at 4.40 p.m.

The post-mortem findings and forensic aspects of this case are discussed elsewhere in this issue (Nickolls and Teare, 1954).

Investigations.—At 9 p.m. on April 26 the *p*H of the vomited mucus was 9 approximately. At 10 o'clock the next morning the haemoglobin was 116%, the white-cell count 104,000 (neutrophils 63%, lymphocytes 20%, monocytes 0.5%, eosinophils 0.5%, basophils 1%, myelocytes 14%, pre-myelocytes 1%); normoblasts 3.5 per 100 white cells. The plasma CO_2 capacity was 13.6 mEq/litre; chloride, 109 mEq/litre; sodium, 153 mEq/litre; potassium, 3.55 mEq/litre. At 2 p.m. the haemoglobin was 125%. Blood spectroscopy showed no significant evidence of acute haemolysis. The urine contained large quantities of blood. All the specimens were saved for further investigation.

Diagnosis.—It was clear on admission that the patient was suffering from severe irritant poisoning, but the nature of the irritant was obscure. None of the common corrosive poisons seemed likely, though the high *p*H of the vomit did suggest the remote possibility that she might have been given caustic soda. The fact that the poison had produced no immediate unpleasant sensation, yet had within two and a half hours severely blistered and excoriated the oral mucosa, prompted the suggestion by Professor C. Rimington that it might have been cantharides. This received further support when the oliguria and haematuria were discovered. It was then learned that the other girl who had become ill after eating the coconut ice had died, and that the post-mortem findings were characteristic of cantharides poisoning.

Discussion

The present case illustrates almost all the common features of oral cantharides poisoning. The distressing gastro-intestinal symptoms, the blistering and excoriation in the mouth, the oliguria and haematuria, and the severe constitutional disturbance are all typical. The abdominal pain and tenderness were unusually slight, and the absence of pain in the loins and in the genitalia was exceptional. It was characteristic that the patient noticed nothing wrong on taking the drug, but the delay of only ten minutes before her symptoms began was unusually short. In most cases thirty minutes to two hours elapsed, and in two (Simpson, 1935; Lynch, 1941) there was no complaint for as long as twelve to fourteen hours. These two, however, had no signs in the mouth: they presented with diarrhoea and urinary symptoms.

The local damage to the mucosa caused by cantharides preparations is probably only superficial in most cases, however extensive it may be. Thus perforation is rare, and rapid healing is the rule in patients who survive. One patient brought up his oesophageal lining almost intact, yet was discharged fit after three weeks with only two small residual healing erosions in the oesophagus (Sann, 1937).

Polycythaemia following the taking of cantharides preparations has been reported only twice before, by Lipsitz and Cross (1917) and by Andrewes (1921), but as these are the only authors who mention blood counts it may not be so rare. Morgulis and Muirhead (1919) investigated this polycythaemia in rabbits and concluded that it was due to haemoconcentration. This, however, does not explain Lipsitz and Cross's case, whose red blood count was 10,400,000 on the third day (haemoglobin 80%) and whose white blood count was above 20,000 for ten days. Nor would it explain our patient's blood picture, which was certainly the result of stimulation of the bone marrow. Such blood pictures are not a recognized feature of irritant poisoning and are probably peculiar to cantharidin, though it is interesting that another vesicant, mustard gas, is capable of inducing an acute leuco-erythroblastic response.

Gormsen (1945), in a comprehensive review, states that even after a severe initial illness most patients poisoned by cantharides preparations will recover. Nevertheless, these drugs are clearly most dangerous. Given by mouth as aphrodisiacs, there is no safe effective dose, and minute quantities may be lethal. Though one patient (Melen, 1922) is known to have survived the equivalent of 50 mg. of pure cantharidin, another died after only 10 mg.; and Nickolls and Teare (1954) point out that an even smaller dose might cause death. The application of cantharides to the skin is also hazardous. There are many reports of urinary tract damage from this cause. Castro (1915) describes a severe sensory ataxy developing in a boy of 5 after the application of a cantharides plaster to the skin and subsequent painting of the raw areas with further cantharidin. The boy recovered in five months. Another patient, while convalescing from a severe illness due to oral cantharides, applied a cantharides blister to his neck to cure a headache: he developed clonic convulsions and died in a few hours (Kempf and Mueller, 1896).

There is no specific treatment of value. It should be kept in mind that the drug is more likely to cause death by systemic than by local effects. It is said that demulcents and magnesium sulphate may diminish absorption, and that fats increase it. Alkalis are recommended by some authors. Sodium bicarbonate failed to help our patient, whose constant retching and extreme throat pain made it impossible to give further drugs by mouth or to pass a stomach tube.

Since cantharides preparations have no special virtue but are highly dangerous, they should no longer be made available for therapeutic purposes.

Summary

A case of cantharidin poisoning in which death occurred is described and clinical aspects of this condition are briefly discussed.

Our thanks are due to Professor M. L. Rosenheim for permission to publish this case, and to Professor C. Rimington and Dr. Donald Teare for their helpful advice.

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CALCIUM CHLORIDE AND ADRENALINE AS BRONCHIAL DILATORS COMPARED BY SEQUENTIAL ANALYSIS

BY

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It has been claimed by Howell (1953) that the inhalation of calcium chloride in the form of an aerosol is useful for relieving the bronchial spasm often present in patients with acute or chronic bronchitis. The use of this substance was suggested by Charlier and Philippot (1949), who noted bronchodilatation in healthy men when a 20% solution of calcium chloride was given by inhalation, the measurement of the bronchodilatation being made by means of tidal-air tracings.

The wheezing associated with acute bronchitis usually subsides rapidly in hospital as a result of treatment with appropriate chemotherapy, and it is probable that the even temperature of a hospital ward has, in itself, a therapeutic action. Wheezing in acute attacks of asthma generally responds to adrenaline by injection or inhalation, but wheezing associated with chronic bronchitis (Oswald, Harold, and Martin, 1953) and other chronic pulmonary diseases, such as coal-workers' pneumoconiosis, is frequently more difficult to relieve, although adrenaline is often effective. It is for this latter type of bronchial spasm that an alternative bronchodilator agent would be useful, and, as a solution of calcium chloride is cheap and easy to prepare, it was decided to carry out a controlled trial in order to assess its bronchodilator effect.

Method of Trial

The simplest and most satisfactory form of trial would have been one in which each subject's wheeze was assessed before and after an inhalation of calcium chloride. However, it would then have been impossible to distinguish between the real effect of calcium chloride and the psychological effect of any form of therapy unless a dummy inhalation were introduced. Ethical considerations precluded any such procedure; subjects suitable for the trial had a specific disability which, it was known, could almost always be relieved by established methods. Accordingly, it was decided that the trial should be a comparative one between the effects of calcium chloride and a known bronchodilator drug, adrenaline, on the same subjects. Adrenaline was used as the standard for comparison since it is generally accepted as being both effective and capable of being used over prolonged periods of time. Its only disadvantages are its occasional undesirable effects on the circulatory system and its lack of stability. It is the drug which would be deposed from first place in the treatment of bronchial spasm by the discovery of a more effective bronchodilator agent.

Suitable subjects with chronic bronchial spasm of diverse aetiology were drawn from the ward of the Pneumoconiosis Research Unit and the general medical wards of Llandough Hospital. Each subject had been in hospital for at least a week, all had chronic bronchial spasm clinically detectable by stethoscopy, none was having chemotherapy for a respiratory infection, and all other bronchodilator drugs were stopped 12 hours before the assessments were made. The assessment of the drugs was made in terms of the expiratory flow rate (E.F.R.)—the timed vital capacity of Gaensler (1951)—which is a measure of the maximum rate at which a subject can expel air from his lungs during a forced expiration. Although this test takes only a few seconds, the flow rate is expressed in litres per minute, normal values in young men lying between 150 and 200 litres per minute. All of our subjects, however, had values of less than 50 litres per minute, these low figures being caused partly by bronchial spasm and partly by chronic pulmonary disease producing a deficient "bellows action" of the lungs. The E.F.R. is known to be extremely sensitive to the presence of bronchial spasm, and may be used as a measure of it (Kennedy and Stock, 1952; Kennedy, 1953) because variations in the bronchial lumina are accompanied by corresponding variations in ventilatory ability. The test can be used repeatedly without causing the fatigue associated with the more conventional forms of maximum voluntary ventilation tests.

The E.F.R. of each subject was determined in the morning as the mean of three successive readings. A 15-minute inhalation of 3 ml. of either adrenaline or calcium chloride was given from a Collison inhaler at a flow rate of 10 litres of oxygen per minute. Neither the patient nor the observer knew which substance was given, the decision depending on the toss of a coin. The E.F.R. was again determined on the completion of the inhalation, and on the evening of the same day the procedure was repeated, using the other substance. The subject was questioned and a clinical assessment of the degree of bronchial spasm was made before and after each inhalation. The errors inherent in making such assessments as opposed to purely objective ones are discussed below.

The trial was carried out on a sequential basis (Wald, 1947), the results being assessed as soon as each subject was tested, the subjects being taken as they became available (effectively at random), and the decision made to continue the trial or conclude it in accordance with a predetermined plan. This plan was based on the following rules, arrived at after careful discussion with our colleagues of the theoretical and practical qualities of calcium chloride and adrenaline:

1. If calcium chloride caused subjects to gain, on the average, 10 litres per minute of E.F.R. more than they gained on adrenaline, calcium chloride would be regarded as superior to a material degree.

2. If the gain of E.F.R. was no greater with calcium chloride than with adrenaline, adrenaline would be preferred in view of its well-established virtues.

3. The risk of making either of the decisions (1 or 2) wrongly as a result of chance fluctuations in the experimental results should be only 1%.

From this plan the interpretation of the sequence of results obtained from successive subjects can be made