group 18-37 years) (Barnett *et al.*, 1946b; Butt *et al.*, 1948). Wolfson *et al.* (1949) use a colorimetric method in which the normal ranges are stated to be 9-25 mg. per 24 hours for males and 7-12 mg. per 24 hours for females. These figures agree well with those of Hamburger (1948), who studied the variation of 17-K.S. excretion with age and sex in normal individuals. The urate estimations were performed colorimetrically by Brown's (1945) method.

Results

The excretion of 17-K.S. was measured in 29 male and 4 female patients suffering from gout. The average age of the subjects was 54.4 years, and the range of 17-K.S. was 1.4-18 mg. per 24 hours, with an average of 9.51 mg. per 24 hours.

The Graph shows the normal variation of 17-K.S. output (for males) with age (Hamburger, 1948). Normal outputs by our method all lie within this range: male cases in this series are plotted in the Graph. The outputs in the four female cases are within the corresponding female range.

17-K.S. in gout (29 males). Broken lines enclose area within which 97.1% of normal values lie (males) Hamburger (1948).

Discussion

Polarographic and colorimetric methods for estimation of 17-K.S. have been discussed by Barnett *et al.* (1946b) and Butt *et al.* (1951). Results obtained by polarography are comparable with those obtained by colorimetry if a colour correction is made. In some urine extracts, however, chromogenic substances are present which are not recognized by polarography, and in these cases the colorimetric method gives values considerably in excess of those found polarographically.

Wolfson *et al.* state that the non-ketonic chromogens are apparently disproportionately high in the urine of gouty patients, and that separation of the neutral ketonic material should be done with Girard reagent T. The polarographic method is particularly suitable here, as the estimation is done on the Girard derivative, and no colour correction is needed.

The 17-K.S. outputs obtained in this series are appreciably higher than those of Wolfson *et al.*, and fail to show any significant deviation from the normal range.

Summary

Urinary 17-K.S. outputs have been estimated in 33 gouty patients. The results show no significant deviation from normal values.

We have been unable to confirm that gout is characterized by a low 17-K.S. excretion, a finding first reported by Wolfson *et al.* (1949) and later by Robinson *et al.* (1949). Therefore we see no grounds for postulating the presence of an abnormal androgen in gout.

Our thanks are due to Professor A. P. Thomson, who was in charge of the clinical cases, and to the nursing staff, whose full co-operation is so essential in the collection of 24-hour specimens of urine.

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ACUTE ACETONE POISONING CAUSED BY SETTING FLUID FOR IMMOBILIZING CASTS

BY

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In recent years lightweight casts have been used for immobilization of limbs. These consist of glass and textile bandages which are set by means of a fluid consisting chiefly of acetone. They have the advantage of being easily penetrable by x rays, and it is therefore unnecessary to remove them when x-raying the immobilized limb. Because of their light weight they are often used for children.

It is not generally recognized that the setting fluid is a potential cause of serious poisoning. Indeed, this is not surprising, since we have found no adequate appraisal of the more severe toxic effects of acetone in the literature. Hamilton and Johnstone (1945), for example, write: "Acetone has an innocent history as far as its industrial use is concerned. Kobert said that it was almost inconceivable that poisoning could follow its use." We have had under our care a case of acetone poisoning following the application of a lightweight cast, and we feel that it is important to draw attention to the potential danger of this method of immobilization.

Case History

The patient, a 10-year-old boy, was being treated in a sanatorium for tuberculous arthritis of the right hip. His condition had improved while he had been immobilized on a plaster bed, and the orthopaedic surgeon in charge of the case decided to have a lightweight hip spica applied.

The cast was applied on January 11, 1952, by a male nurse in an extremely poorly ventilated theatre measuring 21 by 24 by 12 feet (6.4 by 7.3 by 3.7 metres). The room was very warm, being heated by means of metal plates in the walls.

After the occurrence of this case of acetone poisoning, temperatures taken in the room twice daily for one week ranged between 82 and 88° F. (27.8 and 31.1° C.). As the particular day was rather cold it is probable that the temperature of the room was in the region of 82° F. (27.8° C.).

The following details of the events while the patient was in the sanatorium, and before his admission to the Royal Victoria Infirmary, were obtained from the doctor in charge and from the male nurse.

The boy was taken into the theatre at 2.5 p.m. and was allowed to lie on a bed while the solution and bandages were being prepared. This took ten minutes. About 72 oz. (2 litres) of the setting fluid, which consisted of 90% acetone, 9% pentane, and 1% methyl salicylate, was used, the bowl containing the liquid standing near the foot of the patient's bed at a level of 3 in. (7.6 cm.) below it, and at a distance of about 6 feet (1.8 metres) from his head. The application of the cast, which reached from nipple level to the right ankle and included the left thigh, took 15 minutes. Following this the patient was allowed to lie on his bed, about 14 feet (4.3 metres) from his previous position, while a similar plaster was being applied to a second boy, using a further 50 oz. (1.4 litres) of the setting fluid. While his plaster was being applied the patient complained of the acetone fumes. After being in the room for one hour he was removed to a cool well-ventilated ward, and then seemed perfectly well, taking a normal tea at 4.45 p.m. Nothing abnormal was noted in his appearance or behaviour by the doctor while doing his ward round at 7 p.m.

Between 11 p.m. and midnight the night sister reported that the boy was restless and had a headache, and was complaining of his cast feeling tight across his abdomen. She examined it, and found that it was in fact quite loose.

At 3.15 a.m. the patient vomited purplish material (he had been having gentian violet, $\frac{1}{2}$ gr. (32 mg.) t.i.d. for five days, for threadworms). At 4.45 a.m. persistent vomiting began, the vomitus still being stained with gentian violet, and in the meantime the patient became more restless. At 5 a.m. he collapsed, and his plaster was slit down the side at 5.30 a.m. By 7.30 a.m. the vomitus had become brownish in colour, and the boy was by now very pale and almost stuporous. His spontaneous speech was incoherent, but he could answer questions correctly. At 8 a.m. his blood pressure was 80/60. At 10 a.m. he began to complain of thirst and was given sips of water, which he would vomit each time. His cast was removed at 11 a.m. The inside of it was still wet and sticky and smelt of acetone, but the appearance of the patient's skin had not changed where the cast had been in contact.

He fell into a deep sleep at midday, waking periodically, asking for water, and then vomiting about $\frac{1}{2}$ oz. (14 ml.) of brownish material each time after drinking it. At 1 p.m. his condition worsened again, and he expressed the fear that he was going to die. He was "deathly pale," but for the most part lay quietly. During the course of the morning arrangements had been made for his transfer to the Royal Victoria Infirmary, but he was not fit to travel until 2 p.m. He was admitted at 3.15 p.m. on January 12, 25 hours after the application of the cast.

On admission he was extremely ill and was apathetic, breathing deeply, rapidly, and irregularly, with occasional hiccups. His temperature was 97° F. (36.1° C.), his pulse rate 132, and his blood pressure 120/70. His face was pale with a slight malar flush, his ears were pink, and his extremities were warm. He was restless and had a dry mouth and an intense thirst. There was an extraordinarily strong odour of acetone in his breath, stronger than we had ever noted in cases of diabetic coma. Apart from limitation of movement of the right hip, a few small superficial pressure sores over the right calf, and extremely brisk tendon-jerks, no other abnormalities were detected on physical examination. After taking a drink he vomited 2 oz. (57 ml.) of brownish material, which on testing gave a prompt positive benzidine reaction. He passed 9 oz. (255 ml.) of urine in which acetone and diacetic acid were easily detected, and sugar (one plus)

was detected with Benedict's reagent. His blood acetone level approximately 26 hours after the application of the cast was still 15 mg. per 100 ml.

A presumptive diagnosis of acetone poisoning was made and intravenous N/5 saline and 4.1% dextrose given. He remained very restless and continued to vomit blood-stained material. By 5 p.m. his respirations had slowed and he was having regularly recurring periods of apnoea lasting up to 25 seconds. The respirations, though similar to those of Cheyne-Stokes breathing, were more irregular and were interrupted occasionally by deep sighs. Vomiting ceased at 7.10 p.m., and by 8 p.m. it was obvious that his condition was improving. He was in a sleep, from which he could be roused by light touch.

By 11 p.m. his breathing, though still deep, had become regular again, at 28 a minute. He now began to notice people in the room, and volunteered the information that he felt better. His tongue had become moist and his colour more flushed. By the next morning, January 13, his condition had almost returned to normal, but the smell of acetone in his breath, though not pronounced, was still detectable. Acetone and diacetic acid were still present in his urine, but sugar was not found again. His tendon reflexes, though brisk, were less active than on the previous day. Intravenous fluids were discontinued at 8.45 p.m., 2,500 ml. of glucose-saline having been given.

By the fourth day he seemed quite normal, and we could not smell acetone in his breath or detect it, or diacetic acid in his urine.

The second boy, who had a similar cast applied, was 12 years of age. He slept normally that night, appearing perfectly well the next day until 7 p.m., 28½ hours after the application of the cast, when he vomited. He had no further symptoms.

Discussion

References to three similar cases have been found in the literature. Strong (1944) described the case of a 42-year-old physician who had had a body spica applied, using a setting solution of polymerized vinyl acetate, pyroxylin, boric acid, and acetone, followed by an acetone-containing lacquer. He vomited brownish material, and blood clots were aspirated from his stomach. He became comatose and, a mistaken diagnosis of diabetic coma having been made, was given several doses of insulin. He had transient glycosuria, and eventually recovered after an illness lasting several days and complicated by the diabetic treatment given.

Chatterton and Elliott (1946) describe the case of a girl of 10 years. Long leg casts were applied, the setting solution having the same constituents as that in Strong's case. An acetone-containing lacquer was also applied twice. After the second application of the lacquer the patient, who had been restless and having haematemesis, became semi-comatose, with Kussmaul's breathing. She recovered on the third day.

Fitzpatrick and Claire (1947) describe the case of a 21-months-old child with congenital dislocation of the hips. When a similar cast was applied under general anaesthesia recovery from the anaesthetic took approximately 20 hours, whereas on other occasions it occurred normally with the same anaesthetic and a conventional plaster cast.

The Table shows the main signs and symptoms with their times of onset, when stated, in cases of acetone poisoning by this mechanism.

These four cases of acetone poisoning, arising in a similar manner, present features in common which comprise a characteristic picture. After a latent interval of more than six hours the patient becomes restless, and shortly after begins to vomit with gradually increasing frequency. Before 24 hours have elapsed the vomitus contains altered blood, and by this time the patient is becoming stuporous, with Kussmaul's or periodic breathing. The degree of collapse may become profound, with the patient complaining of intense thirst. The smell of acetone in the breath may be striking, and acetone, diacetic acid, and sugar may be found

Author	Symptoms	Time of Onset after Application of Plaster
Strong (1944) ..	Anorexia	6 hours
	Nausea and vomiting	10 "
	Vomiting brownish material	13 "
	Semi-consciousness and deep breathing of Kussmaul type	17 "
	Coffee-ground material and blood clots aspirated from stomach	35 "
Chatterton and Elliott (1946)	Following this, symptoms were confused by reason of diabetic treatment given	
	Fitfulness and restlessness; vomiting; haematemesis	1st day
	Kussmaul's breathing and semi-coma after application of an acetone lacquer	2nd "
	Weakness and listlessness followed by recovery	3rd "
Fitzpatrick and Claire (1947)	Emesis of dark brown material	7 hours
	Failure to recover from anaesthetic	20 "
Present authors	Patient complained of fumes during application; headache; restlessness; plaster felt tight across abdomen	9 hours
	Vomiting started	13 "
	Collapsed condition	15 "
	Vomited brownish material	17 "
	Excessive thirst	20 "
	Deep, rapid, irregular breathing; hiccup with periods of apnoea	25 "
	Proved haematemesis	26 "
	Vomiting ceased	29 "
	Irregular breathing ceased	32 "

in the urine. Recovery begins gradually late on the second day, and is eventually complete.

In considering this problem it is important to remember some of the physical properties of acetone. It is one of a group of volatile anaesthetics. It is heavier than air, so that concentrations of acetone at the level of the patient's face when he lies on a low bed are apt to be high. This may explain why the person applying the casts seems to suffer no ill effects. Acetone is freely miscible with water and therefore easily absorbed through the alveoli, so that high concentrations may be reached in the blood.

Under experimental conditions, probably on account of the relatively low blood concentrations achieved, toxic symptoms are mild. Koehler, Windsor, and Hill (1941) infused 10 g. of acetone in 200 ml. of saline over a period of two hours. The human subjects used for this experiment showed a slight fall in the systolic and diastolic blood pressures, and transient drowsiness was frequently observed. The average maximum blood acetone level in this experiment was 15 mg. per 100 ml. one hour after the injection had stopped, and nearly normal levels were obtained after 24 hours. It is therefore reasonable to assume that in our case, in which the blood acetone level 26 hours after the cast was applied was still 15 mg. per 100 ml., the maximum concentration at some stage after the application of the cast must have been much higher.

Under industrial conditions acetone may cause irritation of the mucous membranes of the eye and respiratory tract, headache, fainting, and, in much higher concentrations, narcosis. In higher concentrations it is more toxic for brief exposures than chloroform and is only slightly less toxic than benzene (Jacobs, 1949). Severe vomiting, haematemesis, and periodic breathing are not features of industrial or experimental acetone poisoning.

It is striking how in the cases of poisoning caused by the application of casts there has been a latent interval before the onset of symptoms, which does not seem to occur under industrial conditions. In the cases described by Strong and by Chatterton and Elliott, and in our own case, severe symptoms started at night. It is not uncommon for people to sleep with their heads under the bedclothes, where the concentration of acetone produced by vapour from the drying cast might be expected to be high. Our patient was accustomed to sleep like this, and this habit may at least partially explain the latent period. In a further effort to explain this, we considered the possibility of absorption of acetone through the skin. The only experimental work on this aspect appears to have been done by Cesàro and Pinerolo (1947), who found no evidence of acetone absorp-

tion through the skin in human subjects, but the exposure to acetone was not nearly as long or as intimate as in the conditions pertaining in the cases we are considering. Proof, therefore, that acetone *cannot* be absorbed through the skin under these conditions is lacking.

Owing to the physical conditions existing in the theatre in which this cast was applied, it is likely that the air near the patient's face contained a concentration of acetone of about 240 mg. per litre. If a normal respiratory rate and normal respiratory exchange are assumed, the amount of acetone inhaled in the 25 minutes might have been as much as 34 g. If a much smaller quantity of air were saturated with acetone vapours, as might occur under the bedclothes, the concentration could rise to 15 g. of acetone per litre. (Estimates made for us by Professor W. F. K. Wynne-Jones.) The recommended maximum allowable concentration for daily eight-hour exposures ranges from 0.5 to 5 mg. per litre of air under industrial conditions (Haggard *et al.*, 1944). The concentration of acetone in the theatre is therefore likely to have exceeded this by far, though the time of exposure was a good deal shorter. Nevertheless, it does indicate the need for careful consideration of the physical conditions under which the cast may be applied, and it is fair to state that the manufacturers warn that it is desirable to use their product in a well-ventilated room.

The possible toxic role of the pentane present in the setting fluid has been considered. It may have an anaesthetic effect, but as it is rapidly eliminated via the respiratory tract it has no cumulative effect, and it is therefore unlikely to have been an important factor.

In conclusion, we would urge that the following precautions be taken in using this method of application of immobilizing casts: (1) As little of the setting fluid as possible should be used. (2) Any lacquer used should not contain acetone. (3) This method should not be used for casts covering extensive areas of the body which require larger amounts of the setting fluid unless ventilation conditions are ideal. (4) During and after the application of the cast ventilation should be good and room temperatures should not be too high, as this would increase the amount of vaporization. (5) A blower or exhaustion fan would increase the rate of drying, but a shock-cradle would seem to be contraindicated in view of the possibility of a high concentration of acetone being reached under the bedclothes. (6) Patients and nurses should be warned of the possible ill effects of the subject's head being under the bedclothes.

Summary

A case of acetone poisoning, following its use in a setting fluid for an immobilizing cast, is described, and three similar cases in the literature are reviewed.

Certain precautionary measures are urged in the application of these casts. The clinical picture is characterized by a latent interval, followed by restlessness and vomiting, proceeding to haematemesis. Progressive collapse occurs, with stupor and Kussmaul's or periodic breathing. Recovery, which begins gradually on the second day, is eventually complete.

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