ACUTE AMPHETAMINE POISONING

AN ACCOUNT OF 3 CASES

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Amphetamine ("benzedrine") and its derivatives, amphetamine sulphate, dexamphetamine sulphate ("dexedrine"), methylamphetamine, and methylamphetamine hydrochloride ("methedrine") are widely prescribed for a number of ills, and their stimulating effect on the central nervous system is becoming well known to the general public. Although the sale of oral and parenteral preparations is controlled under schedule 4, inhalers containing 325 and 330 mg. of amphetamine base or 250 mg. of methylamphetamine can still be bought without restriction for unauthorized use.* In spite of this ready supply only eight cases of acute poisoning with amphetamine or its compounds have been described in this country. All these drugs appear to have similar effects when taken in excess, and the term "amphetamine poisoning" in this account refers to the clinical picture which can be produced by overdosage with any of the group.

The purpose of this paper is to report three further examples of acute amphetamine poisoning. The case reports illustrate the difficulties which may arise when such patients are admitted to the wards of general hospitals, the necessity for adequate sedation in treatment, and the danger of excessive or improper use of a "benzedrine inhaler."

Case 1

A man of 23 attended the casualty department at 7 a.m. on June 7, 1956, complaining of a cramp-like pain over the praecordium, a tingling sensation over the face, and difficulty in breathing. The symptoms had been present for five hours. He denied having taken any drugs or alcohol. His wife stated that on the previous evening her husband complained of nasal obstruction and a frontal headache. At 11 p.m. he began to use a benzedrine inhaler bought the previous day. This seemed ineffective, and so he warmed the inhaler, at first before the fire and later by partial immersion in hot water. He inhaled constantly until 2 a.m., when he became dizzy and complained of inability to breathe and, soon afterwards, of nausea. Benzedrine inhalations were continued until 4.30 a.m. His symptoms persisted and about 6 a.m. his legs became weak, he had precordial pain, his face began to tingle, and he began to sweat profusely. Now very anxious, he called a neighbour and was brought to hospital.

On examination he was anxious and pale, and was sweating profusely. Breathing was shallow and rapid (40 a minute). His pupils were dilated but reacted to light and accommodation. His pulse was regular, 140 a minute, and his B.P. 200/100 mm. Hg. No other abnormal physical signs were present. Blood glucose on admission was 125 mg. per 100 ml. An electrocardiogram showed regular rhythm with auricular premature beats. The pulse was taken every 15 minutes for the next two and a half hours and varied between 146 and 100. He was given 3 gr. (0.2 g.) of soluble phenobarbitone intramuscularly and admitted to the ward. On further questioning he gave a clear account of previous illnesses but was confused regarding the day and date. He remained quiet and co-operative during the day. In the ward the pulse rate slowly fell from 120 to 90 and the blood pressure from 170/100 to 130/80 mm. Hg. Breathlessness and other symptoms gradually disappeared.

He was visited by his wife at 7.30 p.m., and at 8 p.m., after she had left, he suddenly developed tachypnoea 50 a minute and tachycardia 160 a minute. He sweated profusely and demanded oxygen. He then insisted he could hear his wife talking and accused the nursing staff of denying him permission to see her. He was given morphine, ¼ gr. (0.01 g.), subcutaneously and soluble phenobarbitone, 3 gr. (0.2 g.), intramuscularly. At 8.15 p.m. he demanded more oxygen and attempted to get out of the window. He was restrained with difficulty, but eventually jumped out of bed and for a time several nurses were needed to control him. Paraldehyde, 10 ml., was given intramuscularly and he eventually became quieter. At 1.30 a.m. a further 10 ml. of paraldehyde was given, he fell asleep, and the pulse and blood pressure again fell to normal levels.

Next day he could not remember his confusional episode. Dr. I. S. Kreeger, who then examined him, could find no evidence of psychiatric disturbance. He had been a paratrooper with a good Service record. He was happily married and there was no current stress. His wife recalled that her husband had once before used an inhaler for a cold the previous year; but then he had followed the printed instructions and inhaled only occasionally. After three days the patient was discharged, but later he suffered attacks of hyperventilation. These were becoming infrequent when he last attended the out-patient department four weeks later. The urine passed while he was in hospital was found to contain a total of 36 mg. of amphetamine base, which would correspond with an oral dose of 72–130 mg. of amphetamine (Connell, 1957). The benzedrine inhaler, analysed after the patient's admission to hospital, contained only 60 mg. instead of its original 325 mg.

Case 2

A woman of 32 was admitted to hospital at 8 p.m. on July 21, 1956, having swallowed 50 tablets of dexamphetamine sulphate (200 mg.) 12 hours previously. She denied suicidal intent and stated that she had taken the tablets for slimming, but later she admitted to being very depressed by the proposed adoption of her illegitimate son, 2 months old. The father of the child, of whom the patient was very fond, had suggested the adoption but had refused to marry her.

On admission she was aggressive, suspicious, and restless. Her face was flushed, she was perspiring profusely, and her mouth was dry. Both pupils were widely dilated but reacted to light and accommodation. Her pulse was regular at 120 a minute and her blood pressure 180/90 mm. Hg. After a stomach lavage she was sedated with intramuscular soluble phenobarbitone, 6 gr. (0.4 g.) six-hourly. She slept well during the night, and next morning was quite wide awake and co-operative. Her pulse rate was now 80 and her pupils were of normal size; her B.P. was 90/60 mm. Hg. Recovery was uneventful. The above sedation was continued for three days, when she was interviewed by Dr. E. J. Nuffield, who found no evidence of any specific psychiatric disorder other than mild depression. The urine passed in hospital contained 54.7 mg. of amphetamine sulphate, which would correspond with an oral dose of 109–187 mg. of dexamphetamine sulphate (Connell, 1957).

Case 3

A man of 32 was admitted to hospital on July 11, 1956, at 10 p.m. The previous evening he had drunk 12 pints (6.8 litres) of beer and then spent the night at a coffee stall, where he chewed the contents of one and a half benzedrine inhalers (487.5 mg. of amphetamine). He now felt "on top of the world," and drank a further 5 pints (2.8 litres) of beer

*Since this paper was written it is understood that all manufacturers in this country have ceased to make inhalers containing amphetamine derivatives.

at Covent Garden, starting at 6 a.m. During the day he developed substernal pain and palpitation, and at 2 p.m. attended the Royal Eye Hospital, where he was given 3 gr. (0.2 g.) of soluble phenobarbitone intravenously and transferred to King's College Hospital, arriving at 2.45 p.m. After stomach lavage he refused in-patient treatment and left the hospital.

He returned at 9 p.m., having drunk a further 2 pints (1.1 litres) of beer. He was now anxious and sweating, with dilated pupils which reacted normally to light and accommodation. His pulse was regular at a rate of 108 a minute, and his blood pressure 170/120 mm. Hg. His tendon reflexes were brisk. He was given paraldehyde, 8 ml. intramuscularly, and sodium phenobarbitone 6 gr. (0.4 g.), intramuscularly. The latter was repeated six-hourly. He slept uneventfully through the night. His pulse rate rapidly fell to 70 and his B.P. to normal levels. Next day he was quiet and co-operative and was interviewed by Dr. Nuffield, who found no evidence of psychiatric abnormality beyond a history of chronic alcoholism. He went home after three days, having quite recovered.

Discussion

The side-effects of amphetamine compounds when used therapeutically include dryness of the mouth, restlessness, insomnia, irritability, and anxiety, and are relatively unimportant. With larger doses of 10–30 mg. the cardiovascular system is chiefly affected, causing flushing or pallor, palpitation, labile pulse rate and blood pressure, extrasystoles, heart-block, chest pain, and sometimes collapse (Anderson and Scott, 1936). Prolonged use may on rare occasions cause aplastic anaemia (Davies, 1937), and fatal panhaemocytopenia has been recorded with continued overdosage (Mitchell and Denton, 1950). Death, however, is rare in acute poisoning. Only six cases appear to have been reported, and in three of these the role of amphetamine is uncertain. Harvey *et al.* (1949) thought that amphetamine had contributed to the death of a 35-year-old alcoholic who became jaundiced and died after ingesting alcohol together with the contents of two benzedrine inhalers. Post-mortem examination revealed an alcoholic fatty liver with zonal necrosis. The second patient, a student aged 25, after taking an estimated 10 mg. of amphetamine died suddenly during an examination. At necropsy acute gastric and splanchnic dilatation was found. Although he was accustomed to taking amphetamine, his death was partly attributed to the drug (Smith, 1939). Amphetamine was held responsible for the death of a one-year-old child from haemorrhagic gastritis after swallowing 40 mg. of amphetamine together with an unknown quantity of ferrous sulphate tablets (Hertzog *et al.*, 1943).

In animals amphetamine is known to cause cerebral haemorrhage (Ehrich *et al.*, 1939; Ivy and Krasno, 1941), and all three patients in whom acute amphetamine poisoning appeared to be the sole cause of death had cerebral lesions. Pontrelli (1942) described the necropsy findings in a 25-year-old soldier who died after taking 100 mg. of amphetamine. The brain, lungs, and liver were congested, the kidneys showed tubular degeneration, and punctate haemorrhages were present in the pleura and pericardium. Gericke (1945) noted subdural and subarachnoid haemorrhages and petechial haemorrhages in the cerebrum, cerebellum, and pons in a 36-year-old man who had swallowed 120 mg. of amphetamine. Pretorius (1953) found acute internal hydrocephalus in a 3-year-old girl who died after swallowing an estimated 40 mg. of dexamphetamine sulphate. Poteliakhoff and Roughton (1956) have described the occurrence of cerebral haemorrhage with recovery in a man of 42 who dissolved the contents of a benzedrine inhaler in "coca-cola" and drank the mixture.

One common and most alarming result of amphetamine poisoning may be the development of an acute psychosis. Of the eight cases of acute amphetamine poisoning recorded in this country, four had visual or auditory hallucinations (Wallis *et al.*, 1949; Carr, 1954; Patuck, 1956; Shanson, 1956). Another patient was repeatedly admitted to hospital with excitement, confusion, paranoid delusions, and on one occasion depression, each admission being preceded by the ingestion of large quantities of amphetamine (O'Flanagan and Taylor, 1950). Watts (1956) reported the case of a 2-year-old child who swallowed tablets of "edrisal," each containing amphetamine, 2.5 mg., aspirin, 160 mg., and phenacetin, 160 mg. He became very restless and talked all night, at times coherently and at other times "like the wanderings of a lightheaded child." In these cases the amount of amphetamine taken, when known, varied from 55 to 115 mg. One patient extracted the contents of two benzedrine inhalers, but the actual amount ingested was uncertain (O'Flanagan and Taylor, 1950). We estimated that our patient who became psychotic had absorbed 265 mg. of amphetamine.

Acute amphetamine poisoning is commoner than published reports suggest. The severe examples present as an acute mental disturbance and are likely to be seen most often in mental observation wards. Connell (1956) has investigated 42 such cases from the physical and psychiatric aspects in the past two years and has followed the urinary excretion of amphetamine in 10 of these patients. Patients, however, who do not show initial overt mental disturbances at an early stage of the illness may be admitted to general hospitals and the need for heavy sedation may not be appreciated. This may well lead to difficulties and dangers, as shown in Case 1, in which the patient developed an acute psychotic state 12 hours after admission.

Since amphetamine is a barbiturate antagonist (Myerson *et al.*, 1936; Reifenstein and Davidoff, 1938), large doses of these sedatives are required in the treatment of amphetamine poisoning, not only to control a psychotic patient but also as a prophylactic measure, since there is good evidence that mental abnormality may thereby be prevented. In the converse problem of barbiturate poisoning treated with large doses of amphetamine, mental complications are rare. None occurred in 14 patients given up to 400 mg. of amphetamine intravenously in eight hours (Freireich and Landsberg, 1946). Riishede (1950) treated 132 cases with total doses of amphetamine up to 4,850 mg., given intramuscularly over 84 hours. Although these amounts far exceeded reported toxic doses of amphetamine, only 5% of patients became confused or euphoric and only 2% developed hallucinations.

In the cases reported here, after adequate sedation Case 1 recovered within a few hours, and the initial restlessness and aggressive attitude in Case 2 quickly disappeared. There was no overt disturbance of a psychotic nature in the third patient, who, possibly wisely, had taken considerable sedation in the form of alcohol before admission.

All three showed an increased tolerance to hypnotic drugs. The first patient slept for only eight hours after injections of 3 gr. (0.2 g.) of sodium phenobarbitone, 20 ml. of paraldehyde, and $\frac{1}{6}$ gr. (0.01 g.) of morphine within five and a half hours. The second and third patients were wide awake after receiving a total of 12 gr. (0.78 g.) of sodium phenobarbitone by injection during the previous 12 hours.

These three further examples bring the total number of cases of acute amphetamine poisoning reported in this country to 11. In seven of these the source of the drug was an amphetamine-containing inhaler. Two examples of inhalational poisoning have previously been described in this country (Carr, 1954; Shanson, 1956), and we could find no evidence that our first patient took the drug in any other way. Memory impairment caused by amphetamine has been noted previously (Waud, 1938), and possibly explains why this patient inhaled almost continuously for five and a half hours when he had previously used an inhaler normally. Impairment of memory was certainly present eight hours after he had started to inhale.

Summary

Three examples of acute amphetamine poisoning are described. Two patients took the drug orally and one by inhalation. One patient became poisoned by chewing

the contents of one and a half benzedrine inhalers, an unorthodox but readily available source of the drug.

One case developed an acute psychosis, a common feature of severe amphetamine intoxication which requires heavy barbiturate sedation both for prophylaxis and for treatment.

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TRICHOPHYTON RUBRUM INFECTION IN FAMILIES

BY

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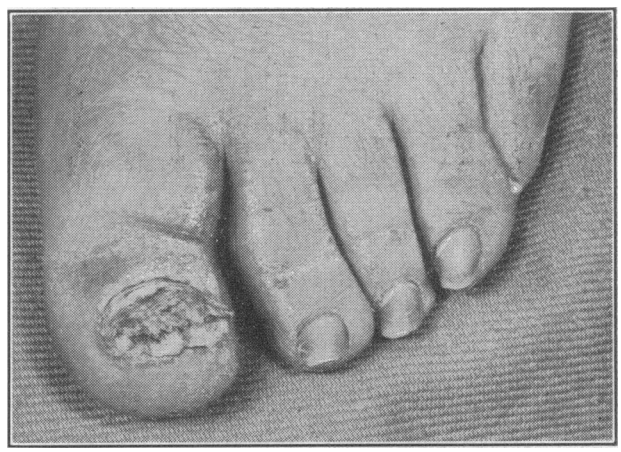
Trichophyton rubrum is the fungus most often isolated from patients with mycotic skin diseases attending the Bristol Royal Hospital. Of the 12 species isolated from 204 of these patients seen in the two years since March, 1954, *T. rubrum* was found 43 times.

The infection is usually first noticed as a scaling or macerated area between the toes indistinguishable from tinea pedis due to other fungi. *T. rubrum* differs from other dermatophytes, however, in that it is much more likely to attack the nails, when their discoloured, misshapen, and broken appearance (see Fig.) may cause the patient much mental distress; treatment at this stage is very rarely successful. It is surprising, therefore, that the epidemiology and prevention of the disease have been so neglected.

Literature

Baer *et al.* (1955) showed the ease with which infective particles can be shed from active mycotic lesions of the feet. After they had soaked the infected feet of 73 patients in footbaths for 15 minutes they were able to demonstrate the presence of fungi microscopically in the water from 54 of the baths, and to obtain cultures of pathogenic fungi from 13 of these. Despite this evidence, these authors deny the importance of cross-infection in the spread of the disease, on the grounds that numerous attempts, by themselves and others, to isolate pathogenic fungi from supposedly contaminated floors have been generally unsuccessful. Recently, however, Gentles and Holmes (1956, personal communication), using a new technique, have been able to isolate from the floors of four pit-head bathhouses the species of fungus predominant in the feet of the bathing miners at each pit.

Numerous surveys have been carried out on the incidence of tinea pedis in many types of community, but little effort has been made to trace the spread of any one fungus. Peck *et al.* (1944), on examining the feet of workers in six factories, found only five cases of *T. rubrum* infection, and all these occurred in the same plant. Gentles and Holmes



Trichophyton rubrum infection of the toe-nails.

(1956, personal communication) produce strong evidence that the habitual use of communal baths is an important factor in the spread of tinea pedis in coal-miners. The infection rate with all species of fungi is 31% of miners using baths against 8% of those who do not. They also found that, among bathing miners, the proportion of the two most important pathogens varied from pit to pit: in eight pits *T. mentagrophytes* was the predominant fungus; in one, *T. rubrum*; and in the tenth the two species were present in almost equal numbers. These figures indicate the importance of cross-infection in a community.

On the other hand, Hopkins *et al.* (1947), investigating fungous infection of the feet of soldiers at a military post, found that the various species occurred in approximately the same ratio in most of the groups examined, and concluded that individual susceptibility to an existing latent infection was more important than exposure to cross-infection. However, three of their 26 groups show considerable variation from the predominant species ratio and four others show slight variation. It is possible that the rapid turnover of personnel in military establishments would often allow insufficient time for any one species to become dominant.

Sulzberger *et al.* (1942) attempted to assess the extent of familial and conjugal infections of the feet and groins by sending questionaries to over 100 American dermatologists. They concluded that among "a sum total probably aggregating hundreds of thousands of patients with fungous infections" of these areas, only four cases of familial infection were proved, and that therefore such infection was of no practical importance. The authors rightly consider that familial infection is not proved unless the fungi are isolated and shown to be culturally similar; yet they include as relevant the replies of 82 dermatologists who did not attempt cultural methods of proof, as well as those of the six who did. Also, no evidence is offered that any of these dermatologists had, as a routine, examined the family contacts of all their ringworm patients, and unless this was done their data can be of little value.

Referring to family infection by *T. rubrum*, Hyman (1953) does not believe that there is any evidence for its existence, while Lewis (1953) thinks it is fairly common, an opinion