SUDDEN DEATH AFTER INTRAVENOUS INJECTION OF A MERCURIAL DIURETIC ("NEPTAL")

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While mercurial diuretics are of great value in the symptomatic treatment of oedema the dangers associated with their use should not be forgotten. The most dramatic of these untoward reactions is sudden death, which occasionally follows directly on the intravenous injection of an organic mercurial. The case here recorded demonstrates this unexpected sequel.

Case History

The patient, a married woman aged 31, was admitted to hospital on March 17 complaining of swelling of the legs (eight weeks), reduction in urinary output (five weeks), dull backache (five weeks), and haziness of vision (four weeks). She had suffered from frequent sore throat for many years, and four and a half years before admission had had an attack of rheumatoid arthritis which responded poorly to treatment with gold injections. In view of this complication the sore throats were regarded more seriously, and a tonsillectomy and complete dental clearance were performed three years previously in an unsuccessful attempt to cure the condition. Two months before her present symptoms appeared in December she underwent a ventrisuspension and appendicectomy.

On examination the patient was seen to be a pale, sthenic, well-nourished woman with a generalized pitting oedema. Fine crepitations could be heard at both lung bases, and a small palpable gland was found in the right digastric triangle. The temperature and pulse were normal, the B.P. was 130/90, and the fundi were normal, without papilloedema, kinking of vessels, or exudates. A complete examination of all other systems revealed no abnormalities.

Laboratory Investigations on Admission.—March 18:—Urine: Albumin present, 0.55 g. per 100 ml. Microscopical examination revealed occasional hyaline casts, erythrocytes, pus, and spheroidal epithelial cells. Blood: Wassermann reaction negative; blood cholesterol, 440 mg. per 100 ml.; serum albumin, 2.4 g. per 100 ml.; serum globulin, 1.8 g. per 100 ml.; blood urea, 16 mg. per 100 ml. Blood count: Haemoglobin, 76%; red cells, 3,790,000; white cells, 8,400 (neutrophils, 54%; monocytes, 4%; lymphocytes, 38%; eosinophils, 4%). The urea clearance was 61% of normal. The diagnosis was subacute (nephrotic) nephritis (Type 2 of Ellis, 1942).

Treatment and Progress Notes.—The patient was confined to bed and given a diet high in protein and low in salt, with iron tonics. On March 19 she developed a left basal pleurisy, and this persisted until death. On March 21 she had an attack of rheumatic pain in both knees, lasting for one day. On the 22nd treatment with a mercurial diuretic ("neptal") was started: 0.5 ml. was given intramuscularly, and thereafter 2 ml. every second or third day, until by April 21 a total of 24.5 ml. had been injected. Good results were observed, diuresis varying between 50 oz. (1.42 kg.) and 110 oz. (3.12 kg.) after each dose. Ammonium chloride, 15 gr. (1 g.) t.i.d., was given orally at the same time. The injections of the diuretic were very painful, and as this pain could not be prevented by preceding the neptal by a local analgesic (procaine) the intravenous route was adopted, to the patient's relief. Two ml. was given intravenously on April 23, 25, 28, and 30. After the last injection she complained of giddiness, and became pale for a few seconds, shortly after the needle had been withdrawn.

On May 1 the patient complained of a sore throat and generalized joint pains. Her knees became swollen and a patellar tap could be elicited on both sides. On the 3rd 2 ml. of neptal was injected into the right median cubital vein, this taking about one minute to carry out. Immediately on withdrawing the needle the patient turned pale and fell back un-

conscious. Cyanosis rapidly supervened, and breathing, which had become gasping, ceased about two minutes after the onset of the attack. A convulsion occurred, with jerking of both arms, and the pupils became widely dilated before death. Artificial respiration was carried out, with intranasal oxygen for twenty minutes, and 1.7 ml. of nikethamide was given intramuscularly and the same dose intracardially, without avail.

The manner of death observed in this patient bore a close resemblance to that witnessed in another person dying of a terminal coronary infarct about the same time. Both of these patients displayed a syndrome of primary cardiac arrest followed by cyanosis, convulsions, and eventual cessation of respiratory movements. On clinical grounds, therefore, it appeared that the injection of neptal brought about a sudden cessation of the heart-beat, presumably by ventricular fibrillation.

Necropsy.—This revealed the large pale kidneys of subacute glomerular nephritis and a left-sided pleural effusion. A small adherent clot was present in one of the cubital veins, but no sign of embolism could be found. Chronic poisoning by mercury could be excluded as there was no stomatitis or haemorrhagic colitis. About 1 or 2 ml. of air was found in the heart. The most probable explanation is that this air was injected into the heart after death during the intracardial injection, for in performing this the needle first encountered lung, and air was withdrawn into the syringe.

Discussion

Since 1925, when Redlich drew attention to three fatalities after intravenous injections of a mercurial diuretic ("novasurrol"), more than a score of deaths attributable to this cause have been recorded. Although the deaths reported by Redlich do not appear to have been directly due to the mercury (one died of a Jarisch-Herxheimer reaction, another from salvarsan encephalitis, and the third—Redlich's own case—from an intestinal obstruction) his report does seem to have stimulated interest. Numerous subsequent cases have been recorded in which the mercurial has been more convincingly incriminated, and from these cases and the animal experimentation which they stimulated it is now possible to come to definite conclusions about the immediate action of mercurials on the heart. These findings are summarized below.

1. Type of Patient

Sudden death after an injection of a mercurial diuretic has occurred in children as well as in young, middle-aged, and elderly patients suffering from such varied conditions as nephritis, nephrosis, cirrhosis of the liver, and heart disease of rheumatic, syphilitic, congenital, coronary, or hypertensive origin. DeGraff and Nadler (1942) have stated that inflammatory disease of the kidney is a contraindication to the use of mercurial diuretics: certainly most of these accidents occurred in cases of nephrosis and Type 2 nephritis, and Evans and Perry (1943) suggest that a lowered plasma protein may be a factor of significance. Nevertheless this toxic effect has been demonstrated on healthy experimental animals, and it would seem that death is the result of a direct action on the heart.

2. Type of Diuretic

In human cases "salyrgan" and "mercupurin" have caused most of the deaths (Ben-Asher, 1945; Sundaram, 1934; Brown *et al.*, 1942; Barker *et al.*, 1942), but deaths are also reported following "esidrone" (Volini *et al.*, 1945), "mersalyl" (Evans and Perry, 1943), and neptal (Greenwald and Jacobson, 1937). Animal experiments also demonstrate variation in toxicity, esidrone and mercupurin being singled out for especially unfavourable mention by Pines *et al.* (1944). DeGraff and Lehman (1942) found that esidrone was more toxic to cats than either mercupurin or salyrgan. Nevertheless on theoretical grounds it seems likely that any organic ionizable mercurial diuretic will be capable of producing sudden death of this type.

3. Route of Administration

So far all but one of the deaths have followed an intravenous injection, the exception being the case of Wolf and Bongiorno (1931), in which an intraperitoneal injection was to blame. It should be borne in mind, however, that DeGraff and Lehman were able to kill dogs with large intramuscular doses: in humans, therefore, it is possible that fatal reactions may also follow intramuscular injections of the mercurial, though this is very unlikely, since rapid elimination would normally prevent the injection from reaching toxic levels.

4. Cause of Death

The manner of death in all these cases has been almost identical. Apparently the heart stops beating before the respiration ceases, and convulsions occur which are probably due to anoxia. This usually takes place within ten minutes of the injection, though in one instance as much as half an hour elapsed before the terminal episode.

Death may occur after the first injection. This has been reported four times—viz., by Sundaram (1934), Cadbury (1936), Barker *et al.* (1942), and Volini *et al.* (1945). These four cases are of great significance, for their occurrence excludes the possibility of cumulative poisoning with mercury as a cause of death, and also rules out anaphylaxis or sensitization, both of which have been considered (Tyson, 1941; Evans and Perry, 1943; Rennie, 1945) in spite of the absence of any clinical evidence in favour of these diagnoses.

Hyman (1942) suggested that these patients died from "speed shock"; but this cannot be accepted, as the clinical picture of "speed shock" is different (salivation, vomiting, diarrhoea, irregular respiration, fall in blood pressure, and bronchospasm). Conclusive evidence to the contrary is provided by Wexler and Ellis (1944), who demonstrated that blood drawn from the patient immediately after death was capable of clotting, since in "speed shock" such blood will be found to be incoagulable.

A considerable weight of evidence has been accumulated to indicate that these deaths are due to the direct toxic action of the mercury ion on the heart. This action was first demonstrated with inorganic salts of mercury by Salant and Kleitman in 1922; they showed that the mercury ion was capable of inducing ventricular fibrillation, which neither bilateral vagotomy nor atropinization could alter. Salant and Brodman (1929) state that adrenaline improves the heart poisoned by mercury while ergotamine increases mercurial toxicity. The same action was demonstrated in the organic mercurial diuretics by Jackson, who in 1926 produced ventricular fibrillation in dogs with salyrgan. His work has been confirmed by other investigators with other diuretics (DeGraff and Lehman, 1942; Pines *et al.*, 1944). From his experiments on the isolated turtle heart Johnston (1941) came to the conclusion that the toxic action of the organic mercurial diuretics was a side action related to their mercury content, and consequently was not essentially different from that of inorganic salts like calomel and bichloride of mercury.

However suggestive they might be, animal experiments alone could not prove that human fatalities were also the result of ventricular fibrillation. This final step has been completed by the unique studies of Volini, Levitt, and Martin in 1945; for in two of their three patients killed by mercurial diuretics simultaneous electrocardiograms were obtained which demonstrate that ventricular fibrillation was the cause of death.

The unpredictable behaviour of the drugs still remains to be explained. Some patients die at the first injection, while others receive many injections only to succumb after

an injection differing apparently in no way from its harmless predecessors—for example, the patient of Wexler and Ellis's (1944) who received a total of 164 ml. before the fatal dose of mercupurin, or the case reported by Barker *et al.* (1942) in which it is estimated that more than 200 injections of mercurial had been given before the one that proved fatal.

5. Premonitory Indications

The occurrence of subacute reactions after any injection of mercurial diuretic should be regarded seriously, and would indicate the need for smaller doses or a different route of administration. Unfortunately such warning is not always given. The case history recorded above demonstrates one warning the significance of which was not appreciated at the time—namely, the attack of giddiness after the penultimate injection. In three out of the four cases quoted by Brown and co-workers (1942) warning symptoms were observed at previous injections. These included dyspnoea, orthopnoea, sweating, pallor, bradycardia, and syncope. Wexler and Ellis have described the immediate non-fatal reactions as of four types: (1) a subjective, indescribable, unpleasant sensation; (2) transitory dyspnoea; (3) apprehension, substernal discomfort, slight increase in respiration and pulse rate, and orthopnoea; (4) moderate collapse, cyanosis, and sweating. The occurrence of any reaction should receive serious consideration.

6. Treatment

In human cases recovery is rare. Tyson (1941) reports the case of a young male nephrotic who became unconscious after 1 ml. of esidrone, with a convulsion, deep cyanosis, dilated pupils, and absent heart sounds. This patient recovered after artificial respiration, adrenaline, nikethamide, and aminophylline had been administered. Andrews (1931) reports a similar case of recovery in a young woman with rheumatic valvular disease, in which consciousness was lost, but the heart did not stop beating, although seriously affected.

On the isolated turtle heart Johnston (1941) found that nikethamide was of no use in treatment but that sodium thiosulphate would restore to normal rhythm a poisoned heart in complete block. Further, if perfused at the same time, this substance would prevent the action of the mercurial. DeGraff and Lehman have confirmed this for the cat. To apply this fact to the treatment of the human being poisoned with a mercurial diuretic would be difficult, although possible. Fortunately, prevention of fatalities is considerably easier than cure.

7. Prevention

The discontinuance of these drugs has never been suggested. A proper perspective of their toxicity will be obtained if it is realized that even when given intravenously they are less toxic than the arsphenamines (DeGraff and Nadler, 1942).

Route of Administration.—In his textbook White (1944) says that the mercurials are "preferably given intravenously" (p. 783); nevertheless since all recorded fatalities have followed intravenous and intraperitoneal injection of these drugs, these two routes should be used no longer. The pain of intramuscular injections might be prevented by infiltrating the injection site with an anaesthetic of long duration, such as "proctocaine."

Choice of Drug.—Esidrone, salyrgan, and mercupurin have been mentioned most frequently as causes of death. They might well be avoided unless it is proved that this frequency was due to their popularity rather than their extra toxicity.

Adjuvants.—Pines and co-workers (1944) found that if 0.5 ml. of 20% magnesium sulphate was injected

simultaneously one could prevent the onset of ventricular fibrillation in dogs even when seven times the normal lethal dose was given. This has considerable clinical significance. Magnesium sulphate should be added to all mercurial diuretics intended for injection. Theophylline is of proved value as an adjuvant, for it not only increases the rate of renal excretion of the mercurial but also serves to reduce the toxicity of certain of these compounds (DeGraff and Nadler, 1942); nevertheless deaths have occurred in spite of its presence.

Other Drugs.—The common cardiac drugs, digitalis, aminophylline, ammonium chloride, and phenobarbitone, have no effect on the toxicity of mercurials (DeGraff and Nadler, 1942).

Rate of Injection.—Contrary to what might be expected, DeGraff and Lehman (1942) found that injecting the mercurial slowly only increased its toxicity. They demonstrated in cats that the slower the injection the smaller the lethal dose, the curve flattening out at a rate of 40 minutes per ml., at which point the toxicity was about three times that of a rapid injection. Human cases have confirmed that dilution is of no value, and fatalities have been reported with dilutions of 1 in 10 (Sundaram, 1934; Barker *et al.*, 1942; Evans and Perry, 1943).

Summary

A case is presented in which sudden death followed the intravenous injection of a mercurial diuretic. Death is presumed to have been due to ventricular fibrillation.

Similar cases are described in the literature, also following the intravenous injection of these drugs. Treatment should consist of intracardiac adrenaline and sodium thiosulphate.

To prevent such sequelae mercurial diuretics should never be given by the intravenous route. The addition of magnesium sulphate to the injection promises to lower its toxicity considerably.

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PLUNGE BATH FOR CASES OF POLIOMYELITIS

The present increase in the number of patients suffering from anterior poliomyelitis has presented problems of treatment not ordinarily encountered in general hospital practice. An underwater therapy pool was constructed within three weeks at the County Hospital, Farnborough, Kent, and the following description by the hospital steward may prove of interest.

To meet an emergency, application was made to the Kent County Council Public Assistance Officer to utilize a building which had formerly been devoted to casual ward accommodation. Permission was promptly given, and in less than three weeks the building was converted into a plunge bath 11 ft. 6 in. (3.5 m.) by 8 ft. 6 in. (2.6 m.) to be used for the underwater treatment of patients suffering from anterior poliomyelitis.

This was effected by constructing a small dam wall across the width of the room and making the walls and floor watertight. The bath is filled with water of the right temperature through a mixing valve, and in order that it may be maintained at a continuously even temperature a thermal control unit has been installed. The bath may be filled to a depth of 3 ft. 6 in. (1 m.) and is equipped with hand rails, slings, etc. An adjoining room has been fitted with dressing cubicles.

The facilities thus provided make it possible to deal with several patients at the same time instead of singly, and the bath replaces an emergency collapsible water dam which was kindly loaned and erected by the Bromley N.F.S. at short notice.

The whole of the work was carried out by the hospital engineering and maintenance staff with the valued advice of the County Architect's Department.

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A circular from the Ministry of Health on the transfer of headquarters hospital staffs to the Regional Hospital Boards under the National Health Service Act points out that the transfer concerns those officers employed immediately before the appointed day "solely or mainly at or for the purposes of any hospital transferred to the Minister" (other than teaching hospitals). Local authorities have been asked for a statement of the numbers and types of staff employed on such work for more than half their time who would be liable for transfer. Many authorities, however, have found it impossible to provide a satisfactory list on this basis. The circular suggests, therefore, that they must relate the number of staff transferred to the amount of work transferred and assess the hospital part of the work in terms of units of staff in different grades. This estimate will be only approximate but should afford both a reasonable guide to the Regional Hospital Board's requirements and a general formula for providing lists of officers for transfer. Replies should reach the Ministry by Oct. 30.