There have been a few previous reports of similar treatment. Two cases receiving parenteral A.C.T.H. had at least a temporary increase in secretion and diminution in size of the parotid glands (Stephens, 1950; Frenkel *et al.*, 1951). Two other cases similarly treated failed to improve (Offret and Forest, 1950; Fitzgerald *et al.*, 1951). Cortisone used subconjunctivally gave no improvement in Duke-Elder's case (1951).

A temporary beneficial effect on the parotid enlargements has also been reported with deep *x*-ray therapy (Heaton and Shannon, 1948; Ellman and Weber, 1949). The response of the parotid enlargements to both A.C.T.H. and deep *x*-ray therapy is consistent with the presence of a chronic inflammatory lesion. However, this does not help us to identify the cause of the syndrome or to distinguish it from Mikulicz's syndrome, with which it is often confused, since this would probably respond similarly (Heaton and Shannon, 1948).

Summary

Two cases of Sjögren's syndrome are described, one of which had hepato-splenomegaly.

Treatment with A.C.T.H. reduced the parotid swellings to normal size, and the improvement was maintained as long as the drug was given.

There was no improvement in the eye and mouth symptoms.

We wish to thank Professor Sir Henry Cohen and Dr. E. T. Baker-Bates for permission to publish these cases.

REFERENCES

Duke-Elder, Sir Stewart (1951). *Brit. J. Ophthal.*, **35**, 637.
Ellman, P., and Weber, F. Parkes (1949). *British Medical Journal*, **1**, 304.
—— —— and Goodier, T. E. W. (1951). *Quart. J. Med.*, **20**, 33.
Fitzgerald, J. R., Bellows, J. G., Donegan, J. M., Gamble, R. C., Krause, A. C., Mann, W. A., Pearlman, M. D., and Zekman, T. N. (1951). *Arch. Ophthal., Chicago*, **45**, 320.
Frenkel, M., Hellinga, G., and Groen, J. (1951). *Acta endocr., Kbh.*, **6**, 161.
Heaton, T. G., and Shannon, E. H. (1948). *Canad. med. Ass. J.*, **58**, 368.
Henderson, J. W. (1950). *Amer. J. Ophthal.*, **33**, 197.
Offret, G., and Forest (1950). *Bull. Soc. Ophtal. Fr.*, No. 9, 759. Quoted by Duke-Elder (1951).
Sjögren, H. (1948). *Acta med. scand.*, **130**, 484.
Stephens, C. A. L. (1950). *Proceedings of the First Clinical A.C.T.H. Conference*, ed. by J. R. Mote, p. 358. Churchill, London.
Weber, F. Parkes (1945). *Brit. J. Ophthal.*, **29**, 299.

SUDDEN DEATH FOLLOWING AN INJECTION OF PENICILLIN

BY

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Allergic reactions to penicillin are not uncommon—Keefer and Anderson (1950) placing them at 1.5–5% of patients treated—and are within the experience of most practitioners. Death due to penicillin therapy, however, is unusual and few cases have been reported.

When a fatal reaction does occur it seems to be due to (*a*) a Jarisch–Herxheimer reaction in known or unsuspected syphilitics; (*b*) severe allergic manifestations, usually occurring after a latent period and slowly progressing to death; or (*c*) anaphylactic shock producing death in a matter of minutes.

Of the few reported deaths attributed to penicillin, only one has been considered anaphylactic. Waldbott (1949) described a patient who, after receiving 50,000 units of penicillin intramuscularly during an acute attack of asthma, reacted immediately with swelling of the mouth, generalized itching, and collapse, with extreme cyanosis and death. She had had penicillin without ill effect several times before, but during the previous month had complained of urticaria and joint pains one week after penicillin therapy. Waldbott thought that the injection must have been intravenous.

O'Donovan and Klorfajn (1946), with an intramuscular injection of 15,000 units of sodium penicillin, produced an anaphylactic-like reaction in a patient known to be penicillin-sensitive. There was a slow recovery over the next two days. Non-fatal anaphylaxis was also reported by Burleson (1950) after the intramuscular injection of 200,000 units of penicillin with procaine.

Other fatal reactions attributed to penicillin sensitivity have been of a more prolonged duration, have frequently involved the skin, and have often occurred after a latent period, during which no signs or symptoms were noted. Thus a case described by Rabinovitch and Snitkoff (1948) developed a maculo-papular rash which progressed to exfoliative dermatitis and death seven days after the last injection of an eleven-day course of intramuscular penicillin. There was a family history of penicillin sensitivity.

Panja and Banerjee (1951) reported a case of an Indian woman who developed blisters of the lip and perineum after penicillin therapy, and who, four months later, had extensive bullae with exfoliation after streptomycin. The condition became very much worse and the patient died when the streptomycin was replaced by penicillin.

Barksdale (1946) reported a case of a sailor known to be sensitive to penicillin who, after his seventh desensitizing dose of 100 units of penicillin, developed a severe cutaneous eruption which progressed to a generalized exfoliative dermatitis, streptococcal septicaemia, and death. A case of Wilensky's (1946) received 30,000 units of penicillin four-hourly in the post-operative treatment of a subtotal gastrectomy. On the fifth day of convalescence the patient had a scarlatiniform rash which later became urticarial. There was a slow deterioration over the next few days, and death ensued.

Berne (1950) described a case in which there was an erythematous rash twenty-four hours after administration of sulphonamides and 30,000 units of penicillin in oil and wax. The condition progressed to an exfoliative dermatitis when the penicillin was repeated, in spite of the fact that the sulphonamides had been stopped. A repetition of the penicillin nine days later, when the skin condition had almost resolved, produced an acute flare-up, leading to generalized exfoliation, purpura, rapid deterioration, and death. Berne was able to demonstrate haemorrhagic necrosis of the bowel mucosa, with a primary lesion in the veins. Penicillin had never been given before.

The only case of fatal hypersensitivity to penicillin recorded in Britain occurred in a 14-months-old child who received "penicillin treatment" for a burn and who died five days later of serous exudation into the pleural cavities, pericardium, and peritoneum (*British Medical Journal*, 1951). Prior to death there had been a history of rash, pyrexia, and swelling of the face. It was not stated whether penicillin had been given before.

Chou and Welply (1949) reported a case in which death occurred two hours after the injection of 40,000 units of penicillin intrathecally as a prophylactic measure.

A case of sudden death following an injection of 300,000 units of crystalline penicillin is now reported.

Case Report

A man aged 67 entered hospital to have a bougie passed under an "umbrella" of penicillin and in conditions of rest. He gave a history of having contracted gonorrhoea in 1910, and of having attended a clinic for venereal diseases from 1930 in order to have bougies passed for a urethral stricture. With the exception of a short period in hospital with cystitis in 1940, bougies were passed at the clinic on an average of once a month until the date of his present admission.

On November 17, 1950, penicillin was given for the first time at the clinic. He received 300,000 units intramuscularly after the passage of a bougie. The type of penicillin was not stated on the clinic record, but it is presumed to have been crystalline penicillin G. This dose was repeated monthly during his routine visit to the clinic until May 4, 1951, when it was recorded for the first time that he received 300,000 units of procaine penicillin. Procaine penicillin was then given monthly until July 20. On August 24 bougies were passed and 300,000 units of procaine penicillin ordered. Immediately after receiving the penicillin intramuscularly the patient collapsed. He became unconscious and cyanotic, and was covered with a fine perspiration. There was a spastic contracture of one arm with deviation of the eyes. Within a short time he recovered consciousness sufficiently to answer questions.

On admission to hospital he was pale and had coarse rigors; he was conscious and had neither contractures nor paralysis. His pulse was rapid but of good volume. He was treated for shock and was discharged as well four days later.

There was no history of a similar occurrence following his previous injections of penicillin, nor was there a history of pruritus or urticaria. He had never complained of asthma, hay-fever, or other allergic condition, and there was no history of a hypersensitivity episode in the past. His Wassermann reaction was negative. He had attended his family doctor with myocarditis for several years, but there was no cardiac decompensation and he was a good worker. He was a heavy drinker, and it was learned that before attending the clinic he had had a hearty meal and had consumed a quantity of beer and spirits.

On September 28 he attended the clinic, where it was decided that a bougie would have to be passed. In the interval, while he had not been feeling in the best of health, he had had no localizing signs or symptoms and had had no skin eruptions. It was decided to admit him to hospital overnight so that he could be observed and the bougies passed the next morning. At this point, with the recent paper of Batchelor *et al.* (1951) in mind, it was thought that the procaine portion of the procaine penicillin had played a part in his recent episode and 300,000 units of crystalline penicillin G was ordered instead.

On the morning of October 5, after a quiet night without sedation and after a moderate breakfast, the patient was examined. He was slightly nervous, but, apart from occasional extrasystoles, the examination was essentially negative. His blood pressure was not taken, but his family doctor states that a recent reading was approximately 185/90 mm. Hg.

Ten minutes after the examination the patient received 300,000 units of crystalline penicillin G dissolved in 3 ml. of sterile saline intramuscularly while resting in bed. This was half of a total preparation of 600,000 units of penicillin dissolved in 6 ml. of sterile saline, the other half having been given to another patient immediately beforehand without subsequent ill effect.

Within a few minutes of the injection the patient began to feel nauseated and started to retch, producing a little vomitus. He became increasingly cyanotic, with shallow gasping respirations, and entered into a state of collapse. It was observed that his lips and tongue were swelling. At this stage his pulse could not be felt nor could his apex beat be heard. Adrenaline and nikethamide were administered without effect.

The cyanosis became intense, his tongue protruded, and there was slight frothing at the mouth. His breathing became progressively more shallow and infrequent, and death followed within a few minutes.

From the time of injection until death ensued not more than 10 to 15 minutes had elapsed.

Post-mortem Report

The relevant post-mortem findings were as follows.

Cardiovascular System.—A few small petechial haemorrhages were seen underneath the visceral pericardium. There was hypertrophy of the right ventricle, and two areas of myocardial fibrosis (2 and 1 cm. in diameter) were seen on the posterior surface of the heart. The coronary arteries showed intimal plaques of atheroma with narrowing of the left descending branch. There was no evidence of recent thrombosis.

Respiratory System.—Several small petechial haemorrhages were seen beneath the posterior visceral pleurae. There was evidence of chronic bronchitis and marginal emphysema. There was a basal congestion of the lungs.

Uro-genital System.—The bladder was hypertrophied, there was a granular cystitis, and a stricture was noted in the membranous urethra.

Central Nervous System.—There was a moderate degree of atheroma, with calcification of the circle of Willis and the basilar artery. A softening of the left cerebellar hemisphere (4 by 3 cm.) was seen.

Discussion

From the post-mortem appearances it is evident that the patient was a "poor risk" for any procedure, and it may well be that the shock of injection was enough to induce coronary spasm and an acute congestive cardiac failure. (The lesion in the cerebellum was proved histologically to be not of immediate origin.)

Clinically, however, the impression was that the phenomenon was anaphylactic in nature. In favour of this theory are the history and the character of his first collapse, the swelling of lips and tongue during his terminal episode, and the fact that the injection, not a new experience, was given under conditions of rest.

It is not sufficiently realized that serious and even fatal reactions may occur with penicillin therapy. Penicillin is still one of our chief weapons in the fight against disease, and it is prescribed daily, often indiscriminately, to large and ever-increasing numbers of the populace. Each year the number of people who have had previous penicillin therapy increases.

It is urgent, therefore, that the question of sensitivity be borne in mind before penicillin is prescribed. The increasing number of antibiotics becoming available for prescription makes the necessity for awareness of this phenomenon even more acute.

A past history of pruritus, urticaria, arthralgia, swelling of any part of the face, or rigors after an injection of penicillin should put one on guard. The delay between injection and reaction is often of some days and the connexion may be missed or misinterpreted. Previous injection of penicillin without ill effect is no assurance that sensitivity has not developed.

When in doubt intradermal skin tests should be carried out, patch tests to the skin being, according to the work of Wilkinson and Zinnemann (1947), not sufficient.

Summary

A case of sudden death following the injection of 300,000 units of crystalline penicillin is reported.

Some of the literature is reviewed.

Attention is drawn to the need to inquire carefully for signs of previous allergy before penicillin is prescribed.

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REFERENCES

Barksdale, E. E. (1946). *J. Amer. med. Ass.*, **132**, 919.
Batchelor, R. C. L., *et al.* (1951). *Lancet*, **2**, 195.
Berne, R. M. (1950). *New Engl. J. Med.*, **242**, 814.
British Medical Journal, 1951, **1**, 1269.
Burleson, R. J. (1950). *J. Amer. med. Ass.*, **142**, 562.
Chou, T. T. S., and Welply, W. R. (1949). *Chin. med. J.*, **67**, 438.
Keefer, C. S., and Anderson, D. G. (1950). *Penicillin and Streptomycin in the Treatment of Infections*. Oxford.
O'Donovan, W. J., and Klorfajn, I. (1946). *Lancet*, **2**, 444.
Panja, D., and Banerjee, A. K. (1951). *Indian med. Gaz.*, **86**, 13.
Rabinovitch, J., and Snitkoff, M. C. (1948). *J. Amer. med. Ass.*, **138**, 496.
Waldbott, G. L. (1949). Ibid., **139**, 526.
Wilensky, A. O. (1946). Ibid., **131**, 1384.
Wilkinson, A. G., and Zinnemann, K. (1947). *British Medical Journal*, **2**, 865.

COMPARISON OF VASOACTIVE DRUGS IN MAN

BY

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The assessment of vasopressor drugs is commonly carried out in experimental animals under controlled conditions. Clinical trials follow, and if these are satisfactory the drug under investigation is added to the list of those already in use, and its properties are defined in terms of the results obtained by animal and human experiment. But, while the experiments in animals are fully controlled, those in the human involve many variables, and results in the latter tend to be coloured by findings in the former, regardless of the possibility of species differences.

In human trials it is desirable, therefore, to eliminate as many variables as possible, and at some stage in the investigation to try to reproduce the clinical conditions under which the drugs are most likely to find their greatest therapeutic application. Since individuals differ widely in their response to pressor drugs, this will involve comparing both of the drugs under trial in the same subject, unless very large numbers are concerned, as in a study by Dripps and Deming (1946) in which 2,500 patients were used to compare the effects of four drugs.

Under normal conditions homoeostatic vascular reflexes are at work which diminish the effects of injected pressor drugs, making it necessary to use relatively large doses in order to obtain a small response (Moe, 1948). Taylor and Page (1951) have shown that powerful components of these compensatory reflexes arise from chemoreceptors in the brain and have their efferent pathway in the sympathetic outflow.

In the experimental animal, stable conditions are efficiently obtained by destructive procedures on the central nervous system which eliminate vasosensory reflexes. Crimson and Tainter (1939) compared the effects of several pressor drugs in cats, in the normal state and in decerebrate shock, and found greatly augmented pressor responses after destruction of the central vasomotor mechanisms. Page and Taylor (1950) showed that a similar augmentation of vasoactive substances occurred after ganglionic blockade with tetraethylammonium chloride (T.E.A.C.), an effect which was intensified when elimination of T.E.A.C. was prevented by preliminary nephrectomy. The same authors found that preganglionic denervation between the sixth cervical and sixth thoracic segments produced the greatest pressor augmentation by local neural destruction.

In man temporary chemical interference with the compensatory vasomotor mechanisms can be obtained either by blocking the sympathetic outflow at the ganglion synapses, with drugs of the methonium group, or by the application of local analgesic to the appropriate sympathetic nerves. The methonium drugs are simple to administer but variable and evanescent in their effects, and are therefore unsuitable for providing a constant base-line of vascular hypotension against which the pressor effects of the test drugs can be measured. Of the nerve-blocking techniques available, subarachnoid and extradural spinal block are the most practical for routine use. Subarachnoid spinal block has a higher morbidity rate and a shorter duration of action than extradural block when administered by the single-dose method, and so the latter was preferred as providing the desired experimental conditions.

In this study conditions provided by depressed vasosensory reflexes have been illustrated by a comparison of the pressor effects of the two optical isomers of methyl amphetamine. The dextrorotatory (D-) form of methyl amphetamine is known as "methedrine" in English-speaking countries and as "pervitin" in Germany, and it is used extensively as a vascular and cerebral stimulant. The laevorotatory (L-) isomer is inferior to the D-isomer as a cerebral stimulant in animals and man (Hauschild, 1938), but little work has been done on the vasopressor properties of the L-isomer in man.

Method

Measurements were carried out on patients during routine surgical operations in which some degree of controlled vascular hypotension was thought desirable. No departure was made from the anaesthetic technique which would have been chosen irrespective of the investigation, and there was no question of treatment becoming subordinate to experiment.

High lumbar extradural spinal block was employed as part of the anaesthetic technique for 15 patients undergoing major abdominal or lower-limb surgery. A solution containing 1:600 "percaine" and 1.6% procaine was used, and injection made in any convenient space between the spines of the twelfth thoracic and third lumbar vertebrae. Dosage varied between 25 ml. and 45 ml., according to the height and age of the patient. Analgesia was carried to the upper thoracic segments so that the greater part of the sympathetic outflow was blocked, and the blood pressure fell to the region of 60 mm. Hg for a period of up to four hours (Bromage, 1951, 1952a). Alterations of blood volume were minimal, the total operative blood loss, estimated gravimetrically by weighing swabs, never exceeding 250 ml. in any one case. General anaesthesia was maintained with intermittent injections of thiopentone and inhalation of a mixture of one part oxygen and two parts nitrous oxide from a semi-open machine.

The limited time factor of a routine surgical operation made it impracticable to compare two pressor drugs of doubtful tolerance potentialities with a third drug, such as adrenaline, which is known to produce no tolerance effects on repeated injection (Chen, 1928). But errors due to tachyphylaxis were minimized by using small quantities