Case 2

A housewife and schoolteacher aged 25 was referred to hospital in July, 1952, with an indefinite history of lassitude and tightness in the chest of seven months' duration. She was unwell during this time, but it was only after taking alcohol that she really felt ill with pain in the chest and back. At first she did not connect the pain with alcohol, but during May and June the symptoms became so acute each time she took an alcoholic drink that she gave up drinking alcohol altogether.

On examination she appeared to be in good general health. She was dyspnoeic on exertion and the left upper zone was dull on percussion. There was an enlarged gland in the left supraclavicular fossa. Biopsy of the gland showed Hodgkin's disease. X-ray examination of the chest revealed a diffuse opacity filling the whole of the left upper zone and enlarged glands projecting laterally to the right from the upper mediastinum. A course of x-ray therapy to the mediastinum and left upper zone in July and August, 1952, was followed by excellent regression of all masses.

FIG. 2.—Case 2.

The patient took the first glass of sherry within one week of completion of treatment with no ill effects. For almost two months she was able to take alcohol with impunity. Then suddenly, in October, after a drink, she experienced acute pain in the region of the left buttock, and, after having a similarly painful experience on two more occasions, again gave up drinking alcohol. An x-ray film of the left ischium on November 17 showed the presence of an oval translucent area consistent with appearances of a lymphadenomatous deposit (Fig. 2). A course of x-ray therapy to the left ischium was given, and, as before, the patient was able to take alcoholic drinks without any ill effects within a week of completion of the treatment.

Discussion

In both cases alcohol produced localizing signs pinpointing, as it were, the site of active lymphadenomatous deposits in advance of clear-cut radiographic changes. Successful treatment, in both cases, was associated with instantaneous disappearance of symptoms which once more preceded the return to normal of radiographic appearances. Such individual hypersensitivity to alcohol, which seems to be confined to sufferers from Hodgkin's disease, is therefore of considerable clinical value as it may serve to betray the presence of active lymphadenoma at a time when the disease gives rise to few signs and so make possible early diagnosis and institution of appropriate treatment before symptoms become severe and unmistakable. The result of treatment in turn may be assessed by means of an alcoholic "test drink," a novel and probably not unwelcome form of investigation to the patient. It may prove useful to include such "diagnostic drinks" among the routine investigations carried out when following up cases of this type and to instruct the patients to report immediately should at any time intake of alcohol be followed by severe pain. What

produces the pain in Hodgkin's disease, and whether it is due to localized oedema as suggested by Hoster (1950), is an intriguing question. So far there is nothing to suggest that alcohol has a deleterious effect on the course of Hodgkin's disease.

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FATAL ANAPHYLACTIC SHOCK DUE TO PENICILLIN

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Allergic manifestations in reaction to various drugs have long been recognized and present a special problem to every physician. Recently antibiotics, and especially penicillin, have been added to the long list of these drugs, and penicillin, because of its wide application, plays a prominent part. The symptoms of sensitivity to penicillin are varied. Most frequent is an urticarial rash, but other skin lesions have been described. Sometimes a syndrome resembling serum sickness with urticaria, fever, oedema of mucous membranes, arthralgia, and lymphadenopathy appears (Wilensky, 1946; Humphreys, 1951; Wilkes, 1951). All these symptoms respond well to antihistamine drugs or adrenaline.

More serious reactions to procaine penicillin have been described by Batchelor *et al.* (1951) in patients undergoing treatment for the later stages of syphilis. The reaction developed immediately after intramuscular injection of 600,000–1,000,000 units of penicillin (five different preparations were involved), the patient experiencing a sensation of impending death (angor animi) and a feeling of prostration for several hours afterwards. There was no circulatory disturbance (pulse and blood pressure normal), respiratory embarrassment, or pain. They stress these facts in order to differentiate this reaction from a similar syndrome with a disturbance of circulation and angor animi associated with severe anaphylactoid reaction. On the other hand, several cases of non-fatal anaphylactic reactions after penicillin have been reported (O'Donovan and Klorfajn, 1946; Burleson, 1950; Mayer *et al.*, 1953), but few cases of sudden death following penicillin and attributed to hypersensitivity have been published.

The first fatal case recorded in Great Britain occurred in a 14-months-old healthy child who had been treated for burns and who died, five days after the penicillin treatment was begun, of cardiac tamponade due to serous effusion into the pericardium. There was also serous effusion into the pleural cavities. During the five days before death swelling of the face, pyrexia, and a diffuse skin rash occurred. The coroner recorded the cause of death as cardiac tamponade due to hypersensitivity to penicillin (*British Medical Journal*, 1951).

The second case published in Britain (Thomson, 1952) was that of a man aged 67 who had bougies passed under an "umbrella" of penicillin. He had had an alarming reaction one month previously after a course of penicillin injections, and he died ten to fifteen minutes after a later injection of penicillin, with symptoms described by the author as anaphylactic in nature.

In the United States, of the few reported cases of deaths due to penicillin hypersensitivity, Waldbott's (1949) case is of particular interest because of several features in common with the case reported below. The patient, a woman aged 39 who suffered from bronchial asthma and had had penicillin before, died almost immediately after receiving an intramuscular injection of penicillin during an acute attack of asthma. The symptoms preceding the fatal collapse were tightness in the nose and throat, swelling of the mouth, generalized itching, severe dyspnoea, and cyanosis. More recently another fatal case of anaphylactic shock has been published by Mayer *et al.* (1953). A man who had had repeated penicillin treatment for syphilis had a fainting turn after penicillin had been given three months before receiving the fatal dose. He complained of a peculiar pain in his chest immediately after the injection, and in a few minutes became comatose and died.

Case Report

A married woman aged 31 had suffered from bronchial asthma for two and a half years. A feature of the case was frequent association between respiratory infections and asthmatic attacks. In January, 1952, she was treated with penethamate ("estopen"; benzylpenicillin diethylamino-ethyl ester hydriodide), 500,000 units daily, for four days and adrenaline hydrochloride as necessary. She had no unusual symptoms. During August she had a course of peptone injections. In the second week of December she developed another respiratory infection and again an attack of asthma. On December 11 she had 8 minims (0.5 ml.) of 1/1,000 solution of adrenaline hydrochloride with immediate relief from her asthma. Immediately following this 500,000 units of penethamate was given by intramuscular injection. Almost immediately she complained of a little headache and a feeling of faintness. Both these symptoms passed in a few minutes. The following day 500,000 units of penethamate and 0.75 ml. of hyperduric adrenaline were given. Five minutes later she complained of precordial pain, which lasted only several seconds. She appeared quite normal and conversed normally for a further five minutes, when she suddenly collapsed and lost consciousness. Respirations became gasping and infrequent, the pulse was rapid, but there was neither spasm nor convulsion. The intervals between respirations became longer, and she died after a few minutes.

Necropsy.—The pupils were dilated and the lips cyanosed. The brain showed no abnormality. The lungs were pale and inflated, and there were a few petechial haemorrhages beneath the posterior visceral pleura. The bronchi were dilated, and the bronchial mucosae thickened and congested and covered with mucus. Both chambers of the heart were contracted and empty. There were no other gross pathological changes. The cause of death accepted by the coroner was anaphylactic shock caused by penicillin in a case of bronchial asthma.

Discussion

As early as 1919 Cooke emphasized that hypersensitivity to drugs is an allergic reaction. Among 15 cases he found 3 with obvious manifestations of allergy, and there was a family history of allergy in the other 12. Waldbott's case was that of an asthmatic who after previous administration of penicillin developed urticaria, some aggravation of the asthma, joint pain, and fever. He had had experience of other cases of severe asthma occurring after initiation

of the second or third course of penicillin. In Thomson's case there was a history of an alarming reaction to penicillin one month before the fatal dose.

All six cases reported by Mayer *et al.* received previous penicillin therapy and five gave a history of previous hypersensitivity to penicillin. Five of the patients, including one with a definite history of allergic manifestations, recovered from the anaphylactic shock and one died with symptoms almost identical with those of our case. That procaine cannot be blamed for these reactions was evident from the intradermal tests, which were positive to penicillin and negative to procaine in all cases in which they were done. Furthermore, the demonstration of passive transfer of circulating reagins to penicillin was successful in four out of five cases studied by Mayer *et al.*

There seems to be no doubt that any kind of penicillin can produce allergic reactions, and death has been reported after both crystalline and procaine penicillin. There is no predictable pattern in penicillin hypersensitivity reactions—several courses of penicillin may be symptomless before and even after severe allergic reactions. Nevertheless we should like to emphasize again the importance of careful inquiry for signs of previous allergic phenomena before penicillin is repeatedly administered to any patient, and special caution when dealing with allergic patients. In the presence of a history of allergy, skin-testing is indicated, and, if positive, further administration of penicillin should be avoided.

O'Donovan and Klorfajn succeeded in desensitizing their patient, but other authors doubt the possibility of successful desensitization. Burleson feels that diphenhydramine ("benadryl") hydrochloride (30 to 40 mg.) when given intravenously to his patient was a select and life-saving drug. Humphreys's patient was given adrenaline without any effect, but subcutaneous injection of mepyramine maleate ("anthisan"), 0.05 g., produced great relief.

In our case the simultaneous administration of adrenaline with the first injection of penicillin might have prevented severe reaction, and the fact that slow-acting hyperduric adrenaline was given with the second dose might have allowed the fatal reaction to take place.

Waldbott recommends intradermal testing in any allergic patient who had previous injections of penicillin in doses of 100 to 300 units and, if results are negative, in larger doses of 3,000 to 5,000 units intradermally 15 minutes later.

Summary

The trivial allergic reactions to penicillin are well known; the fact that fatal accidents occur is, however, not generally realized, and should certainly be emphasized in the light of the recent controversy on the abuse of antibiotics.

Death in anaphylactic shock due to penicillin hypersensitivity is described, and some of the relevant literature is reviewed and discussed.

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The St. John Ambulance Association has recently published a booklet of instruction for air attendants, and issued regulations for a St. John Air Attendants' Course. The syllabus includes instruction on the effects of altitude on the human body, the selection of patients for travel by air, preparation and equipment for the flight, routine care of patients in flight, tropical medicine and hygiene and inoculations and vaccinations, and emergency midwifery.