ACUTE IMMEDIATE REACTIONS TO PENICILLIN

BY

G. W. LEWIS, M.B., Ch.B.
General Practitioner, Leeds

Severe reactions, often fatal, occurring immediately after the administration of penicillin continue to be reported in this and other countries. The now extensive literature was reviewed by Calvert and Smith (1955). Cases have since been reported by Winton and Nora (1955), Dubberley (1955), Wright (1955), Bhattacharya (1955), Tidswell (1955), and Bell (1956).

Many of the reactions described are typically anaphylactic in type. In others vasomotor collapse may not be a prominent feature and bronchiolar spasm and angio-neurotic oedema do not occur, the main reaction being one of acute emotional upset. This type of reaction occurs usually within seconds of an injection of procaine penicillin, often after several injections of a course have been given without ill effect, and in a number of instances further injections of the same material have been given without incident. Batchelor *et al.* (1951) believed this type of reaction to be due to accidental intravascular injection of emboli consisting of agglomerations of crystals.

Angor animi and cacogeusia have been described as features of both this and the anaphylactic type of reaction.

Penethamate hydriodide ("neo-penil," "estopen") has earned a particularly bad reputation for producing severe and dangerous reactions, possibly on account of an inherent toxicity of this compound rather than on account of its penicillin content (Welch *et al.*, 1953).

The reaction potentiality of the very slowly absorbed repository penicillins is uncertain, but Anderson (1954) described a severe and protracted reaction following a single injection of benzathine penicillin.

The following comments were made in the *British Medical Journal* (1955b): "The frequency of accidental intravenous injection as a factor is still uncertain and calls for closer investigation. . . . More exact information is needed on the relative degrees of danger associated with soluble and procaine penicillin, and on whether sensitivity to procaine itself is a factor."

Since nearly all injections of penicillin given in hospital are administered by the nursing staff it was thought that more intimate information on these problems might be obtained from general practitioners, as they have to administer most of their injections themselves. Therefore the College of General Practitioners made an appeal to all members to supply information on any acute immediate reactions to penicillin seen by them. In order to define "immediate reaction" the arbitrary figure of one occurring within 15 minutes of the injection was adopted. The case reports which follow were obtained in this way. Cases 3 and 4 (Lewis, 1953, 1954) and Case 2 (Singh, 1955) have been described elsewhere. The cases have been divided into three groups.

Group 1

Case 1

A middle-aged medical practitioner described his own experience. There was no personal or family history of allergy. After an appendicectomy in 1949 he had a chest infection for which he was given twice-daily injections of

500,000 units of crystalline penicillin. On the third day he developed pyrexia and irritation of toes and groins in the same distribution as he had had a fungus infection whilst serving in the Western Desert. On ceasing the penicillin treatment his temperature fell to normal and the irritation subsided. In 1951 he had an acute sinusitis which was treated with daily injections of 300,000 units of procaine penicillin for four days without any ill-effect.

In September, 1954, he developed a very painful boil inside his nostril. A colleague gave him an injection of 1,000,000 units of crystalline penicillin followed immediately by 900,000 units of procaine penicillin in aqueous suspension. His experiences are best told in his own words "About 15 minutes after the injection I felt nauseated and shortly afterwards became very red in the face. This was followed by swelling of the upper lip, and I felt so ill that I decided to drive to the local hospital. During the drive I had a feeling of constriction in the chest and a conviction of impending doom. I could feel that my heart rate was greatly accelerated and irregular. Having reached the hospital, I staggered in, dimly remember being led to a side-ward, and then lost consciousness. I vaguely remember being looked at by a sister several times and by one of my colleagues, but regained full consciousness only after two hours, feeling very weak, itching as though I had a thousand fleas, and with a stiff, swollen upper lip. I was told that my pulse had been very fast, thready, and irregular. I was given promethazine hydrochloride ("phenergan") and spent the rest of the day in bed in a sleepy state, possibly due to the promethazine hydrochloride. The next day, though feeling weak and a little itchy, I was able to carry on with my work. One week later, whilst on holiday, the severe itching returned, with large urticarial weals all over my body."

Case 2

A medical practitioner aged 53 had received many previous injections of penicillin. On the last occasion, following an injection of procaine penicillin, he developed slight and transient swelling of the face. In January, 1955, having decided to give himself a further course of penicillin, he took two tablets of mepyramine maleate about five minutes before an injection of procaine penicillin in aqueous suspension which he administered to himself. Immediately after the injection he developed dryness of the throat and redness of the eyes, followed by a choking sensation, loss of sphincter control, and unconsciousness. He was given 0.5 ml. of a solution of adrenaline, 1 in 1,000, by an attendant.

When seen a few minutes later he was unconscious, incontinent, and sweating profusely. His breathing was laboured and stertorous and his pulse was impalpable. As he had already been given adrenaline, nikethamide was injected. After about two minutes he regained consciousness and complained of a burning sensation in the epigastrium and severe buzzing in the ears. He was given 30 min. (1.8 ml.) of aromatic spirit of ammonia but again lapsed into unconsciousness, with an impalpable pulse, profuse sweating, and dyspnoea with laryngeal stridor. A further injection of nikethamide and 1 ml. of adrenoephedrine was given. He regained consciousness in about two minutes, again complained of a burning sensation in the epigastrium, and was shivering violently. The shivering continued for half an hour. When seen one hour later he had slight swelling of the upper lip, slight puffiness of the face, and complained that his whole body was aching. Next morning he seemed in perfect health, but 24 hours later he again developed aching of the whole body, which persisted for quite a long time.

Group 2

Case 3

A woman aged 34, with no personal or family history of allergy, had received courses of penicillin three and a half years and one year previously without incident. In September, 1953, she had acute otitis media, and 1,000,000 units

of crystalline penicillin was injected into the buttock. One minute later she suddenly lost consciousness. Her pulse was rapid, feeble, and irregular, but there was no evidence of cyanosis or respiratory embarrassment. She recovered consciousness in half a minute and repeatedly stated that she was dying. During the next 15 minutes her pulse became stronger and slower but was still irregular and she continued to feel very weak and ill. She then quite suddenly developed a severe colic, felt deep in the pelvis, with exacerbations and remissions each lasting about 10 seconds. These pains were described as "like labour pains, not a bellyache." This colic remained severe for half an hour, then ceased suddenly, and a few minutes later she seemed to be normal and had a strong regular pulse. An adrenaline injection was prepared but was not used. Twenty-four hours after the attack she began to menstruate, 10 days before her period was due. She had never previously had the slightest menstrual irregularity and had never suffered from dysmenorrhoea. Fifteen days later an intracutaneous injection of 4,000 units of crystalline penicillin produced neither an immediate nor a late reaction.

Case 4

A robust man aged 38 with no personal or family history of allergy had received a seven-day course of penicillin injections 20 months previously. A few days after the termination of this course he developed a rash which cleared quickly. In October, 1954, he developed a large carbuncle in his back with considerable surrounding cellulitis. Streptomycin was injected for two days with no improvement, so treatment was changed to daily injections of 900,000 units of procaine penicillin in aqueous suspension. After four days of this treatment without incident the cellulitis had resolved and the core was separating. For the next three days he received only local treatment, but the local condition deteriorated and daily injection of 900,000 units of procaine penicillin was resumed.

Four hours after the second injection of the resumed course he felt faint for a minute or two. Next day he received a similar injection into the buttock. Within seconds he lapsed into semi-consciousness with a rapid, irregular pulse and a conviction of impending doom. There was no cyanosis, respiratory embarrassment, or overfilling of neck veins. He was able to answer simple direct questions throughout. After about one minute he complained of severe throbbing in his back, indicating the tip of his fourth lumbar spine as the exact spot, and of paralysis from that level downwards. He could not feel the chair beneath him but could raise both feet just clear of the ground with difficulty. His arms felt numb and heavy. His pulse was still irregular, rate 160 a minute. About three minutes from the onset of the attack his legs felt a bit better and the throbbing in his back had ceased, but he then developed crippling substernal pain and complained of "pounding of the heart." His pulse was still irregular, rate 140. About six minutes from the onset of the attack he felt much better; the palpitation had ceased and sensation had returned to his body and legs. He had a feeling of coldness from the waist downwards and of tingling in the arms and fingers. These sensations passed quickly and 10 minutes later he seemed normal and cheerful. His pulse was regular, rate 80. He was given a card to place in his wallet stating that he had suffered a severe reaction to penicillin.

Case 5

A man aged 50 had had one injection of penicillin, probably crystalline, four years previously without incident. He was given an intramuscular injection of 500,000 units of crystalline penicillin for an acute bronchitis of three days' duration. Within two minutes of the injection he collapsed. His pulse was weak, rapid, and irregular, and the skin pale and cold. Within a further two minutes he showed signs of reviving, and the injections of adrenaline and nikethamide which had been prepared were not given. When able to

speak he said he felt very weak and was sure he was dying. He experienced a vague pain in the right leg as he was reviving. The chest infection was short-lived, but his recovery from the effects of the reaction was protracted. One month after the attack he still felt so weak that he was unable to walk more than about 50 yards (45 m.). Three months later he was in excellent health.

Case 6

A man aged 60 who had no personal or family history of allergy and who had never previously had penicillin by mouth or by injection was given a course of penicillin injections for a carbuncle. The course consisted of daily injections of 600,000 units of procaine penicillin in aqueous suspension. Five injections were given without incident. About half a minute after his sixth injection he turned pale and said he felt sick and queer, and that he was about to die. His breathing became rapid and shallow and his pulse impalpable. He next complained of a severe throbbing headache and then lost consciousness. He remained unconscious for about two minutes. As he was recovering he complained of severe substernal pain, but after lying recumbent for a while this eased off and in 15 minutes he had recovered sufficiently to go home. On examining the syringe used for the injection it was noted that the dregs were slightly blood-stained.

The practitioner recording this case reports that over a period of five years he has discarded a syringe of procaine penicillin on three occasions because traction on the plunger had withdrawn blood.

Case 7

A married woman aged 35 was given daily intramuscular injections of 600,000 units of procaine penicillin in aqueous suspension for chronic sinus infection and bronchitis. So far as could be ascertained she had not previously had penicillin by injection but had applied penicillin cream for an infected dermatitis four years previously. The injections were given by the district nurse, the first four without incident. Immediately after the fifth injection the patient collapsed, with greyish pallor and feeble pulse. When seen about half an hour later she had recovered considerably but was still very frightened. Following the attack her personality changed; previously jolly and active, she became depressed and anxious. Her menses were diminished and she suffered from hot flushes. She was now sensitive to all forms of penicillin and also to chloramphenicol and sulphonamides. She had improved somewhat one year later, when she left the district, but was still far from being her old self.

Case 8

A woman aged 54 was a chronic invalid with a history of rheumatoid arthritis, paroxysmal tachycardia, asthma, bronchiectasis, and emotional instability. She is believed to have had injections of penicillin on previous occasions. In October, 1955, it was decided to give her a course consisting of 500,000 units of penethamate hydriodide plus 1 g. of streptomycin sulphate daily on account of an acute flare-up of her bronchiectasis. When both preparations had been mixed in one syringe, the syringe used was filled to capacity, rendering it impossible to withdraw the plunger before injection, and the full injection was given into the buttock. This was followed immediately by exclamations of fear and by dizziness, confusion with partial loss of consciousness, and a complaint of pain up the back of the neck. There was no evidence of collapse, and recovery was complete within about 15 minutes without treatment. Intradermal injections of penethamate hydriodide and of streptomycin sulphate a few days later produced no reaction and she was subsequently given five daily injections of 600,000 units of procaine penicillin in aqueous suspension without ill effect.

The practitioner recording this case believes that the reaction was due to accidental intravascular injection of some of the material.

Group 3**Case 9**

A guardsman aged 21 who had had a boil on one of his fingers for several days was prescribed a course of penicillin injections. There was no personal or family history of allergy. Three years previously he had been given a course of penicillin injections with no ill-effect. An injection of 600,000 units of procaine penicillin in aqueous suspension was given by an experienced orderly. Within seconds he complained of feeling queer and collapsed. When seen, almost immediately, he was shocked, with cold sweating hands, impalpable radial pulse, regular apex beat of 120, dyspnoea with rapid deep breaths, and bouts of intense shivering; he complained of "pins-and-needles" in, and inability to move, his lower limbs. There was no withdrawal of the feet or movement of the great toes on plantar stimulation. He was restless and very anxious. He remained conscious throughout. Within a few minutes he was given 1 ml. of 1 in 1,000 adrenaline solution. After about 30 seconds his dyspnoea ceased and he began to feel better, but one minute later all his symptoms reappeared in full. A further 1 ml. of the adrenaline solution was given and again he improved, this time permanently. The whole episode lasted about five minutes. Later that day he felt quite well.

The practitioner who treated this case mentions that he has since given penicillin injections himself whenever possible and has been surprised to find how easily blood is aspirated into the syringe occasionally.

Case 10

A healthy woman aged 55 gave no history of allergy. She had received several previous courses of penicillin injections without incident. In August, 1955, on account of an abscess, a course of injections of procaine penicillin in aqueous suspension was given, the dose being one injection of 600,000 units daily. The first three injections were given without incident. During the fourth the plunger was withdrawn and about a quarter of the dose injected before it was realized that a trace of blood had entered the syringe. The needle was withdrawn a little before completing the injection. Within a few seconds she felt dizzy and became confused and obviously frightened, calling for her husband and child in anguish and complaining of failing vision. The pulse and colour remained good and none of the classical signs of shock were present. Five minims (0.3 ml.) of adrenaline solution 1 in 1,000 was injected and in about 10 minutes she had recovered completely. Ten days later an intradermal injection of procaine penicillin produced a slight red flare.

Case 11

A man aged 56 gave no personal or family history of allergy and had not had penicillin previously in any form. He had an excision of caecum and ascending colon performed in February, 1956, on account of chronic infection with an abscess cavity extending into the substance of the iliacus as far as the periosteum. For six days before and six days after operation 900,000 units of procaine penicillin in aqueous suspension was injected daily without incident. Six days after the last injection he developed a pyrexia, and it was decided to give him a further course of procaine penicillin. Immediately after the first injection of 900,000 units, given into the left buttock, he complained of severe stabbing pain across the buttocks and extending up the back of the spine to the occiput, and that his head felt "muffled and numb." He had a feeling of impending death, but this passed quickly. There was no clouding of consciousness or any evidence of circulatory collapse. He recovered his composure within about half a minute and felt much better, but his left arm and leg seemed "numb and bloodless." This passed quickly, and within 15 minutes he felt normal. The attack was attributed to accidental intravascular injection. Four further daily injections of 900,000 units of procaine penicillin were given without incident. Three months after the attack his head still felt a bit numb and his legs were still weak.

Case 12

A middle-aged woman who had suffered from bilateral bronchiectasis for many years had received numerous courses of penicillin injections during acute exacerbations. The earlier courses consisted of various preparations of soluble penicillin, but for the past eight years a course had consisted of five daily injections of 900,000 units of procaine penicillin in aqueous suspension. In October, 1953, immediately after the last of five daily injections, she became unconscious, with stertorous breathing and Jacksonian movements of the left side of the body. Both pupils were widely dilated and her pulse was weak, rapid, and irregular. She recovered consciousness after about five minutes and had a premonition of death; the pulse became more irregular and she lapsed into unconsciousness again. The pulse slowly became more regular, and in a further 20 minutes she had recovered sufficiently to be taken home by car.

Discussion

There seems little doubt that many of the acute reactions described in the literature after the administration of penicillin have been anaphylactic. This is suggested by the following facts: crystalline penicillin has been given intravenously in very large doses without incident (Janowitz *et al.*, 1948; Whipple, 1951); there is usually a history of previous penicillin therapy and often of a mild reaction following one of the preceding doses; some but by no means all patients can be shown, by means of cutaneous and intradermal tests, to be sensitized following the reaction; the clinical picture of an acute reaction bears a close resemblance to those following anaphylactic reactions to foreign sera and proteins; and the pathological findings in fatal cases of acute reactions to penicillin (Harpman, 1952; Curphey, 1953; Rosenthal, 1954) are essentially similar to those resulting from serum and foreign protein anaphylaxis (Vance and Strassmann, 1942). Most of the fatalities with penicillin have been attributed to profound circulatory failure or to asphyxia due to intense bronchospasm.

The sensitizing agent usually incriminated is injected crystalline or procaine penicillin; but sensitization, and even severe reactions, may occur after oral administration or topical application. Severe reactions have been reported after the use of penicillin tablets (Welch *et al.*, 1953; Bell, 1956), lozenges (Mayer *et al.*, 1953; Calvert and Smith, 1955), "aerosol" (Leibowitz and Schwartz, 1950; Blanton and Blanton, 1953), ophthalmic ointment (Carter and Cope, 1954), and after instillation into the sinuses (Everett, 1951; Weiss, 1953) and application to a wound (Irwin *et al.*, 1951). It has been claimed that penicillin O is antigenically different from penicillin G (Volini *et al.*, 1950), but this has been disproved (Siegal, 1951; Feinberg *et al.*, 1953). The simultaneous administration of an antihistamine has been shown to be without significant protective value (Mathews *et al.*, 1955); and the danger of relying on the simultaneous administration of either adrenaline or cortisone in sensitized individuals is illustrated by the fatal cases of Pick and Patterson (1953) and Winton and Nora (1955).

Waldbott (1953) has suggested that a major factor in the production of anaphylaxis in man is accidental intravenous injection or introduction into a vein by back-seepage. From his experience with foreign proteins he emphasized that, except in highly sensitized individuals, intravenous injection produces a much more rapid and profound anaphylactic reaction than does local injection. Rosenthal (1954) failed to find any evidence of penetration of a vein by the needle in the course of necropsy on six cases of acute reaction to penicillin, but in a case before the Westminster coroner (*British Medical Journal*, 1955a) in which a woman aged 72 died within five minutes of an injection of 500,000 units of crystalline penicillin, the pathologist reported that a vein in the arm showed evidence of having been transfixed by the needle. It is thus probable that both the type and the severity of the anaphylactic type of reaction to penicillin

may depend on whether any of the material has reached the blood stream directly as well as on the degree of sensitization of the patient.

Everything that has been said of crystalline penicillin applies equally to procaine penicillin, but in the case of the latter it is necessary to consider whether all or part of the reaction might not be due to the procaine moiety. Provided procaine is absorbed slowly, large doses can be given without producing central effects, but the toxicity of procaine is enormously increased if rapidly injected intravenously. Martin (1928) described acute toxic reactions to procaine as being of two types. One is characterized by clonic convulsions due to irritation of nerve centres, and may be followed by respiratory paralysis. The other is characterized by an abrupt fall in blood pressure, also probably due to central irritation, in which the patient becomes cold, clammy, and dazed. Buff (1950) described a syndrome due to procaine toxicity which is characterized by tachycardia, tremor, irregular respiration, blurring of vision, sweating, paraesthesiae, dilated pupils, and intense anxiety with an amini—a symptom-complex which is very reminiscent of some of the acute reactions described following injections of procaine penicillin. State and Wangenstein (1946) found that intravenous injection of procaine at a rate in excess of 8 mg. a minute caused flushing, dizziness, and generalized numbness.

Commercial preparations of procaine penicillin contain 32–40% by weight of procaine base (Batchelor *et al.*, 1951) and an injection of 600,000 units of procaine penicillin will contain about 240 mg. of procaine base (Goodman and Gilman, 1955). The accidental intravascular injection of all or part of this dose within a period of, say, half to one minute would be expected to produce an immediate reaction on the basis of the known toxic effects of procaine without there being any need to invoke the phenomena of sensitization, hypersensitivity, or idiosyncrasy. Such a toxic reaction might well resemble an anaphylactic reaction in many of its features. If, however, there were smooth-muscle spasm, or if the attack were accompanied or followed by urticaria or angioneurotic oedema, none of which is a manifestation of procaine toxicity, the reaction might be a mixed one, some of the symptoms being due to procaine toxicity and some to the intravascular injection of penicillin in a slightly sensitized individual.

In those instances of acute reaction to procaine penicillin in which subsequent injections of the same material have been given without incident, as in Case 11 of this series and in five of the eight cases reported by Batchelor *et al.* (1951), it is probable that the reaction was due to the procaine moiety gaining direct access to the blood stream, but the danger of assuming that any reaction following injection of procaine penicillin is due to its procaine content alone is borne out by the experience of Thomson (1952). His patient developed a severe immediate reaction after an injection of procaine penicillin. On the assumption that the reaction was due to procaine hypersensitivity this patient was given an injection of crystalline penicillin five weeks later and died in profound shock within 15 minutes.

It is believed that the diverse pattern of acute immediate reactions to injected preparations of penicillin is due in part to variation in the degree of sensitization of the patient, and in part to direct entry of injected material into the vascular system. In the present series there was direct evidence of intravascular injection in three instances. It is suggested that the reaction in the cases placed in group 1 was due to intramuscular injection of penicillin in sensitized individuals, in group 3 to rapid intravascular injection of procaine, and in group 2 to intravascular injection of penicillin in slightly sensitized individuals. Of the cases placed in group 2, the preparation used in Cases 3 and 5 was crystalline penicillin, whereas in Cases 4, 6, and 7 the preparation was procaine penicillin, and the reaction in these may have been due, in part, to the procaine moiety. In Case 8 the reaction followed an injection of penethamate hydriodide and may have been due to the known toxicity of this compound, since

subsequent injections of procaine penicillin were given without incident. Alternatively, the reaction may have been due to the streptomycin administered at the same time.

Precautions

The following precautions are suggested as a means of minimizing the incidence and severity of acute reactions to penicillin preparations.

1. *Reduction of Incidence of Sensitization.*—Topical application of penicillin in the form of cream, ointment, lozenges, chewing-gum, tulle gras, aerosol, etc., is of very doubtful value and probably should be abandoned. Oral and parenteral administration should be confined to cases in which there is a clear indication.

2. *Careful History-taking.*—Inquiry should be made concerning any personal or family history of allergy, and details obtained of any previous treatment with penicillin—parenteral, oral, or topical. An effort should be made to elicit any evidence of a reaction following previous administration of penicillin, a point being made of inquiring about any reaction experienced within 10 days, as late reactions might not have been interpreted as being due to the penicillin. Even a mild reaction such as irritation or a mild pyrexia is significant.

3. *Handling of the Suspicious Case.*—In the allergic individual, one who has experienced a mild reaction previously, and those who have received many previous courses of penicillin it may be wise to carry out dermal and intradermal tests where feasible, using solutions of crystalline penicillin. A positive reaction would indicate the need to exercise extreme caution; a negative reaction means absolutely nothing. In all suspicious cases the technique suggested by Waldbott (1953) of injecting a small amount of the preparation and then waiting 45 seconds with the needle *in situ* before giving the rest of the dose has much to recommend it. Alternatively, it may be possible to give a preliminary test dose by mouth as suggested by Schiller (1953), since any reactions to penicillin by this route are likely to be less acute than when it is given parenterally. The patient should be kept under observation for 20 minutes after the injection, and a solution of adrenaline should be at hand ready for immediate use. Several writers have suggested that the arm or leg should be used for the injection in preference to the buttock, so that a tourniquet can be applied immediately should a reaction occur.

4. *Spacing of Injections.*—The interval between individual injections of a course should never exceed 10 days, the time required for sensitization to become established.

5. *Technique of Injection.*—A wide-bore needle, not smaller than a No. 1 serum needle, should be used for both crystalline and procaine penicillin so that blood will be readily aspirated if the needle penetrates a vein. To the same end, the syringe should never be filled to capacity. After insertion of the needle, traction should be applied to the plunger and should be prolonged in the case of procaine penicillin, as it is difficult to recognize the entry of a small amount of blood and the blood takes time to reach the side of the syringe on account of the viscosity of the suspension. The patient should be recumbent or sitting on a chair in such a way that there will be little or no movement during the process of injection; and should the position of the needle change, even slightly, during the injection, this should be halted and traction again applied to the plunger to ensure that the needle is still outside a vein. The injection should be given slowly and without applying more than light pressure on the plunger. Not infrequently there is considerable resistance when beginning an injection of procaine penicillin, due to blockage of the needle by an agglomeration of crystals. In this event it is probable that the preceding traction on the plunger could not have produced blood even if the needle had been in a vein. The needle should be withdrawn, the block cleared by pressure on the plunger, and the needle reinserted. After completion of the injection, pressure should be applied to the injection site for a few seconds to prevent

oozing, but the injection area should not be massaged for fear of producing back-seepage of the injected material into a punctured vessel.

All nurses, and other personnel who may be required to give penicillin injections, should receive instruction on the minutiae of the injection technique.

6. Precaution Against Repetition.—All patients who have suffered an acute immediate reaction from the administration of penicillin should be given a card or disk indicating this fact, and this should be carried in the wallet or handbag.

Treatment

The fact that so many of the patients in this series recovered rapidly without treatment suggests that the claims made for this or that treatment may be unjustified, recovery occurring in spite of treatment rather than because of it. However, since it is impossible to forecast the train of events and there is a danger that severe bronchospasm may occur rapidly, it is best to regard every acute reaction as an anaphylactic one so far as immediate treatment is concerned. At the first sign of an acute reaction 0.5 ml. of a solution of adrenaline 1 in 1,000 should be injected intramuscularly. This should be repeated as required or injection of the solution continued at the rate of 0.1 ml. a minute until the attack shows signs of terminating. An intravenous anti-histamine such as diphenhydramine hydrochloride in a dose of 50–100 mg., or of promethazine hydrochloride in a dose of 25–50 mg., may also have some value, but they tend to produce a state of drowsiness lasting several hours. Positive-pressure oxygen should be administered where indicated and if available, and in cases where recovery is delayed intravenous hydrocortisone has been found to be valuable.

Those patients who experience weakness and malaise for a considerable time after the reaction, such as Cases 5, 7, and 11 in this series and one of the cases described by Bell (1956), may benefit from the administration of neostigmine, as did three of the patients described by Winston and Nora (1955). Acute reactions believed to be due to procaine toxicity in which there is evidence of gross central stimulation, such as generalized convulsions, might be expected to benefit from the administration of an intravenous barbiturate.

Summary

Twelve instances, from general practice, of acute immediate reactions following injection of preparations of penicillin are recorded.

The nature of these reactions and their possible modes of production are discussed. It is suggested that they may be produced in one of three ways: (1) intramuscular injection of penicillin in sensitized individuals; (2) accidental intravascular injection or back-seepage in sensitized individuals; or (3) accidental rapid intravascular injection of procaine penicillin suspensions.

A scheme for minimizing the incidence and severity of these reactions is outlined and suggestions are made for treatment.

I am indebted to Drs. C. A. Brockbank, S. D. Singh, A. C. Cattanach, A. A. Fullerton, A. R. Montgomery, J. Macdonald, A. Gilston, and L. S. Calvert for allowing me to quote their case reports, to the other practitioners who sent reports on penicillin reactions which did not quite fall within the arbitrary definition of immediate reactions, and to the College of General Practitioners and the *Practitioner* for publishing my request for case histories.

REFERENCES

- Anderson, H. C. (1954). *Lancet*, 2, 1157.
 Batchelor, R. C. L., Horne, G. O., and Rogerson, H. L. (1951). *Ibid.*, 2, 195.
 Bell, R. C. (1956). *Ibid.*, 2, 439.
 Bhattacharya, B. (1955). *British Medical Journal*, 2, 972.
 Blanton, W. B., and Blanton, F. M. (1953). *J. Allergy*, 24, 405.
British Medical Journal, 1955a, 1, 1289.
 — 1955b, 2, 311.
 Buff, I. E. (1950). *Amer. Practit. (Philad.)*, 1, 347.
 Calvert, R. J., and Smith, E. (1955). *British Medical Journal*, 2, 302.
 Carter, E. S., and Cope, C. B. (1954). *J. Allergy*, 25, 270.
 Culphey, T. J. (1953). *N.Y. St. J. Med.*, 53, 1107.
 Dubberley, C. L. (1955). *British Medical Journal*, 2, 563.
 Everett, R. (1951). *J. Amer. med. Ass.*, 146, 1314.
 Feinberg, S. M., Feinberg, A. R., and Moran, C. F. (1953). *Ibid.*, 152, 114.
 Goodman, L. S., and Gilman, A. (1955). *The Pharmacological Basis of Therapeutics*, 2nd ed. Macmillan, New York.
 Harpman, J. A. (1952). *British Medical Journal*, 2, 392.
 Irwin, J. W., Graham, M. J., Jacobson, B. M., and Burrage, W. S. (1951). *New Engl. J. Med.*, 245, 246.
 Janowitz, H. D., Schneierson, S. S., Sussman, M. L., and King, F. H. (1948). *J. Lab. clin. Med.*, 33, 933.
 Leibowitz, H., and Schwartz, E. (1950). *Ann. Allergy*, 8, 668.
 Lewis, G. W. (1953). *British Medical Journal*, 2, 778.
 — (1954). *Ibid.*, 2, 1168.
 Martin, E. G. (1928). *J. Amer. med. Ass.*, 91, 555.
 Mathews, K. P., Hemphill, F. M., Sheldon, J. M., Lovell, R. G., and Forsythe, W. E. (1955). *J. Allergy*, 26, 78.
 Mayer, P. S., Mosko, M. M., Schutz, P. J., Osterman, F. A., Steen, L. H., and Baker, L. A. (1953). *J. Amer. med. Ass.*, 151, 351.
 Pick, F. J., and Patterson, J. F. (1953). *British Medical Journal*, 2, 605.
 Rosenthal, A. (1954). *N.Y. St. J. Med.*, 54, 1485.
 Schiller, I. W. (1953). *J. Allergy*, 24, 383.
 Siegal, S. (1951). *Amer. J. Med.*, 11, 196.
 Singh, S. D. (1955). *J. Indian med. Ass.*, 24, 645.
 State, D., and Wangenstein, O. H. (1946). *J. Amer. med. Ass.*, 130, 990.
 Thomson, W. O. (1952). *British Medical Journal*, 2, 70.
 Tidswell, T. H. (1955). *Ibid.*, 2, 721.
 Vance, B. M., and Strassmann, G. (1942). *Arch. Path. (Chicago)*, 34, 849.
 Volini, I. F., Shlaes, W. H., and Felsenfeld, O. (1950). *J. Amer. med. Ass.*, 143, 794.
 Waldbott, G. L. (1953). *J. Amer. med. Ass.*, 151, 1023.
 Weiss, L. R. (1953). *J. Allergy*, 24, 407.
 Welch, H., Lewis, C. N., Kerlan, L., and Putnam, L. E. (1953). *Antibiot. and Chemother.*, 3, 891.
 Whipple, R. L., jun. (1951). *Amer. Heart J.*, 42, 414.
 Winton, S. S., and Nora, E. D. (1955). *Amer. J. Med.*, 18, 66.
 Wright, D. C. (1955). *British Medical Journal*, 1, 724.

CHLORAMPHENICOL IN TREATMENT OF ACUTE RESPIRATORY INFECTION

BY

A. H. IOANNIDIS, M.B., Ch.B.
Clinical Assistant

AND

J. McC. MURDOCH, F.R.F.P.S., M.R.C.P.Ed.
Senior Medical Registrar

From the Royal Infirmary, Edinburgh, and the Department of Therapeutics, University of Edinburgh

During recent years medical teaching in this country has tended to limit the use of chloramphenicol primarily to the treatment of the typhoid group of infections in view of its alleged toxic effects on the haemopoietic system; it has been suggested that respiratory infections are more appropriately treated with other chemotherapeutic agents. The view is now generally held, however, that the micro-organisms commonly invading the human respiratory tract are of a mixed type. Of these, probably the most important in the United Kingdom are the *Haemophilus influenzae* and the pneumococcus (*Lancet*, 1955). The former organism is highly sensitive to chloramphenicol both *in vitro* (Fairbrother, 1956) and *in vivo* (May, 1953a, 1953b, 1954; Elmes, Knox, and Fletcher, 1955; Franklin and Garrod, 1953). Cohen and Schwartz (1950) believed chloramphenicol to be the antibiotic of choice in acute respiratory infections of undetermined origin, in the absence of an influenza epidemic or a "common cold."

Tunbridge (1953) points out that in infections usually of mixed origin it is advisable to use a chemotherapeutic agent which is effective against both Gram-negative and Gram-positive organisms, as well as against some virus infections. Penicillin alone is not always effective, as it has a limited action against Gram-negative organisms, especially *H. influenzae* (Stuart-Harris *et al.*, 1953), and May and Oswald (1956) have suggested that a combination of penicillin and streptomycin gives prompt and complete remission of exacerbation in the early stages of chronic bronchitis.