unwittingly influence the opinion of some doctors. (2) That the effort to discredit medical evidence by counsel in cross-examination may confuse a medical witness not experienced in courts of law, and distort the reasons on which he bases his opinion. (3) That the conflict of opinions expressed by doctors in courts serves to bring the medical profession into disrepute. (4) That the references to which a doctor can point in support of his opinion are so limited by legal requirements of evidence that a sound opinion may appear to lack a proper basis.

While these objections have a certain amount of justification it must be admitted that opinions expressed by doctors often differ very widely, and it would seem that where different opinions are put forward medical evidence can be assessed only by the recognized methods of examination and cross-examination in order to arrive at the truth. The difficulties met with in assessing medical evidence have been recognized by legislation, which under the Workmen's Compensation Act provides for a medical referee. The Workmen's Compensation Act also provides that the medical referee may enlist the services of a specialist. It is common knowledge, however, that these provisions are not availed of fully by the courts, and in cases in which mental illness is at issue it is practically unknown that the courts employ an independent psychiatrist to assist the judge. It should be very apparent that only a person highly trained in psychology and mental illness is capable of following the anamnesis on which the diagnosis and prognosis are based. It would seem, therefore, that when mental illness is a matter of litigation it would be a good thing if the courts had a psychiatrist of well-recognized experience and standing to help in assessing mental illness in such cases, as it must be extremely difficult, if not impossible, for a judge to distinguish between the various points on which conflicting opinions are based.

Summary

There is no medical entity called a compensation neurosis. So-called compensation neuroses do not differ from neuroses in which only the desire for treatment is involved.

It is essential, in dealing with an alleged case of neurosis, to make as accurate a diagnosis of the illness as possible—whether neurasthenia, obsessional or anxiety state, or hysteria—and to assess the contributory or precipitating agents.

Accurate assessment of the nature of the neurosis is one of the best guards against malingering.

Predisposition is one of the most important factors in mental illness, and consists in a susceptibility to disease which remains latent under normal conditions but may be activated by exceptional stress.

Only the very mild cases and malingerers recover after settlement of compensation claims; the more serious cases are not affected.

Medical witnesses often differ in their opinions of cases, and judge or jury should not have to decide between them. Delicate decisions that have to be made by the court should be based on the advice of a properly constituted panel of specialists in neuropsychology.

The Lasdon Foundation Inc. has made a grant of \$15,000 to Harvard Medical School and the Peter Bent Brigham Hospital to support research on the homologous transplantation of human and animal kidneys. The work will be under the direction of Professor G. W. Thorn and Dr. B. F. Miller. In previous investigations on this subject at Harvard the kidney has been transplanted into the subject's thigh and attached to the vessels of the leg. The Harvard workers hope that their studies will also throw light on the related problems of the homologous transplantation of skin and endocrine tissue.

CLOSTRIDIAL MYOSITIS ASSOCIATED WITH INJECTIONS OF SODIUM SULPHATHIAZOLE

BY

SIDNEY SHAW, M.D.

AND

W. E. EVANS, M.D.

(From the Departments of Clinical Pathology and Morbid Anatomy, Charing Cross Hospital Medical School)

Of the many papers which record the occurrence of gas-gangrene as a complication of drug injection in man we have examined 39, published between 1931 and 1950, but find no reference to the occurrence of this infection at the site of injections of sulphonamide. The case presented here is that of clostridial myositis associated with injections of sodium sulphathiazole.

Clinical Record

A married man aged 54, a butcher and gardener by occupation, was admitted on May 12, 1950, from the casualty department to the medical ward for the treatment of bronchitis. There was a history of angina pectoris of some eight years' standing, and he had been in the habit of drinking six to ten pints (3.4 to 5.7 litres) of beer daily.

Diagram of events. Each arrow represents an injection.

The day after admission he had a severe haematemesis followed by collapse, for which morphine, $\frac{1}{2}$ gr. (11 mg.), was injected, and eight pints (4.5 litres) of compatible blood was transfused during the subsequent twenty-four hours. On May 14 his temperature rose to 102.8° F. (39.3° C.), early bronchopneumonia was diagnosed, and intramuscular injections of penicillin were begun, 200,000 units being given at intervals of six hours. The pyrexia was maintained during the next day, and intramuscular injections of sodium sulphathiazole were begun, the first of 2 g., then subsequent four-hourly injections, each of 1 g., as a 33.3% solution in apyrogenic sterile distilled water; injections of penicillin and sulphathiazole were made into the lateral thigh muscles. Administration of morphine was stopped on this day, a total of five injections, each of $\frac{1}{2}$ gr., having been given into the arms and the first of two intramuscular injections of paraldehyde, 5 minims (0.3 ml.), was administered. There is no record of the site of injection of the paraldehyde.

The temperature fell to normal on May 16; penicillin was discontinued on the 18th, when a total of 3,400,000 units had been injected; and on the 20th the injections of sulphathiazole were stopped, a total of 32 g. having been administered intramuscularly.

There was steady clinical improvement until May 28, eight days after the last injection, when the temperature rose sharply from normal to 103.2° F. (39.5° C.), the right thigh became uniformly swollen and hot, and an effusion developed into the right knee-joint. The condition was thought to be femoral thrombosis or a deep abscess in the thigh, and four-hourly injections of penicillin, each of 200,000 units, were begun.

No improvement in the general or local conditions occurred, and in the early morning of May 29 the patient woke up, complained of pain in the chest, gave three gasping respirations, and died.

The above diagram illustrates the sequence and timing of events.

Post-mortem Findings

The post-mortem examination was conducted thirty-two hours after death, the body having been stored at about 4° C. Externally the body appeared well nourished, there was some pallor of the lips and nail-beds, and the livid markings were light pink in colour. Needle-puncture marks were seen on the lateral aspect of each thigh, the right thigh was swollen, and the right knee-joint was enlarged by effusion. The skin of this region was tense and discoloured by patchy blue and pink markings, and there was "marbling" due to prominence of the superficial veins. The left thigh appeared normal in size and colour. The scrotum was red and oedematous. Incisions into the right thigh revealed widespread necrosis with liquefaction and gas production in the lateral group of muscles deep to the injection marks in the skin, the appearances being typical of clostridial myositis. Similar changes, but without gas production, were found in the right psoas and iliacus muscles. Several localized areas of coagulative necrosis, each deep to an injection puncture in the skin, were found in the lateral muscles of the left thigh; no necrosis of the superficial fat was present, and each necrotic area lay deeply in muscle. There was no evidence of infection in this thigh.

Considerable haemolysis was present in the general circulation, with staining of the blood vessels. Little aortic atheroma was found, but a solitary plaque was demonstrated in the upper part of the anterior descending branch of the left coronary artery, immediately below which was a recent ante-mortem occluding thrombus. No evidence of gas embolism could be demonstrated in any part of the circulatory system.

Chronic bronchitis was found, and a partially healed acute gastric erosion was seen on the posterior wall of the cardiac end of the stomach; no free blood was present. The liver was slightly enlarged by fatty change and discoloured by haemolysis. The spleen was slightly enlarged, dark red in colour, and congested. Blood-stained urine was present in the bladder. The brain was oedematous, a few cerebral petechial haemorrhages were seen, and there was blood-staining of the cerebrospinal fluid.

Microscopy.—Histological examination confirmed gas-gangrene of the muscles of the right thigh, and many Gram-positive bacilli were seen in sections. Neither clostridial lesions nor organisms were found in sections of the liver and other viscera, and the necrotic masses in the left thigh were also free from any infection.

Bacteriology.—A direct smear from the necrotic muscle of the right thigh showed pus cells and Gram-positive bacilli. Anaerobic cultures produced a heavy pure growth of *Clostridium welchii*, while aerobic cultures remained sterile. No organisms were cultured, either by aerobic or by anaerobic means, from the brain and cerebrospinal fluid or urine, and only coliform bacilli were grown from the spleen. The *Cl. welchii* was found to be resistant to penicillin and sulphonamides. Efforts to trace the source of the infection were unsuccessful. Suitable cultures were attempted from ampoules of sulphathiazole, apyrogenic distilled water, and paraldehyde, each from the same batch as that injected in this case. Scrapings from the two ward sterilizers were cultured, and the surgical spirit was similarly investigated, but no clostridia were grown.

Experimental Investigations

The pH of the sodium sulphathiazole, when made up as a 33.3% solution in sterile distilled water, is about 10.5, and it was thought desirable to investigate the growth of *Cl. welchii* in alkaline media. This investigation was deferred because of extensive structural laboratory alterations, and the original strain of *Cl. welchii* was inadvertently destroyed during the delay; subsequently three further strains of *Cl. welchii* were used.

Tubes containing 0.1% glucose broth, set up to cover a pH range of 10.5 to 4 by adding varying quantities

of concentrated sulphuric acid and concentrated sodium hydroxide, were inoculated with the clostridia. No growth occurred at pH 10 and higher or at pH 6 and lower, and the latter observation was confirmed on repeating the experiment from pH 7 and below.

In order to avoid precipitation of calcium from the media, two further experiments were performed; in the one concentrated hydrochloric acid and in the other glacial acetic acid was substituted for sulphuric acid. As growth had been shown to occur on the alkaline side of neutrality, only tubes with pH values of 7 and below were set up. No growth occurred at pH 6 and below with hydrochloric acid, or at pH 5.5 and below with acetic acid. The tubes in which no growth occurred were reinoculated and further incubated, but again there was no growth (see Table).

Effect of pH on Growth of *Cl. welchii* in 0.1% Glucose Broth

pH	Conc. H ₂ SO ₄ and Conc. NaOH	Repeat with Conc. H ₂ SO ₄	Conc. HCl	Glacial Acetic Acid
10.5	—			
10.0	—			
9.5	+			
9.0	+			
8.5	+			
8.0	+			
7.5	+			
7.0	+	+	+	+
6.5	+	+	+	+
6.0	—	—	—	—
5.5	—	—	—	—
5.0	—	—	—	—
4.5	—	—	—	—
4.0	—	—	—	—

+ = Growth. — = No growth.

It thus appeared that the inhibition of growth was related to the acidity and not to calcium precipitation. We have since found references to the effect of pH on the growth of *Cl. welchii*, in which it is shown that this organism is cultured only with difficulty at low pH values (Gale, 1941; Gale and van Heyningen, 1942).

Discussion

The depth, position, and number of the necrotic foci in the muscles of the left thigh indicate the sodium sulphathiazole as the necrotizing agent in this case, and as injections of the compound were given into each thigh it is reasonable to suppose that similar necrotic lesions had been present in the right thigh, later becoming unrecognizable when the myositis developed. We have seen identical foci of muscle necrosis due to sodium sulphathiazole injections in other cases, and similar lesions are mentioned in the literature (Banks, 1940; Selbie and McIntosh, 1943). The necrosis seems to be due to the very alkaline reaction of the injection solution.

It is well known that deep necrosis of muscle is a favourable site for infection by clostridia, and the local pH in this case would have been above 7.7, though reduced from the initial high pH of the solution by buffering in the tissues and by dilution by oedema. There can be little doubt that the infection began in a sulphathiazole-induced necrotic focus in the right thigh: the organism isolated from the muscle happened to be resistant *in vitro* to penicillin and to sodium sulphathiazole; but, even had *in vivo* sensitivity to the latter been a characteristic of the bacillus, infection could still have occurred, as dormant spores might well have persisted in the tissues until the effective concentration of the sulphonamide became reduced, when active infection of the necrotic muscle would occur.

It has been shown that if an injection of *Cl. welchii* into the thigh muscles of mice is followed one hour later by injection of sulphathiazole into the same site, then only a small percentage of the mice survived (McIntosh and Selbie, 1943).

The source of the *Cl. welchii* in this case was not discovered: skin contamination from the bowel is a possibility,

the organism being a normal inhabitant of the intestinal tract of man. The customary brief skin "cleansing" with alcohol would not be sufficient to kill spores. Alternatively, the organism may have been present in any of the injection solutions or apparatus; proof of this is impossible to obtain.

Summary

Myositis due to *Clostridium welchii* infection was found in the region of injections of sodium sulphathiazole at the post-mortem examination of a man who died of acute coronary thrombosis. It is believed that the very alkaline solution of sulphathiazole was responsible for muscle necrosis, and that accidentally introduced infection of a necrotic focus led to gas-gangrene. The possible source of the infection is mentioned, and some simple experiments in the culture of *Cl. welchii* at varying pH values are described.

We are grateful to Professor H. W. C. Vines for valuable advice and to Mr. H. Neville Stafford, coroner for Westminster, for permission to publish.

REFERENCES

- Banks, H. S. (1940). *Proc. roy. Soc. Med.*, 33, 555.
 Gale, E. F. (1941). *Biochem. J.*, 35, 66.
 — and van Heyningen, W. E. (1942). *Ibid.*, 36, 624.
 McIntosh, J., and Selbie, F. R. (1943). *Lancet*, 1, 793.
 Selbie, F. R., and McIntosh, J. (1943). *J. Path. Bact.*, 55, 477.

PETHIDINE AND THE TRIPLE RESPONSE

BY

B. L. FINER, M.B., B.S.

AND

M. W. PARTINGTON, M.B., B.S.

(From the Department of Physiology, London Hospital Medical College)

Zuck (1951) and Pearce (1951) observed that the intravenous injection of pethidine was followed by the appearance of a wheal extending proximally along the line of the vein. Nasmyth and Stewart (1950) observed that the injection of pethidine into human skin produced a triple response which was reduced in extent by antihistamines, and suggested that pethidine was a histamine liberator. We have made similar observations. In view of the widespread use of pethidine and reports of unexpected hypotension and collapse following its administration (Giff, 1947; Butler, 1951; Zuck, 1951), it was decided to investigate the production of this triple response further. The results are reported below.

Methods

Intradermal injections (0.1 ml.) were made into the skin of the forearm with a Mantoux syringe.

The effects of intravenous injections were studied under two different sets of conditions. (1) *Venous congestion*:—A sphygmomanometer cuff was placed round the upper forearm and pumped to 70 mm. Hg. The injection (in a volume less than 0.5 ml.) was made into a small wrist vein. Immediately the needle was removed, pressure was applied with a pad of cotton-wool over the site where the vein had been punctured to

prevent blood leaking out of the vein. The pressure in the cuff was maintained for three to four minutes after the injection and then released. (2) *Circulatory occlusion*:—A sphygmomanometer cuff was placed round the upper forearm and pumped to 70 mm. Hg. This pressure was maintained for one minute to congest the vessels of the forearm and then raised to 200 mm. Hg. One minute later the injection was made into a wrist vein, and after a further five minutes the pressure was released.

The Intravenous Injection of Pethidine and Histamine

A triple response is seen over the veins in the forearm if pethidine (25–100 mg.) is injected into a wrist vein with an unrestricted circulation in the arm. The reaction is more conveniently studied if smaller doses (5–15 mg.) are used with some obstruction of the venous return as described above.

Within 30 seconds of injection under these conditions an intense sensation of itching spreads up the forearm. This is often followed by a change in the colour of the vein to a characteristic mauve or plum colour. At the same time a flare appears in the skin round the site of injection and then on each side of the vein for a distance of up to 3 cm., progressively following the vein up the forearm. Within five minutes of injection a wheal appears, localized at first to a thin strip over the vein, but later spreading a few millimetres into the skin on each side. If the vein divides, the flare and wheal follow the branches. Sometimes an unaffected area of skin is seen between the site of injection and the changes higher up in the forearm. Whealing and flaring may occur distal to the site of injection and occasionally discrete wheals form in the skin. Massive wheals are sometimes seen. The typical appearance following an injection of pethidine under these conditions is shown in Fig. 1.

Within two or three minutes of the intravenous injection of pethidine with the circulation *occluded*, a red reaction is seen in the skin. A number of discrete irregular red areas appear, some distal and some proximal to the site of injection. The areas lie over and on each side of the veins in the forearm. They increase in size slowly and may coalesce. When the circulation is re-established and the reactive hyperaemia has subsided the forearm is seen to be extensively whealed, and the margins of the wheals roughly correspond with the margins of the previously observed red reactions. Surrounding all the whealed areas there is a bright red arteriolar flare. On four occasions after the pressure in the cuff was released, the subject's face was seen to flush, and a characteristic metallic taste and a transitory headache were experienced, indistinguishable from those produced by injections of histamine.

All these changes, except the very large wheals, may be reproduced exactly if histamine (15–30 µg. in terms of the base) is substituted for pethidine in the above experiments.

The lymphatic vessels play no part in this response, as the following experiment shows: if pethidine or histamine

FIG. 1.—Changes in the forearm after 15 mg. of pethidine injected intravenously. Sphygmomanometer cuff (at 70 mm. Hg) at the elbow for four minutes after injection.