treated. *Result*:—The histological appearances were the same as those shown by the controls (Plate, Fig. 2). No burning had occurred.

Application of Short-wave Dielectric Heating.—Glass electrodes of 2-in. (5-cm.) diameter, 4 in. (10 cm.) apart, were arranged so that the current passed through the animal's body and the metal. In these experiments only tantalum gauze was used. Three animals were treated. In the first and second, current of a strength usually employed on human beings was passed for five and ten minutes respectively. No rise in general body temperature occurred. In the third rat the current, greatly in excess of that ever used on man, was passed for five minutes, at the end of which time the animal's rectal temperature was 105° F. (40.6° C.). *Result*:—No evidence of burning was found in any of the animals in the region of the implant or elsewhere.

Application of Electromagnetic Induction Heating.—Two animals were used, both of them with tantalum gauze implant. The maximum output that could be obtained from the machine (Victor inductotherm) was passed through a coil made up of three turns of wire, in the centre of which the animal was placed. In the one, the current was passed for five minutes; in the other, for ten minutes. *Result*:—No burning occurred in either animal.

Summary and Conclusions

It would thus appear to be safe to use any of the above forms of medical diathermy on patients with metal in their body walls, in the small amounts and in the form of wire of fine diameter, such as is likely to be employed in the repair of herniae. The absence of any burning in the electromagnetic induction experiments is probably due to the rapid conduction of heat away from the metal by the body fluids. It must be admitted, however, that the above experiments do not exclude the possibility of harmful effects in cases in which the metal insert is large and is implanted in relatively avascular tissue such as bone. Considerable heating might then occur and cause necrosis, especially if the metal can be magnetized, as, for instance, in the commonly employed stainless steel tri-fin nail used in the treatment of fracture of the neck of the femur.

I wish to express my thanks to Professor Cappell and Mr. W. W. Galbraith, heads of the departments of pathology and urology, for their interest and criticism of this article; to Dr. J. M. A. Lenihan, physicist to the Western Infirmary, Glasgow, for his help in the physics involved; and to Miss Ritchie, of the x-ray department, for the skiagram reproduced above.

Fifteen overseas students are taking part in a survey of British voluntary social services arranged by the British Council between June 16 and June 30. The students, who come from 11 countries, are taking long courses of study in this country in subjects which include law, local government, science, youth organization, and social science. The first visit was on June 19 to the Wimbledon Guild of Social Welfare, and St. Pancras Rotary Club entertained the group to lunch the following day. Other visits were to the British Red Cross Society on June 21, Dr. Barnardo's Garden-City Home at Ilford on June 23, and the clinic of the People's Dispensary at Ilford on June 24. On June 26 the students will visit the headquarters of the W.V.S., and in the evening they will visit boys' and mixed clubs in London. On June 28 they will be shown over the British Legion Village, near Maidstone, Kent, and the survey concludes with a visit to the National Institute for the Blind. The countries from which the students come are: Ceylon, China, Egypt, Finland, India, Indonesia, Mauritius, Norway, Persia, Siam, and the U.S.A.

HISTOLOGICAL REACTIONS TO INJECTIONS OF PROCAINE PENICILLIN IN OIL

BY

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[WITH PHOTOGRAPHIC PLATE]

Procaine penicillin, suspended in a vegetable oil and given by intramuscular injection, is now widely used. Review of the literature yields little information regarding the histological reaction of human tissues to injections of therapeutic substances suspended in oil and apparently none about the effects on human or animal muscles of procaine penicillin in oil. There are, however, reports of the changes produced by vegetable oils in animals and by penicillin in both man and animals.

This paper gives an account of the histological changes occurring in the deltoid muscles and adjacent lymph nodes of a patient who had received intramuscular injections of procaine penicillin in arachis oil. The commercial preparation used contained 300,000 units of penicillin G in combination with 120 mg. of procaine suspended in 1 ml. of arachis oil.

Clinical Summary

A foreman builder aged 67 was admitted on May 3, 1949, with subarachnoid haemorrhage complicated by a respiratory infection leading to empyema. While in hospital he was found to have an aneurysm of the aorta. His general condition deteriorated, bed-sores and a urinary infection developed, and he died on June 26, 1949.

He received the following treatment. On May 7 and 8 50,000 units of penicillin in saline were given every three hours intramuscularly on 16 occasions and then discontinued. A total of 85 g. of sulphadimidine was administered orally over the next eight days to May 15. From May 16 to 24 10,000 units of penicillin in saline were given intramuscularly three-hourly; the dose was then increased to 30,000 units three-hourly until June 2. These intramuscular injections were made into the buttocks, thighs, and deltoid regions. On June 2 procaine penicillin in arachis oil was substituted, 300,000 units being administered intramuscularly once daily and continued until June 16, when the dose was doubled to 600,000 units daily. This was maintained until the patient's death on June 26. During the last 14 days, because of extensive bed-sores over the sacrum and buttocks, many of the injections of procaine penicillin in oil were made into the deltoid muscles. No reaction was noted clinically at the sites of injection.

Pathological Findings

A necropsy which was performed on June 28 showed a wasted man with large bed-sores over the sacrum and buttocks. There were several needle-marks in a small area over both arms above the deltoid insertions. The clinical findings of subarachnoid haemorrhage, aortic aneurysm, and empyema were confirmed. Underneath the needle-marks seen on the skin of each deltoid region was an area in the muscle about 6 by 3 cm. which was greasy to the touch and showed some free oil in its deeper part. No scarring of the muscle was obvious macroscopically, but some minute cystic areas and one small haemorrhage were observed. The remainder of the muscle appeared normal. The right and left axillary lymph nodes were not enlarged: several were taken from each lateral group for microscopical examination.

Histological Appearances

From the affected areas of both deltoid muscles several blocks of tissue were examined and all showed similar appearances. The muscle was oedematous and the perimysium

contained a large number of oily globules (Plate, Fig. 1). In the paraffin sections these were represented as spaces and in frozen sections as round areas staining bright red with Scharlach R. They varied in size from over 2 mm. down to extremely finely divided droplets. This oily material was associated with a marked cellular reaction in the connective tissue and some degeneration of adjoining muscle bundles (Fig. 2).

The cellular reaction varied little from one area to another, being composed mainly of small round cells and large mononuclear phagocytes with smaller numbers of eosinophils and a few multinucleate giant cells. In some places, however, eosinophils were particularly numerous, and in those areas immediately surrounding the oil globules large mononuclear and multinucleate phagocytes were predominant (Fig. 3). There was no evidence of any acute inflammatory reaction, neutrophil leucocytes being scanty. Around some globules there was little cellular reaction, but around others it was pronounced. The muscle bundles associated with the areas of cellular reaction showed disintegration and disappearance of muscle fibres and some replacement by cellular fibrous tissue. The oily material was being taken up by many of the cells, which in the frozen sections were seen to be distended by finely divided oil. There was little evidence of chemical breakdown of the oil. Fatty acid crystalline deposits were not found, but a few small areas staining deeply with haematoxylin suggested the presence of calcium salts. In frozen sections of the muscle stained by Nile-blue sulphate some of the oil was coloured blue. These lesions were localized: the muscle a short distance beyond the edge of the oil was histologically normal.

The axillary lymph nodes had some "sinus catarrh" with large numbers of foam cells mainly in the peripheral sinusoids. Frozen sections confirmed that these cells contained very finely divided globules of oil.

Discussion

The histological changes observed in this case may have been due to either or both of the constituents of the injection—namely, procaine penicillin and arachis oil. Concerning arachis or similar vegetable oils, there seem to be reports in the literature of animal experiments only. Brown *et al.* (1944) have studied the reaction of rabbits and rats to several vegetable oils injected intramuscularly. In all, the results were similar but differed in intensity. After 24 hours there was a moderate increase in round cells and the oil was diffusely scattered through the muscles, tending to accumulate along fascial sheaths and also between muscle bundles. By the third day the oil was in small cyst-like droplets surrounded by a layer of fibrin and large cells of epithelioid appearance; outside this were leucocytes and wandering cells. The leucocytic reaction reached a peak between the third and sixth days and then subsided slowly. In rats, but not in rabbits, arachis oil induced some muscle necrosis and oedema.

Romansky and Rittman (1944) have described similar tissue changes in hamsters following intramuscular penicillin in a beeswax-peanut-oil mixture, but muscle necrosis was not a feature. Working with albino rats, Emery *et al.* (1942) found that oil cysts up to 2 mm. in diameter, and persisting for several months, were produced in response to four different vegetable oils injected intramuscularly. Deanesly and Parkes (1933) have described oil cysts in rats and mice following the subcutaneous injection of olive, sesame, and castor oils. The last remained in the tissues for long periods.

According to Anderson (1949) minute cysts with thin fibrous walls have been found in the muscles of patients dying one to two months after the injection of penicillin in beeswax and peanut oil. These may have been oil cysts of the kind found in animal experiments.

In the human subject muscle necrosis at the site of injection of penicillin has been recorded. Nelson-Jones and

Williams (1945) have described aseptic muscle necrosis at the site of administration of penicillin by continuous intramuscular drip. Call and Gilbert (1947) reported two cases which received intramuscular penicillin and developed multiple abscesses three to four weeks later at the sites of injection. Cutting *et al.* (1945) gave rats daily subcutaneous injections of penicillin for six months and found haemorrhages, foreign-body giant cells, and excess of fibrous tissue in the injected areas. They have suggested that these changes may be due to trauma or mild infection, as no sterile precautions were taken.

I have not been able to find an account of the histological effects, if any, produced by intramuscular procaine in man or animals.

The histological changes recorded in the present case resemble those produced in rats by arachis oil, but differ in two features. First, the muscle degeneration and oedema are more extensive. Secondly, in animal experiments eosinophils were inconspicuous, whereas in the case reported they were numerous. The muscle degeneration and oedema are not surprising, as owing to the bed-sores on the thighs and buttocks this patient had more than one injection of procaine penicillin in oil into the area of muscle examined. (Most manufacturers advise against this, but, as in this case, it may occasionally be unavoidable.) It is not possible here to decide whether the procaine penicillin itself was wholly, partly, or not at all responsible for the cellular reaction and muscle changes. In view of the animal experiments with oil alone it is unlikely that procaine penicillin was wholly responsible.

The eosinophil reaction may have arisen in response to the arachis oil, though this has not been reported in experiments on rats or rabbits. On the other hand, penicillin is a known cause of eosinophilia and is perhaps a more likely cause for the eosinophils in this case. Orland *et al.* (1944) have described allergy to procaine, but there is no record of procaine causing an eosinophilia. Frozen sections showed that the oil was being actively taken up by the phagocytic cells and had been carried to the adjacent lymph nodes. It is possible that phagocytes may ultimately remove all the oil and damaged muscle and a fibrous scar remain.

Summary

The histological changes following the intramuscular injection of procaine penicillin in arachis oil are described.

The oil occurred in small cysts surrounded by a cellular reaction in which eosinophils were conspicuous. Some muscle degeneration and oedema were present. Fat-bearing phagocytes were plentiful around the oil and in adjacent lymph nodes.

The histological features have been compared with the reactions of animal tissues to arachis oil and penicillin which have been described separately by previous observers.

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J. V. DACIE, E. DRESNER, D. L. MOLLIN, AND J. C. WHITE: AMINOPTERIN IN ACUTE LEUKAEMIA

FIG. 1.—Case 1. Bone-marrow smear on admission. ($\times 400$.) FIG. 2.—Case 1. Bone-marrow after first course of aminopterin. ($\times 400$.) FIG. 3.—Case 4. Bone-marrow before aminopterin treatment. ($\times 470$.) FIG. 4.—Case 4. Bone-marrow after first course of treatment. ($\times 470$.) FIG. 5.—Case 5. Bone-marrow before treatment. ($\times 470$.) FIG. 6.—Case 5. Bone-marrow after treatment. ($\times 470$.)

PETER STORY: HISTOLOGICAL REACTIONS TO INJECTIONS OF PROCAINE PENICILLIN IN OIL

FIG. 1.—Deltoid muscle (haematoxylin-eosin): oil cysts, muscle degeneration, and oedema. ($\times 65$.) FIG. 2.—Degenerate muscle fibres and cellular reaction round oil droplet in deltoid muscle; H.-E. ($\times 125$.) FIG. 3.—Oil globule surrounded by foam cells and a multinucleate giant cell; H.-E. ($\times 300$.)