several separate examinations with the patient rotated in oblique positions in order to bring each diameter in turn parallel with the film. Linear objects can be measured provided that they are parallel with the film.

The calculation of the size of the tumour or cavity in the lung and its depth from any part of the chest wall is a simple matter. A double exposure on one film will suffice, or two separate films may be taken if preferred. The method can be used as a check on tomography. The size and depth of opaque cerebral tumours could be determined in a similar manner. The dimensions of a vesical or biliary calculus, or other opaque object, could be determined and compared with its dimensions at a subsequent examination. The results would be comparable even though the position of the object had changed. No doubt other applications of this method will present themselves.

Summary

A new radiometric method is described.

It is claimed to be a method of precision, as the human factor in first estimating the distance of the object from the film is eliminated.

The application of the method to cephalometry and pelvimetry is described in detail.

Other applications in surgery of the brain, chest, abdomen, and pelvis are indicated.

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INTRAMUSCULAR INJECTION OF MEPACRINE (ATEBRIN): HISTOLOGICAL EFFECT

BY

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This note describes a histological examination of the effect of injecting mepacrine methanesulphonate (atebrin musonate) intramuscularly. Owing to the shortage of quinine, mepacrine will be used more extensively than in the past. When oral administration is impracticable it will be necessary to inject the drug intramuscularly or intravenously; in order to assist the choice between these two routes information is presented about the local effects caused by intramuscular injection.

Literature

Many clinical observations on the subject have been reported, but histological observations have not been described. Field, Niven, and Guest (1937) injected two doses each of 0.375 g. musonate into 284 patients. Local reactions were usually unimportant, but occasionally there was a little tenderness and induration at the site; in one case an abscess with atebrian-stained contents developed. During the Ceylon malaria epidemic (1934-5) 681 patients were treated with similar doses; 21.3% developed pain at the site of injection, and in two cases abscesses occurred. (When quinine was injected 36% of 424 patients suffered from pain, but there were no abscesses.) In a later series of 530 cases treated in the field most patients complained of pain for 2 to 4 days, some suffered from painful swelling and induration at the site, and in two instances abscesses resulted. Pain after the injection of atebrian was less frequent than after the injection of quinine; it might be severe. Abscesses were indolent and slow to heal; they were similar to those caused by quinine, and tracked along the fascial planes in the same way. Hay, Spaar, and Ludovici (1935) treated 3,500 cases; pain was negligible and no abscesses were observed. Simeons (1936) injected two doses each of 0.3 g. into 2,800

people. With good aseptic technique no abscesses occurred; but with a second series of 2,800 cases, in which aseptis was less satisfactory, there were 49 abscesses. Clinical series in which the local reactions were considered as unimportant are also reported by Carman and Cormack (1936), Eckhardt (1933), Kröber (1936), Seelig and Singh (1936), Sicault (1934), Siegenbeek van Henkelom and Overbeek (1938), van Slype (1935), Vardy (1935). Dove (1942) recommends the intramuscular injection of atebrian as being less harmful than quinine. The injection is not painful, and if done with sterile precautions will not cause abscesses; Dove prefers it to intravenous injection of atebrian.

Experimentally Hecht (1933) injected 0.1 c.cm. of a 1% solution of the hydrochloride—i.e., 1 mg.—apparently subcutaneously; it caused hyperaemic swelling, which disappeared in 24 to 48 hours without necrosis. Hicks (1935) injected 10 to 20 mg. atebrian musonate intramuscularly into 8 monkeys, which were killed two days later. In one case he found macroscopically an area of congestion 1×0.5 cm., haemorrhage, and oedema, but the rest showed no gross changes; no histological observations were made.

Summing up the literature, it is generally considered that the intramuscular injection of atebrian is as a rule innocuous, but pain and swelling occur in some patients, and, rarely, abscesses may result.

Experimental Results

The present experiments were made by injecting mepacrine methanesulphonate (quinacrine), 50 mg. in 0.5 c.cm. of distilled water, into rabbits weighing 1.5 to 2 kg. Most of the injections were made into the muscles of the thigh or of the loin, but some were made under the skin of the abdominal wall. If larger quantities—e.g., 70 mg. per kg.—were injected the rabbits were often prostrated in about 5 minutes, and some died; apparently absorption is very rapid. Injections were also made into rats. The rabbits were killed after 1 to 5 days and the rats after 1 to 14 days; the site was excised, fixed in formal-saline, and examined by the usual histological methods.

Naked-eye Appearances.—After intramuscular injection the macroscopic evidence of injury was usually slight. The muscles might be somewhat swollen and small haemorrhages might be present along the needle track. In the thigh, the intermuscular space along the sciatic nerve was often stained yellow from hip to knee. But in most cases there was little to be seen, and the site of injection was often difficult to identify. After subcutaneous injection the skin was usually greatly swollen, sometimes becoming as much as 1 cm. in thickness, the swollen area being 4 cm. in diameter. The swelling occurred in the connective tissue of the skin, which was stained yellow and distended with fluid. After 5 days the affected part was converted into a hard dry necrotic mass. The underlying muscles were little affected.

Microscopical Appearances.—Sections taken 1 to 2 days after intramuscular injection showed areas of necrosis in the muscles. The affected fibres were swollen, structureless, and eosinophilic, and the nuclei were destroyed. A moderate amount of fluid (often albuminous) was present between the fibres, but cell-infiltration was minimal. The areas of necrosis seen on the slide (transverse section) measured 0.5 to 1 cm. across, but they probably extended over a greater distance in the longitudinal direction. In cases in which the site involved an intermuscular space the connective tissue was greatly distended with fluid and a moderate number of cells, most of the cellular elements being necrotic. Nerve trunks showed haemorrhage and degenerative changes, and the outer coats of the larger blood vessels were necrotic. The necrosis also involved the superficial layers of the adjacent muscles. At the edges of the necrotic region there were moderate collections of cells. In the adjacent areas the muscle fibres were often swollen, and stained irregularly. After 4 to 5 days the cellular reaction around the area of necrosis was more pronounced, granulation tissue began to appear, and a zone of demarcation became established.

After subcutaneous injection the appearances were similar. The deeper connective tissue of the skin was greatly swollen with fluid, and towards the edges it was patchily infiltrated with cells, many of which were degenerate; the whole tissue had undergone necrosis over a considerable area. The sub-

cutaneous layer of muscle was necrotic; the epithelium was limited in extent, it being apparently more resistant than the deeper tissues.

In rats the histological reaction was similar. When 0.75 mg. dissolved in 0.15 c.cm. was injected intramuscularly the lesion was small, but when it was injected subcutaneously considerable oedema and necrosis occurred. When 20 mg. in 0.3 c.cm. was injected very extensive oedema and necrosis occurred, whichever route was employed.

The damage caused by mepacrine was compared with that caused by quinine. The monohydrochloride was employed. This is less acid than the more soluble bihydrochloride generally used clinically, and consequently the lesions should be less extensive, being due only to the quinine radical and not to the acid part.

When 20 mg. dissolved in 0.6 c.cm. of water was injected intramuscularly into rabbits the lesions were closely similar in appearance and extent to those caused by 50 mg. of mepacrine. In rats the lesions produced by 10 mg. of quinine were less extensive than those produced by 20 mg. of mepacrine, but those caused by 4.5 mg. of quinine were greater than those caused by 0.75 mg. of mepacrine.

Discussion

Since the macroscopic evidence of injury is usually slight compared with the microscopical evidence, the present findings are easily reconcilable with those reported in the literature. They show that the intramuscular injection of mepacrine always causes a limited area of necrosis around the site of injection, presumably due in large part to the direct action of the mepacrine base. With 0.375 g. (as for man) instead of 0.05 g., the extent of the damage would be somewhat larger, but still not great enough to constitute an absolute contra-indication to the practice in selected cases. As compared with quinine, the damage caused by 50 mg. of mepacrine was similar in extent to that caused by only 20 mg. of quinine. Since the standard dose of mepacrine methanesulphonate (by intramuscular injection) is 0.375 g., while an average dose of quinine is 0.5 g. ($7\frac{1}{2}$ gr.) of the bihydrochloride (which is more acid than the monohydrochloride and possibly more injurious locally), it would seem that a therapeutic injection of mepacrine should cause less than a third of the damage done by a therapeutic injection of quinine.

The relative and absolute merits and demerits of the administration of mepacrine by intramuscular injection cannot properly be discussed here. According to Hecht (1936) most of the mepacrine is absorbed from the site in one to three hours; and this statement about the rapid absorption is in agreement with my own experience and with the reports reviewed above. Clearly, mepacrine should not be injected by any route unless it is impracticable to give it by mouth. The intravenous route avoids local damage, but entails a certain risk to life unless the injection is given very slowly; the intramuscular route is certain to cause a small amount of local injury, but the risk to life from over-rapid absorption is much less (although this is not absolutely excluded, since 4 patients died from mepacrine intoxication out of the 681 treated by intramuscular injection during the Ceylon epidemic). The choice between the two routes of injection must depend upon clinical experience and upon the discretion of the medical man responsible for the case.

Summary

A review of the literature shows that intramuscular injection of mepacrine (atebrin) is considered to be free from local reaction in most cases, to cause pain and swelling in some cases, and to cause local abscesses in rare cases.

Mepacrine methanesulphonate (atebrin musonate) was injected intramuscularly and subcutaneously into rabbits and rats. The macroscopic lesions were often inconspicuous, but microscopical examination always showed a certain amount of necrosis at the site of injection. The damage caused by a therapeutic injection of mepacrine is similar in kind to that caused by a therapeutic injection of quinine, but probably less than one-third as extensive. For patients who cannot take mepacrine by mouth this local damage does not contraindicate parenteral injection, but its occurrence should be borne in mind when choosing between the intramuscular and the intravenous routes.

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POST-VACCINIAL ENCEPHALOMYELITIS

BY

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The nervous complications of vaccination have been recognized for many years. Turnbull (Turnbull and McIntosh, 1926) reported a fatal case occurring in 1912, but chief interest in the condition arose after 1923. The Report of the Committee on Vaccination was issued in 1928. The cause of the nervous complications of vaccination is still unknown. The condition very rarely follows vaccination in infancy; adults who are undergoing their primary vaccination are most susceptible. The patient whose case is described below had been successfully vaccinated in infancy: a well-marked scar could be seen close to the present pustule. According to her, considerable bleeding occurred at the time of the vaccination, and it seems likely that a "cross-hatching" method was employed. Some authorities consider that linear scratches are not so likely to be followed by nervous complications as "cross-hatching" methods.

In this patient the cerebral symptoms preceded the spinal symptoms by two days, and consisted of lethargy, mental confusion, and insomnia. The interval between vaccination and the onset of symptoms was 15 days; the average period is said to be about 12 days. The paraplegia developed very rapidly, and was complete in 12 hours. Bronchopneumonia and cystitis are the usual causes of death. In the present case cystitis gave rise to the main anxiety. Sulphanilamide certainly kept the urinary infection within bounds, but had no apparent effect on the nervous symptoms. On the whole the administration of plasma appeared to be beneficial, but it is difficult to estimate its value in a condition such as this, in which there is a strong tendency to spontaneous recovery. The plasma seemed to have a very favourable influence on the mental symptoms; these passed off after the first dose. The mortality of post-vaccinial encephalomyelitis is between 50 and 60%, but the prognosis is probably better in the spinal forms than in the severe cerebral types.

As a result of experience in treating the present case it is advised that suitable serum or plasma should be given as soon as possible. This is obtained from a person vaccinated about 21 days earlier. When mass vaccination is going on at the time there will probably be little difficulty in obtaining a suitable donor. In other circumstances it would be necessary to vaccinate a donor; the interval of waiting before the plasma can be obtained would then be a great drawback. One might seek some service or institution—e.g., a hospital—where the entrants must be vaccinated before admission, and it might be possible to find there a recently vaccinated individual who would consent to act as donor. The plasma used in the present case contained 3.8% sodium citrate solution. Originally 50 c.cm. of citrate was added to the blood as preservative; 220 c.cm. of plasma was obtained, and presumably nearly all the citrate was in the plasma.

It is interesting to note that the patient had an attack of tetany during the administration of the plasma. There had