able from those caused by the methanesulphonate, which were described in the previous note and which were confirmed in the present work. The lesions produced by quinine dihydrochloride could not be definitely distinguished from those due to mepacrine; at the margin between the surviving and the swollen coagulated muscle fibres, groups of shrunken basophilic fibres were found, but these also occurred to a less extent in some of the sections of tissue with mepacrine. The necrosis produced in the loin by 20 mg. of quinine was not quite so extensive as that produced by 43 or 50 mg. of mepacrine, but that produced by 10 mg. of quinine in the thigh of rats was not conspicuously greater than that due to 4.3 or 5 mg. of mepacrine.

When mepacrine dihydrochloride or methanesulphonate was injected subcutaneously into rabbits or rats it caused necrosis of the epidermis, subcutaneous layer of muscle, deep connective tissue, and part of the muscle of the abdominal wall. The deep connective tissue was greatly distended with fluid and contained variable numbers of cells; at first these were principally polymorphs, but after a few days mononuclears predominated. By seven days the necrotic area was surrounded by a zone of granulation tissue. With subcutaneous injections of quinine dihydrochloride (20 mg.) the oedema, necrosis, and cell infiltrations were somewhat less extensive than with mepacrine (43 mg.). In rats 10 mg. of quinine caused somewhat less swelling and cell infiltration than 4.3 mg. of mepacrine, but the necrosis was equally extensive.

Pieces of tissue injected with mepacrine were fixed in formalin, cut as frozen sections, and examined on a fluorescence microscope. The necrotic muscle fibres shone bright yellow; connective tissue and the outer coat of blood vessels from the areas of necrosis shone a little; other tissues were hardly visible.

Discussion

From the above experiments it is clear that there is no difference in the local toxicity of mepacrine dihydrochloride and that of mepacrine methanesulphonate, although methanesulphonate is more convenient to use owing to its greater solubility. The necrosis caused by mepacrine is indistinguishable in type from that caused by quinine dihydrochloride. The relative amounts of necrosis which will be produced in man by therapeutic injection of the two compounds are difficult to predict from animal experiments, since the size of the lesion is not proportional to the dose. As described above, when given by intramuscular injection 43 mg. of mepacrine caused somewhat more necrosis than 20 mg. of quinine; but the necrosis produced by 4.3 mg. of mepacrine injected into the thigh of rats was not conspicuously less than that produced by 10 mg. of quinine. When injected subcutaneously into rats, 4.3 mg. of mepacrine produced more swelling and cellular reaction than 10 mg. of quinine did, but the necrosis was no more extensive. Since the therapeutic dose of mepacrine by injection is only one-half to one-third that of quinine, it is probable that the necrosis produced by intramuscular injection of mepacrine will be less extensive than that produced by quinine; and this conclusion agrees with the clinical reports reviewed in the previous paper. Nevertheless it is clear that the local damage produced by intramuscular injections of mepacrine is far from negligible.

Mepacrine given by intramuscular injection is rapidly absorbed. As concluded in the previous note, the damage caused is not sufficient to contraindicate its use if the patient's life or health is in danger, but it is great enough to make this method of administration inadvisable if the patient can possibly take the compound by mouth. Intravenous injection of mepacrine has been found in American experience to be dangerous to life, and its use has been condemned. Subcutaneous injection of mepacrine is not recommended under any circumstances; it was included in the present experiments for technical reasons as being a sensitive method of displaying the effect of injected substances upon the tissues.

Summary

The histological effect of intramuscular and subcutaneous injection of mepacrine dihydrochloride (atabrine dihydrochloride) in rabbits and rats was compared with those of mepacrine methanesulphonate and of quinine dihydrochloride. Mepacrine dihydrochloride has the

same acidity in solution as the methanesulphonate, but it is less soluble (solubility 1 : 30 at room temperature) and therefore slightly less convenient to use; the local toxicities of the two compounds are indistinguishable one from another. The injection of therapeutic doses of mepacrine produces necrosis of the tissues around the site of injection; this necrosis is identical in type with that produced by the injection of therapeutic doses of quinine dihydrochloride, but it is probably somewhat less extensive.

It is considered that mepacrine dihydrochloride is suitable for administration by intramuscular injection, although it is less convenient than mepacrine methanesulphonate; but this route should not be used if it is practicable to give the compound by mouth. Mepacrine should not be given by subcutaneous or intravenous injection.

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REFERENCE

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STERILIZATION OF THE SKIN BY COLOURLESS FLAVINE (5-AMINO-ACRIDINE)

BY

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In the *British Medical Journal* of May 18, 1918 (p. 562), one of us (V.B.), in conjunction with Carl Browning, introduced a new antiseptic solution which we named violet-green (sometimes known as "Bonney's blue"), for sterilizing the skin; this, because it was entirely non-irritant, could be applied in strength for many hours without harming the skin. The bacteriological investigations then undertaken showed that, to sterilize the skin completely, the time over which the antiseptic can be applied is even more important than its absolute bactericidal power; or, in other words, more effect is obtained from a bactericide of moderate potency which can be applied for a long time than from one whose potency is of a very high order but which, on account of its effect on the skin, can be applied for only a very short time. Violet-green, however, combined high bactericidal power with non-irritancy and therefore amply filled the bill, and since its introduction it has been extensively used not only in surgery and obstetrics but in dermatology as well. It has, however, been objected against it that it intensely stains the bed-linen of the patient and the hands of the nurses. This is true, particularly when one is unaccustomed to its use. On the other hand, applied to the vagina, the staining is a great advantage when—as, for instance, in total hysterectomy—that canal has to be opened from above, for the deep coloration defines it very clearly.

The recent production of colourless flavine* (5-amino-acridine) suggested to one of us (V.B.) the making of a solution similar to violet-green, but containing, instead of 1% of equal parts of crystal violet and brilliant green, 1% of colourless flavine, in the same solvent—namely, equal parts of rectified spirit and water. The presence of water appears to be, in general, a necessity for the full development of antiseptic action; and, in connexion with that requirement and the pale yellow powder with which this paper is concerned, an analogy may be drawn between it and another and very homely yellow powder, called mustard, which, pungent and tear-provoking when mixed with water, can yet as a dry powder be placed on the tongue without any taste or discomfort. The spirit is added to counteract the grease of the skin, which checks a purely watery solution from spreading itself and delays absorption.

It should be noted that colourless flavine is not really colourless, but has a pale lemon tint, which just stains sufficiently to show the limits of its application—a very desirable property in any antiseptic used for the skin. To make the solution, the flavine is first dissolved in the water and then the spirit is added.

Method of Application.—The skin of the operation area, having undergone the usual cleansing, is first painted with the solution and then covered with a piece of double-thickness lint,

* Made by Glaxo Laboratories, Ltd.

soaked to capacity in the solution; this in turn is covered by a sheet of waterproof material and fixed on by a binder or bandage. The compress is applied 6 hours before the operation, and is removed on the operating table.

Bacteriological Tests.—These were carried out on 38 consecutive cases prepared for abdominal section. In each case, when the compress was removed, a platinum loop was made to streak the prepared skin surface and was then streaked on the surface of human blood-agar in a Petri dish. Four such streaks were made from different parts of the prepared area and were streaked on four different areas of the plate. As a control, four similar streaks were taken from an area of skin just outside the prepared area and streaked on the surface of another blood-agar plate. Multiple streaks enable a judgment to be made between growth indicating permanent diffuse infection and growth indicating chance contamination or loop-holes in the preparation.

Results

Prepared Areas.—Of the 38 plates from the 38 prepared areas, 29 showed no growth at the end of four days' incubation and 9 showed growth. Of these 9, one exhibited it on 3 of the 4 streaks, four on 2 of the 4 streaks, and four on 1 streak only. No plate had growth on all 4 streaks. Moreover, the bacterial colonies were few and isolated, except on the plate which showed growth on 3 streaks, and in this case there were other reasons to believe that the preparation had not been carried out thoroughly. As regards the growth on the other plates, these too were probably due to imperfect preparation, though in lesser degree. The effect of the antiseptic, however, is best displayed by comparing the number of sterile streaks with those not sterile; for of the total 152 streaks made from the prepared areas only 15 showed growth. From these the following organisms were identified: *Staph. aureus haemolyticus*, from 9 streaks; non-haemolytic *Staph. aureus*, from 1 streak; and *Staph. albus*, from 9 streaks.

Controls from Unprepared Areas.—All the 38 plates from the 38 unprepared areas showed growth at the end of four days' incubation. Growth occurred on all four streaks in 36 of them, and on three out of four streaks in 2. Counting the number of streaks instead of the number of plates, it is seen that of the 152 streaks made from the unprepared areas 150 showed growth and only 2 remained sterile. The growths in most cases were profuse, and the following organisms were identified: *Staph. aureus haemolyticus*, from 118 streaks; non-haemolysing *Staph. aureus*, from 10 streaks; *Staph. albus haemolyticus*, from 17 streaks; non-haemolysing *Staph. albus*, from 86 streaks; *Str. haemolyticus*, from 1 streak; non-haemolysing streptococcus, from 16 streaks; *Staph. citreus*, from 4 streaks; and diphtheroid organisms, from 30 streaks.

In addition to these tests one of us (S.A.), in order to ascertain the depth to which the antiseptic effect reached, on 13 occasions took cultures from the cut edge of the skin after the incision was made. In 12 cases no growth occurred, but in the remaining case *Staph. aureus haemolyticus* grew. This was the same case in which 3 of the 4 streaks taken from the prepared area showed growth and in which there was a strong suspicion that the area had not been properly prepared.

Discussion

It is to be noted that *Staph. aureus haemolyticus* was by far the commonest organism recovered. It occurred in 35 of the total of 38 plates taken from the unprepared areas, and the frequency on the skin of an organism so potent for mischief gives all surgeons cause to think furiously. The danger to surgical achievement which lurked in unsterilized skin, and the need to abolish it, were taught by the great thinker Lister. Then, in reaction, arose the soap-and-water school, headed by Lawson Tait, which asserted that simple cleanliness was enough: that good surgical results can be so attained is true, for healthy tissues have strong resisting powers. Later still, another school of thought emerged which, recognizing the difficulty of completely sterilizing the skin, employed as the chief line of defence cotton or rubber sheeting to cut out the skin—and this remains the usual practice to-day. But, although the soap-and-water school as such has disappeared, there remain some persons who, believing that swabbing with an antiseptic immediately before the operation sterilizes the skin,

unknowingly depend on what its adherents depended on. The bacteriological investigations carried out in connexion with violet-green showed quite conclusively that such brief applications do not effect sterility, though they do enfeeble the organisms so that growth on the agar plate is delayed as compared with that on the controls. Iodine is the best of these perfunctory applications, because it has superior power of penetrating organic material—a quality made use of in the sterilizing of catgut.

Organisms entrenched in the skin are very stout enemies, and to knock them out a vigorous and, above all, prolonged attack is required. Those who do not appreciate this fact ascribe the satisfactory healing of the wounds they make to the perfunctory measures they have taken, though in reality they owe it to that natural tissue resistance which enabled the soap-and-water school to make good its claim. But every now and then the enemy gains a foothold, and failure of the wound to heal kindly leaves the operative result something less than perfect and the surgeon with his pride hurt—and sometimes worse things happen. Surgical success depends on so many factors that the share taken by rigid antisepsis cannot be assessed in figures, though it can be perceived by anyone who studies attentively over a number of years the results of different surgeons practising different degrees of antisepticity. But whatever the share is, everyone must agree that operative infection arising from the skin is a theoretical possibility, and it is the duty of a surgeon to close all doors against all possibilities, theoretical or otherwise. To ensure, as far as may be, initial sterility of the skin should be the first line of defence against infection from the skin, and sheeting the second line, in case the first fails. For those who object to violet-green on the score of staining, the solution we describe, if used in the manner set forth, efficiently and inoffensively sterilizes the skin.

Our thanks are due to the pathological department of Cheltenham Hospital for the work it has done for us.

PITUITARY CACHEXIA TREATED WITH CORTICOTROPHIC HORMONE

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Panhypopituitarism, not the result of pituitary necrosis following pregnancy, has been regarded as a clinical entity (Fraser *et al.*, 1941). We (Hemphill and Reiss, 1940, 1942) have described cases in which severe melancholic depression associated with clinical pituitary cachexia—namely, emaciation, asthenia, loss of hair, desiccated skin, and low output of 17-ketosteroids—developed after the menopause. Although there was usually evidence of polyglandular insufficiency, where the skin was dry, hair brittle, and 17-ketosteroids low with subjective complaints that the “bowels did not operate,” adrenocortical failure seemed the most important endocrine disturbance. On this hypothesis a number of such cases have been treated with corticotrophic hormone. This treatment was on the whole promising, and early results have been recorded already (Hemphill and Reiss, 1940, 1942). The case described below showed such extreme emaciation that the picture was that of advanced Simmonds's disease. Complete physical recovery followed treatment with two courses of corticotrophic hormone. The mental condition cleared up some time later.

Case Record

A woman aged 41 was admitted to the Bristol Mental Hospital on Dec. 21, 1940. She was married, but had never been pregnant. There was no history of antecedent mental or physical illness. The menses ceased abruptly at the age of 39 without hot flushes or other subjective menopausal disturbances. About six months before admission she became depressed, lost appetite, and imagined that her viscera were deranged and the bowels “stopped up”; she attempted suicide. This was the mental condition on admission. Physically she was thin, weak, and frail-looking; height 5 ft. 6 in.,