FIG. 3.—Trial 3, showing 200 mg. of quinalbarbitone to be superior to 400 mg. of methypyrlyone.

FIG. 4.—Trial 4, in which there was no important difference between 100 mg. of quinalbarbitone and 400 mg. of methypyrlyone.

and 200 mg. of ascorbic acid as hypnotics. To reach this conclusion 51 patients were studied, of whom 24 stated there was "no difference" between the drugs. The second trial (Fig. 2) showed that 400 mg. of methypyrlyone was superior as a hypnotic to 400 mg. of ascorbic acid. This study required only 12 patients, as 8 stated a preference for powder A, and 4 "no difference" results were obtained. Trials 3 and 4 were planned to allow a comparison to be made of the hypnotic effect of 400 mg. of methypyrlyone with the hypnotic effect of quinalbarbitone in the commonly prescribed doses of 100 or 200 mg. The results (Fig. 3) indicated that 200 mg. of quinalbarbitone was superior to 400 mg. of methypyrlyone; the "eastern" boundary was crossed after 37 preferences and there were 30 "no difference" results. When the hypnotic effect of 400 mg. of methypyrlyone was compared with that of 100 mg. of quinalbarbitone, no important difference was found; this trial required 40 patients, 16 of whom found "no difference" between the drugs.

Discussion

There are many factors which can be considered while comparing the therapeutic value of two hypnotic drugs. The present trials have not sought to define the time of onset of hypnotic action, or its duration, the presence of disturbing dreams, or toxic effects. In this study, only the patient's judgment of the quality of sleep after different hypnotics has been used. It is interesting to note, however, that the data obtained during these clinical trials also permit of some comment on the degree of correlation existing between a clinician's assessment and that of the nurse. When the preferences for the sequential analysis were based on the nurses' considered opinions, the paths travelled in the same directions as in Figs. 1-4, but more slowly. The latter was due to the greater number of "no difference" results offered by the nurses.

Summary

The hypnotic effect of methypyrlyone (noludar) has been compared with the hypnotic effect of quinalbarbitone, using the double-blind technique. Powders of ascorbic acid were used as a control. The results were assessed by sequential analysis.

No important difference could be detected between the apparent hypnotic action of 200 mg. of methypyrlyone and the control powder. When the hypnotic effects of 400 mg. of methypyrlyone and 100 mg. of quinalbarbitone were compared no important difference was discovered.

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RATIONALE OF ANTIHISTAMINIC THERAPY IN THERMAL INJURY AN EXPERIMENTAL EVALUATION IN THE GUINEA-PIG

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Clinical trials with antihistamines in the early treatment of burns suggest that these drugs, applied locally or given orally, are useful in combating pain, blistering, oedema, and infection, and consequently in accelerating healing (see correspondence in the *British Medical Journal*, cited by Sevtitt, Bull, Cruickshank, Jackson, and Lowbury, 1952). This clinical finding is consistent with Lewis's (1927) observation that the triple response elicited by pricking histamine into human skin is also induced by thermal injury, and with the fact that histamine is readily released *in vitro* by heat from the skin of various species of animal (Rosenthal and Minard, 1939). However, in human volunteers given an oral antihistamine immediately after experimental burns were made, Sevtitt *et al.* (1952) could not confirm the clinical findings; and the increased vascular permeability induced by high-temperature burns in rabbits (Weeks and Gunnar, 1949) and by thermal injury in anaesthetized guinea-pigs (Sevtitt, 1949) is not antagonized by high doses of antihistamines. Evidence of this kind from the rabbit and guinea-pig must be given

considerable weight because in each animal histamine has the same high order of permeability-increasing potency as it has in man (Miles and Wilhelm, 1958a).

In re-examining the possible role of histamine in thermal injury, we investigated the response in guinea-pig skin to a *minimal* injury that consistently induced a substantial increase of vascular permeability. A minimal injury avoids two factors that possibly complicated the interpretation of the work of Weeks and Gunnar (1949) and of Sevi (1949): firstly, the pharmacological picture is less likely to be complicated by non-specific breakdown products that almost certainly appear after high-temperature injury; and, secondly, since the stimulus is not painful, it permits the investigation to be made in unanaesthetized animals, thus avoiding the depression which anaesthesia induces in the permeability response of the peripheral vessels (Miles and Miles, 1952).

After establishing the maximal tolerable stimulus first on ourselves and then on guinea-pigs, thermal injury was induced by applying a copper disk, 9 mm. in diameter, maintained at a temperature of 54° C. by flowing water at a constant temperature, to the depilated skin of the back of the trunk of guinea-pigs for periods up to 30 seconds. This degree of heat stimulus is so mild that it can be applied to completely unrestrained animals without their moving away from the disk. The animals, 650–750 g., were previously given intravenous pontamine blue, 50 mg./kg. Such animals are referred to as “blueed.” Increased vascular permeability at the heated sites, indicated by the local exudation of the blue dye, was graded —, ±, +, ++, +++, up to +++++; ± represents the faintest trace, and +++++ an intense dark blue.

We found at heated skin sites two distinct permeability responses: an immediate response, best elicited by five seconds’ heating, which appears in less than one minute, and is almost certainly mediated by liberated histamine; and a delayed response, which appears one hour after 20 seconds’ heating and which is apparently not induced by histamine, or in any way dependent on the magnitude of the immediate response to liberated histamine which precedes it.

The Immediate Response

Skin sites heated at 54° C. for five seconds become erythematous in 30–40 seconds, and blue after a further 5–10 seconds; the blueing is maximal (++ to +++) in five minutes (Fig. 1). Tested by the technique of Miles and Miles (1952), the permeability of the blood vessels in the heated skin returns to its normal low level in 10 minutes (Fig. 2, A). The heated skin neither blisters nor becomes necrotic.

This immediate response is highly susceptible to anti-histamines previously injected locally into the skin or given intravenously. In our hands the preferred antihistamine in guinea-pigs (Mason and Wilhelm, to be published) is triprolidine (“actidil,” see Green, 1953). The prior *intracutaneous* injection of 2 µg. of triprolidine base in 0.1 ml. of saline into the test site consistently decreases responses of ++ to +++ to less than ±, and even 0.02 µg. has a substantial effect (Fig. 1). However, the application immediately after heating of lint squares soaked in a 1% solution of triprolidine does not affect the response. Thermal lesions were also compared in the same animal before and after the *intravenous* injection of triprolidine. Intravenous triprolidine antagonized the immediate response even more effectively than intracutaneous; doses of 100 µg./kg. decreased responses of ++ to +++ to less than ±, and of as little as 10 µg./kg. to ± (Fig. 1).

In unblued guinea-pigs, slight oedema of the heated skin corresponded in onset and development with local blueing in blued animals, and had the same susceptibility as local blueing to intravenous triprolidine. Erythema, however, was not affected by triprolidine.

Eight other antihistamines, in intravenous doses of 1 mg./kg., each substantially antagonized the immediate response in blued animals; but in doses of 0.1 mg./kg. they decreased the response in the following descending order of potency: triprolidine, mepyramine, chlorpheniramine, tripropellamine, promethazine, diphenhydramine, chlorcyclizine, thenalidine, and antazoline, the last two having only a slight effect. These drugs are effective in practically the same order as inhibitors of the permeability increase induced by intracutaneous histamine and by the histamine-liberator 48/80.

FIG. 1.—Maturation of the immediate permeability effect in the blued guinea-pig during the 30 minutes following a mild heat stimulus to the skin (A); and the influence of prior treatment with the antihistamine triprolidine, 0.02 µg. (B) and 2 µg. (D) intracutaneously, and 10 µg./kg. (C) and 100 µg./kg. (E) intravenously.

FIG. 2.—The biphasic nature of the permeability effect of a moderate heat stimulus in the skin of the guinea-pig.

The high susceptibility of the immediate response to small doses of antihistamines suggests that only small amounts of histamine are liberated. This is supported by the low histamine content that we found in intercellular perfusates (Miles and Wilhelm, 1958b) from skin strips, 10 by 30 mm., which had been heated *in vivo* (0.015–0.03 µg. of histamine per heated strip, compared with <0.007 µg. per control strip). Furthermore, when finely chopped and washed skin from normal animals was heated in Locke's solution at 54° C. for five seconds to five minutes, the Locke's solution contained only 1–5% of the histamine liberated by heating at 95–100° C. for five minutes (cf. Rosenthal, Samet, Winzler, and Shkolnik, 1957). Skin, in pieces 5 by 5 mm., heated at 98° C. for five minutes yielded only 20% of its

histamine (cf. Rosenthal *et al.*, 1957). All the liberatable histamine was, in fact, released at this temperature, because when this heated skin was finely chopped the remaining 80% readily leached into the suspending fluid.

The Delayed Response

Sevitt (1958) records that, in anaesthetized guinea-pigs, heating at 60° C. for 10 seconds induces substantial local oedema maximal eight hours after injury. We induced a similar delayed response in our unanaesthetized animals by heating for 20 seconds at 54° C. The immediate response was now minimal, being represented by only a thin ring of blueing not more than 1 mm. wide at the periphery of the heated site; and, like that to 54° C. for five seconds, it was abolished by prior antihistamine treatment. However, after a half to one hour, additional blueing appeared within the peripheral ring of colour, and the entire lesion became evenly blueed (++ to ++++) during the next two to three hours. This delayed response is illustrated by the experiment recorded in Fig. 2, B, in which intravenous dye was given to animals bearing lesions from one minute to 30 hours old.

In anaesthetized animals, heating at 58° C. for 10–20 seconds hastened the development of the delayed response; but, even so, central blueing did not appear until the lesions were 5–10 minutes old, and took 60–90 minutes to mature.

We were unable to identify the permeability factor mediating the delayed response. Intravenous triprolidine, 0.1–1 mg./kg., given before or during the development of the lesions, did not affect the response; and inhibitors of the globulin permeability factor in guinea-pig serum and tissue fluid of the skin (Miles and Wilhelm, 1955, 1958b; Wilhelm, Miles, and Mackay, 1955) were also ineffective.

The serum-globulin permeability factor in the guinea-pig, as well as in other species, including man (Mill, Elder, Miles, and Wilhelm, 1958), is a protease that is highly susceptible to soya bean trypsin inhibitor (S.B.T.I.) and to the esterase inhibitor di-isopropyl fluorophosphonate (D.F.P.; see Becker, 1958; Miles and Wilhelm, 1958a). Injected locally into the skin, both before and during the development of the delayed response, relatively large doses of S.B.T.I. and of D.F.P. each failed to affect the response. Intravenous S.B.T.I. also was ineffective; and, contrary to Spector and Willoughby's (1958) finding in the rat, intraperitoneal D.F.P. in our guinea-pigs induced only a non-specific depression of the vascular responsiveness. The immediate response was also insensitive to local S.B.T.I. and D.F.P.

Summary and Conclusions

Mild heat treatment of the skin of the guinea-pig is followed by an immediate and short-lived increase in vascular permeability, which is mediated by histamine. With moderate heat treatment the immediate response is followed by a delayed and more prolonged response, which, so far as our evidence goes, is mediated neither by histamine nor by other recognized endogenous permeability factors.

If it is justifiable to generalize from the guinea-pig to man, then we expect a substantial liberation of effective histamine only in the very mild burn with no ostensible damage to or rupture of the skin; and little or none in moderate or severe burns, owing to changes in the tissues that either inhibit histamine liberation, restrain the movement of liberated histamine to susceptible blood vessels, or otherwise alter the capacity of the vessels to manifest a permeability effect.

Since the histamine effect lasts only 10 minutes, in any efficient treatment of mild burns by an antihistamine, the drug would have to be applied within a few minutes, either locally in a form capable of rapid pene-

tration of unbroken skin or intravenously. Moreover, since the intensity of the delayed vascular response we observed was not diminished when the early histamine effect was neutralized, the antihistamine would do nothing to inhibit these delayed effects, even supposing the burn were severe enough to induce them.

It is possible, however, that histamine liberated and held in the tissue of more severe burns might later be released to the detriment of surrounding tissues and consequently that prophylactic antihistamine might diminish later deleterious responses to the injury. An *in vivo* experimental proof of such an action in severe burns was beyond the scope of this investigation.

As regards the delayed permeability response, the time relation of which is similar to that induced in the guinea-pig by bacterial infection (Burke and Miles, 1958) and certain bacterial toxins (Elder and Miles, 1957), we have as yet no evidence of the nature of the mediating factor and can offer no rationale for its treatment.

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Minds Matter: A New Approach to Mental Health is the title of a 62-page booklet published by the Conservative Political Centre on behalf of the "Bow Group." The author, Miss BERYL COOPER, is a 30-year-old Birmingham graduate who is stated to have worked for seven years in the Hospital Service, three of them "as hospital secretary at a teaching hospital in London." After an introductory chapter on the extent of the present problem, Miss Cooper discusses in turn past and present legislation on the care of the mentally ill, the Royal Commission's report, local responsibilities and voluntary sources of help, costs and staffing, the administrative structure, and community services. She ends with a "four-point plan for mental health": (1) Certification to be abolished, with admission to mental hospitals to be voluntary whenever possible and with a procedure as simple as with general hospitals. (2) Most patients to be treated at home so that they do not become cut off from the community. (3) Hostels for milder cases and the old, training-schools for the younger, and more "day" and "night" hospitals to be built. (4) 138 new committees to take over hospital administration now shared between 14 regional boards and 400 management committees, and be financed by five-yearly direct Government grants.