Original Articles

THE INTRADERMAL METHOD OF INJECTING HYDNOCARPUS PREPARATIONS IN LEPROSY

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THERE is a consensus of opinion among those who have used the intramuscular and intradermal methods of injecting hydnocarpus preparations in leprosy that the latter is much more effective than the former. Given intramuscularly we have only the general effect of the drug; whereas when injected into the skin lesions the local effect is superadded to the general, and possibly the general effect is increased by this method as will be pointed out later.

It is not difficult to demonstrate the relative effectiveness of the intradermal method, by choosing a patient with marked symmetrical lesions and injecting intradermally the lesions in the one side of the body, leaving those on the other side as a control. While both sides may show improvement, the progress made on the injected side is much more marked.

The question arises, how does intradermal infiltration act in clearing up leprotic lesions?

(1) There can be no doubt that a very important part of the action is due to the local irritant effect of the drug. There is the primary acute effect when infiltration takes place into the intercellular spaces and a more prolonged though milder effect after the esters have been absorbed by the local cells. Sections of infiltrated areas show that esters persist in the cells for many months, and there is clinical evidence that after a single infiltration improvement continues for a very long period.

(2) It has not yet been proved whether hydnocarpus esters produce any special local effect on the *M. lepræ* apart from the counter-irritation caused by their physical properties.

In other words, would another preparation possessing equal absorbability by the local cells and equal irritating power be as effective in its local action? That is a question which it should not be difficult to decide by controlled experiments. To do this patients with marked, extensive, symmetrical lesions should be chosen, lesions of the one side of the body being infiltrated with hydnocarpus esters and those of the other side with the drug to be tested. The attached photographs (figs. 1, 2 and 3) show the effect in a patient whose right side was infiltrated with hydnocarpus esters and the left side with sodium hydnocarpate solution.

(3) The third part of the action of hydnocarpus esters when infiltrated into the dermal lesions is somewhat hypothetical. The breaking down of lepromata due to the local action of the esters probably leads to the setting free

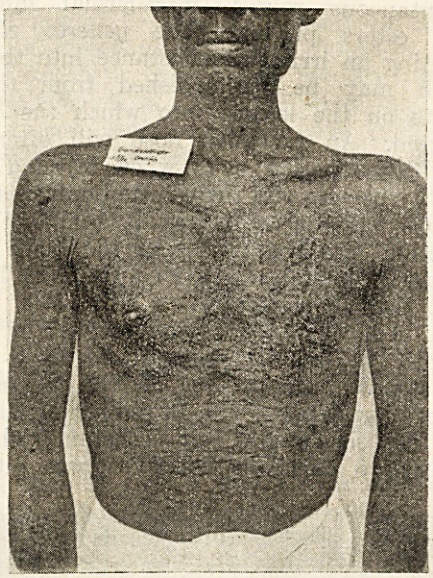

Fig. 1.—Right side was infiltrated with hydnocarpus esters—the left simultaneously with equal doses of 3 per cent. sodium hydnocarpate solution.

in the body of antigens of *M. lepræ* and encourages the formation of antibodies, in other words internal autovaccination is carried out.

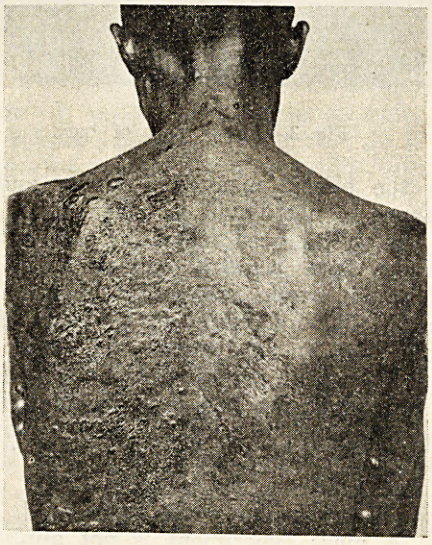

Fig. 2.—Upper part of back of same patient.

Various attempts have been made to treat leprosy by inoculations with suspensions of *M. lepræ*. This form of treatment is rendered difficult by our inability so far to cultivate this organism outside the human body. There is reason to believe, however, that a similar effect

(autovaccination) is secured as one of the several benefits of intradermal infiltration of lepromata.

(4) In common with the intramuscular and subcutaneous routes, intradermal infiltration with esters produces the *general* effect of injecting an irritating substance into the body, which may be distinguished from the *local* effects on the lesions into which the drug is injected. An excessive dose will often cause a febrile reaction even when injected into a healthy person, and there is no doubt that many leprous patients are markedly benefited by the injection into the tissues of the body of any irritating substance provided the dose be sufficient and not excessive.

(5) The fact that hydnocarpus or chaulmoogra oil and its preparations have become the standard drugs used in the treatment of leprosy predisposes one in favour of the belief that this oil contains some substance which has a curative effect in leprosy, apart altogether

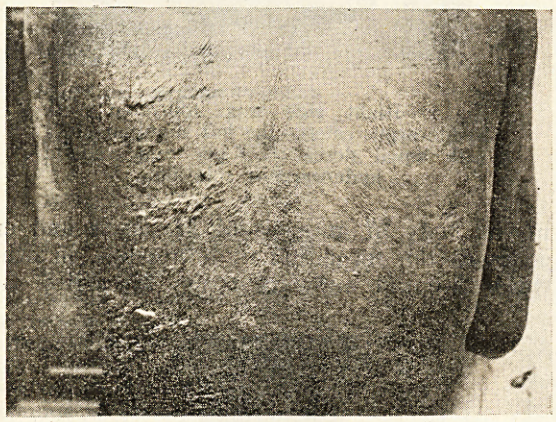

Fig. 3.—Lower part of back.

from the effects mentioned above and which substance is not found in other oils.

It has so far been found impossible to carry out on a large scale a well-controlled experiment which would prove this in a convincing manner. The difficulties in the way of carrying out such an experiment are many :—

(*a*) In such an experiment it would be necessary to exclude the first four effects of injecting hydnocarpus oil or esters, that is to say if the intradermal method were used; and the third and fourth effects would have to be excluded if the intramuscular route were used.

(*b*) A mass experiment is not applicable to a disease which does not yield to mass treatment. There can be no doubt that good therapeutic effects in leprosy can only be looked for when each individual case is studied and treated separately. After all the most important part of the treatment is to raise the general resistance of the patient, and this is done largely by dealing with accompanying diseases, errors of diet, harmful habits, etc. These predisposing causes vary in every case. Thus each case must be studied carefully before treatment begins. Also injections of hydnocarpus have to be regulated throughout the treatment according to the resistance of the patient and according to the effect produced by the previous injection.

(*c*) A third difficulty in carrying out such a controlled experiment is that progress under any treatment is slow. If injections are given compulsorily, against the will of the patient, then their beneficial effects are apt to be negatived to a certain extent by the psychological condition of the patient. Treatment is seldom effective without his willing and intelligent cooperation. On the other hand if volunteers are chosen for such an experiment it is often difficult to get sufficient suitable cases together and to persuade them to undergo treatment for a sufficiently long time. This is especially so in the case of the controls who would have to be injected with some inactive substance which the patient could not distinguish from hydnocarpus.

The form of controlled experiment which is likely to be practicable is to find out a substance, such as the ester of another oil, and, using hydnocarpus esters as the standard, test it out by the intradermal method as to its power to clear up marked lesions. This can be done by the method mentioned in the second paragraph of this paper. Having secured a drug with powers equal to the standard in clearing up local lesions, it should be tested out in a large-scale comparative experiment, every second patient that appears would be treated with the new drug, alternate patients being treated with the standard.

By following out this method many of the objections to an experiment with a neural control are obviated. A number of years would be required to carry out the experiment convincingly, but if the cases treated with the new drug showed results equally beneficial to those shown by the standard, one would be justified in stating that the standard did not contain special beneficial qualities differing from or in excess of those of the new drug.

Technique for giving intradermal injections

The low viscosity of hydnocarpus esters as opposed to hydnocarpus oil makes the former more suitable for infiltration than the latter. The oil however if pure and of low irritating power can be used after heating to about 45°C. to make it as thin as possible. Any needle of medium thickness may be used, but if the esters are used a fine needle is preferable. If many patients have to be treated as is the case in a leprosy clinic we may use a short, guarded needle with a point about 3 mm. in length and a collar which prevents the needle entering further than that distance into the skin. With this needle a practised worker can

give some 100 punctures in a couple of minutes and infiltrate some 5 or 6 c.cm. in an area of some 14 square centimeters. Not more than about 0.03 c.cm. (½ a minim) should be injected at any one point. The needle should be sloped so that the drug enters the corium, not reaching the subcutaneous tissue except in cases where the subcutaneous tissue is leprotic. On the other hand it should not be injected too superficially into the epithelium. If correctly infiltrated a wheal of about 8 to 10 mm. diameter should at once rise round the puncture as a centre, or at least the skin markings over this area should stand out in marked relief as compared with the surrounding skin. As to what areas of the body surface should be infiltrated it may be stated that all regions of the skin showing deep analgesia are suitable for this purpose. In advanced cutaneous leprosy this may involve almost the whole skin surface. In such cases the spaces between the punctures should be increased so that at each sitting it is possible to cover a fairly large area. In this way, giving infiltrations once or twice a week, it may be possible to cover the whole area of the body in about ten months. On returning to the parts first treated after this period it is generally found that they have improved considerably in appearance and that the deep analgesia has distinctly diminished. Thus on reinfiltration of the skin for a second time more pain is felt by the patient, but he is generally willing to submit to this because of the marked improvement which he himself can notice in his lesions.

In patients with comparatively few macules all the lesions may be infiltrated in a few sittings. Reinfiltration of a lesion should not take place until all induration caused by the former injection has entirely disappeared; this is generally three or four weeks. When the lesions are few and small in size they may all be infiltrated at one sitting and the patient may be told to return after a month's time. Or he may be given weekly intramuscular or subcutaneous injections in the interval until the lesions are ready to be reinfiltrated. In patients with high general resistance and a few early lesions not showing acid-fast bacilli six infiltrations at monthly intervals are generally sufficient to clear them up. When acid-fast bacilli are present a longer course is necessary and weekly injections should be given, these being intramuscular when sites for intradermal injections are not available.

In cases of neural leprosy in which acroteric lesions with glove-stocking anæsthesia are present, infiltration should be given first at the proximal margin of these lesions, working down gradually towards the periphery. As these are ascending lesions the proximal part is the last to be affected and therefore clears up most rapidly on infiltration. Care should be taken in treating the dorsum of the foot to infiltrate only a small portion of the skin at any one sitting, as, if the patient is walking about, an extensive infiltration is apt to lead to considerable pain and swelling because of the dependent position of the part.

With regard to the drugs used for infiltration it is important that these should be of low irritant quality. The esters prepared at the Calcutta School of Tropical Medicine mixed with 4 per cent. creosote have been found uniformly non-irritating. These esters are prepared from a pure quality of oil. The method adopted by the Culion Leper Colony as described in the appendix of the report of the Manila Leprosy Conference (*Philippine Journal of Science,* April 4, 1931) is applicable to oils of less purity, the excessive irritant qualities being removed by the process, especially by heating for a definite time at a definite temperature with half per cent. iodine. One of the objections formerly raised to the intramuscular injection of hydnocarpus oil, was that it took a long time to absorb and that in consequence indurated areas or even abscesses were formed which were slow in disappearing.

In the intradermal method delayed absorption is proving an asset rather than a disadvantage, as the slow absorbability of the drug secures its presence in the cells of the infiltrated areas for a long time and the continuation during that period of the beneficial effect; whereas a watery solution like that of sodium hydnocarpate is quickly absorbed. There is evidence that the local effect of a slowly absorbed preparation like the esters in an infiltrated leprous lesion is of much more importance towards the recovery of the patient than the general effect of a form of the drug which is quickly absorbable, such as the watery solution of sodium hydnocarpate: *vide* experiment referred to in (2) and figs. 1, 2 and 3. Hydnocarpus esters have generally been selected as the preparation of choice for intradermal infiltration. The pure oil has generally been considered too viscous or too slow in absorption for the purpose. It has been found however that by heating the oil to about 48°C. before injection its viscosity is considerably decreased, and if not more than 0.03 c.cm. (½ a minim) is injected at each puncture, the initial reaction caused by the infiltration soon passes off. A simple method of heating the oil to the right temperature is to place it in a separator inside an asbestos-lined box; a thermometer is immersed in the oil and projects through the cork at the top of the separator and through a hole in the top of the box. The outlet and stop-cork of the separator project through a hole in the bottom of the box. The oil is heated by means of an electric bulb placed inside the box alongside the separator or by means of a lamp or gas jet. In countries where many indigent patients have to be treated, and where a good supply of pure oil pressed from ripe

fresh hydnocarpus seeds is available, the advantage of being able to substitute the oil for the esters is obvious. Pure hydnocarpus oil of low irritant quality can generally be obtained in India at one rupee a pound or less.

A comparative experiment is being carried out on the lines indicated above to show the relative values of the oil and the esters, but the result of this is not yet available.

'MERCUROCHROME-220 SOLUBLE' IN LEPROSY WORK

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Introduction

'MERCUROCHROME-220 SOLUBLE', a complex organic preparation of mercury containing from 23 to 24 per cent. of metallic mercury, has been in use practically since 1922. According to Solis-Cohen (1928), Piper seems to have been the first in America to utilize therapeutically the germicidal properties of this preparation, by administering it intravenously in puerperal and post-operative septicæmias. Following the initiative of Piper in America, physicians and surgeons in other parts of the world began to utilize increasingly this mercurial preparation in all septicæmic conditions, and a fairly extensive literature has now accumulated on the use of this preparation. As is the case with so many of the newer organic mercurials and arsenicals, this drug also seems to have been used in various diseases; and with the passage of time the limitations to its use have become apparent.

A close study of all the available literature concerning this drug shows that it acts almost like a 'specific' in *B. coli* infections; and remarkable success has been claimed for it in cases of septicæmia due to *Streptococcus hæmolyticus*, and staphylococcus; but rather disappointing results are reported in cases of gonococcal arthritis in particular. Thus Redewell and Potter (1925), who have used mercurochrome intravenously in 496 cases of gonococcal arthritis, report only 24 cures with mercurochrome alone, which comes to roughly 5 per cent. This evidently means that the drug by itself has practically no value in gonococcal arthritis. The same authors, however, record in the same communication, that they obtained brilliant results in 'complicated' cases of arthritis.

What exactly they mean by 'complicated' is not clear. We take it that they mean arthritis of undetermined ætiology—possibly due to mixed infections.

Also it is now clearly recognized that mercurochrome has got the following advantages over the other mercurials:—

(*i*) It is comparatively non-toxic.
(*ii*) It is a more efficient germicide.
(*iii*) It has a remarkable penetrating power.

In short, it may be said that this preparation approaches Ehrlich's ideal of a *therapia sterilans magna* much more than the other mercurials, organic or inorganic.

A study of the literature on this drug further reveals that in cases of arthritis of obscure or undetermined origin (which form a considerable proportion of our patients in this country, specially in institutions which care for a large number of lepers of different types and stages) it has given fairly good results.

It is a matter of common experience with workers in leper asylums and colonies, in this country, to meet with numerous cases of acute and chronic sepsis, arthritis, myositis, neuritis of leprous or possibly of non-leprous origin and vague pains all over the body. In such cases although they may yield to one or other of the many empirical remedies in use at present, still the relief obtained in the majority of instances is only temporary. Even non-specific protein-shock therapy, which has so far been regarded as a panacea in these cases, has failed to give permanent relief. So any remedy which promises to give lasting relief is worth a serious trial.

With this object in view, we tried Mercurochrome-220 soluble in one case presumably of acute sepsis, in a few cases of chronic sepsis, in intractable arthritis, and in vague nerve pains, and our results are recorded in this paper. As will be seen later, in some of these cases at least, almost all of the hitherto advocated forms of treatment had been tried and mercurochrome was used as a last resort.

As we have had the opportunity to treat a few cases of *B. coli* infections also with mercurochrome, such cases are also recorded, to confirm the value of this drug in such cases.

Dosage and method of administration

As suggested by J. H. Hill (1924) and Young (1924), we have used a 1 per cent. solution of the drug in distilled water intravenously. The dosage recommended by the above-quoted authorities was strictly adhered to in the first few cases. But, as the symptoms of mercurialism that appeared after the injection were rather troublesome to deal with and as the febrile reaction to injection which sets in usually within about 4 hours after the injection was fairly high, we thought it advisable to give slightly small doses of the same strength of slightly smaller doses of the same strength of often as we considered it necessary. The results, as will be seen from the clinical reports of the later cases, have amply justified our departure from the recommended dosage. We