

STAINING BY IODIZED DRUGS

To the EDITOR:

I have recently been visited by a representative of one of our leading drug firms who have been requested by their home office to find out about the staining of the skin by iodized ethyl esters in intradermal use. I noticed that that effect was very marked when we visited Culion. It is still more marked in the rather lighter Chinese, and I should imagine it is very bad in white-skinned races. I recall being told that eventually the stain disappeared completely, but can you add to the information by telling me how long it takes in doing so? These people are really rather worried about it.

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JAMES L. MAXWELL, M.D.

To the EDITOR:

I would like to inquire about experience with trouble from pigmentation of the skin following intradermal use of iodized esters with benzocain. We use 0.5 per cent iodine and 2 per cent benzocaine, as stated in my paper.*

Administration Headquarters
Nauru
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ALAN M. B. GRANT, M.B., B.S., (SYD.)
(Acting Administrator)
Government Medical Officer

Reply from Dr. José Rodriguez, Chief, Eversley Childs Treatment Station,
Cebu, P. I.:

The staining produced by the intradermal injection of the iodized ethyl esters is proving to be a handicap to this otherwise very useful treatment in the circumstances under which we work. When the intradermal method was first started at Culion there was of course no way of knowing how long the stains would remain. We noted in a number of instances that in sites which had been

* The paper referred to will appear in an early issue.—EDITOR.

injected only once or twice the staining faded in from four to six months. This led us to hope at that time that the stains would not remain long. We have since learned, however, that in many of the cases repeatedly injected at the same site the stain remains for many years, perhaps permanently. We have seen cases in which the staining was still quite bad after eight years. On the other hand, we have also observed injected sites on which the staining had become markedly diminished after three years in spite of numerous repeated injections. There seems to be considerable individual variation in the duration of the staining, although as a general rule the greater the number of repetitions of the injections in one site the more long-standing will be the staining at that site.

At the present time we seldom use the undiluted preparation on the face or other exposed portions of the body for the intracutaneous treatment. When there is very marked erythema of the face we sometimes inject the drug undiluted, but this is not done more than once or twice. Such injections often improve the appearance of the patient by masking the flushing. When there is marked dilatation of the cutaneous blood vessels, such as is the case when there is much redness, the resultant staining usually does not remain long.

Our routine procedure at present is to mix the iodized ethyl esters and whole oil in varying dilutions, or else to employ the plain whole oil undiluted. The objection to the latter is that although the thickness of the oil itself can be overcome by warming it before injecting, it seems to be much more slowly absorbed than the iodized esters, so that after repeated intracutaneous injections the parts remain raised, boggy, and doughy in consistency, producing a deformity almost as bad as the original lesions. In our experience the addition of even small amounts of the iodized esters seems to favor absorption of the oil.

For the unexposed portions of the body we employ a half-and-half mixture of the oil and the iodized esters. For the face we combine the two drugs in varying proportions, depending on the degree of redness or flushing present, ranging from 1 part of the esters added to 9 of oil to 1 part of the former and 4 parts of the latter. Some of our attendants have become so skillful in determining the proportion to use that after a few treatments the resulting staining closely approaches the shade of the brown skin of our patients. At any rate, when these mixtures are used the absorption is fairly rapid and the staining is minimized and does not last very long.

We have not yet found any remedy for the staining once it has been produced. The condition may be improved, however, by repeated intradermal injections with purified oil to the stained area. Some of our paroled patients claim to have derived considerable benefit from local injections of milk at the sites, but we have not had the opportunity of checking up these results.

Reply from Dr. C. B. Lara, Chief Physician, Culion Leper Colony:

Referring to the question about the persistence of the dark stain following intradermal use of the iodized ethyl esters, I furnish herewith some recent observations which are to the point. They have to do with a group of 92 cases that were observed for periods up to practically three years between the date of the last intradermal injection given in the face and the time the patients were paroled. The data are given in the accompanying table.

TABLE 1.—Persistence of staining from iodized ethyl esters of *Hydnocarpus wightiana* oil in 92 cases observed for various periods before parole after the last intradermal injection.

Period after last injection before parole	Cases in group	Degree of stain								Total Stained	
		Definite		Slight		Very slight		None		No.	%
		No.	%	No.	%	No.	%	No.	%		
0 to 4 months ..	17	4	23.5	6	35.3	7	41.2	0	0.0	17	100.0
5 to 8 months ..	15	3	20.0	5	33.3	5	33.3	2	13.3	13	86.6
9 to 12 months ..	16	2	12.5	4	25.0	2	12.5	8	50.0	8	50.0
13 to 16 months ..	11	0	0.0	1	9.1	5	45.4	5	45.4	6	54.5
17 to 20 months ..	11	0	0.0	1	9.1	2	18.2	8	72.7	3	27.2
21 to 30 months ..	16	0	0.0	0	0.0	4	25.0	12	75.0	4	25.0
Over 30 months ..	6	0	0.0	0	0.0	0	0.0	6	100.0	0	0.0

It is seen that, though the stain may in some cases persist for nearly three years after injection, it disappeared within one year in over half of this group, and in the cases where it was still visible beyond that time it was only slight or very slight. Our cases are now being paroled after an average pre-parole negative period of from at least 12 months to nearly 2 years, and the question of stain is no longer important as the intradermal injections in the face are usually discontinued several months after the cases have been declared negative. If it becomes necessary to resort again to intradermal injections, uniodized preparations are usually employed.

As for the factors responsible for the persistence of the stain, it would seem that that of absorption of the drug is important. For this reason patients showing marked persistence of the stain are advised to stimulate circulation in the stained parts, especially by means of measures such as friction, massage, etc. The writer doubts whether the complexion has anything to do with the matter. Naturally, the stain will be more noticeable in light-skinned individuals and will be more apparent as long as it persists. A few very light-skinned individuals, like some of the mestizos we have in the Colony, have shown rather rapid disappearance of the stain. Nevertheless, persons of approximately the same complexion show very marked variation in the persistence of the stain.

Iodine staining by the injected drug may more or less limit the application of the intradermal method of treatment, especially among out-patients, a factor which should be given due consideration. However, the writer still prefers to continue the iodized ethyl esters as the standard anti-leprotic drug in Cullion because the added iodine seems to be beneficial therapeutically. Observations during the last three years have tended to confirm the writer in this opinion. A great majority of our patients do not seem to object to the stain; most of them expect to stay here for some years, and they have ample time for it to disappear before they are paroled. The possibility of obtaining a non-irritating iodized preparation that does not stain has been considered by the writer for some time, but unfortunately without success so far.

Reply from Dr. Robert G. Cochrane, Medical Secretary, British Empire Leprosy Relief Association:

The question of the staining property of iodized esters and the length of time the stain remains in the tissues is an important one, especially in the light colored races. I have been using iodized esters in European patients over the past eighteen months, and in one patient in particular the stain is still well marked, although some of the patches were injected as long as eighteen months ago. It is very difficult to say how long this stain lasts, but apparently it will last for at least a period of two years.

It is for this reason that I have largely ceased using iodized esters for European patients and am now using hydnocarpus oil and creosote. The drawback to this preparation is its viscosity, but if it is heated to about 50° to 55°F. it can be injected fairly easily. It is too early to make any comment with regard to the relative efficacy, but the irritation is no more than that produced by iodized esters although the initial injection is somewhat more painful owing, I presume, to the presence of creosote.

These remarks apply also to the creosoted esters. A firm in England made for me for a short time a preparation which was called Special Esters which did not produce any staining in the skin, but I had to cease using it because it was too irritating. A report on the relative efficacy of this preparation and the iodized esters is published in the April number of *Leprosy Review*.