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DESENSITIZATION FOR DAPSONE DERMATITIS

BY

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Sensitivity to dapsone occurring in a definite though inconstant proportion of leprosy patients is a well-recognized disadvantage of sulphone therapy. The unidentified allergen may be a modified sulphone molecule or a breakdown product formed in the liver. Some aspects of this sensitivity and of successful attempts at desensitization may be of interest to other workers besides leprologists.

Presenting Features

The commonest presenting features of sensitivity to dapsone are seen in the skin. Their gravity ranges from a relatively banal type of fixed eruption characterized by a few hypermelanotic macules (Browne, 1959) to a widespread bullous eruption proceeding to ulceration. On the other hand, a generalized sensitization of the skin may occur, with a diffuse papular irritating eruption—the "fifth-week dapsone dermatitis" of the early days of (high-dosage) sulphone therapy—which may be succeeded by a fatal exfoliative dermatitis (Allday and Barnes, 1951; Garrett, 1951; Barnes and Barnes, 1951) or by a widespread post-inflammatory hypermelanosis. If the superficial strata of the epidermis are sensitized, then cleavage may show itself clinically by toxic epidermal necrolysis (Browne and Ridge, 1961).

In addition to these cutaneous manifestations there may be systemic symptoms of serious import, such as persistent pyrexia ("drug fever"), severe generalized malaise, albuminuria, toxic hepatitis, lymphadenopathy (rarely proceeding to suppurative adenitis), leucopenia, severe and progressive anaemia, and acute psychosis. Any sign of sensitivity, cutaneous or systemic, may recur on subsequent ingestion of dapsone even in very low doses (of the order of 0.01 g. or less), or of a drug acting parallergetically. Such subsequent episodes may be more serious than the original reaction, and are sometimes fatal.

While sulphone dermatitis is probably of less frequent occurrence now than formerly, yet it still accounts in the aggregate for a considerable toll of suffering, and necessitates the interruption—or even the definitive suppression—of anti-leprosy treatment. The condition may arise within a few minutes of the ingestion of the first standard dose of 0.1 g. of dapsone. In patients who have had no access to clandestine supplies of the drug, the possibility of sensitization from a previous dose can be excluded, though parallergetic sensitization with a sulphonamide cannot always

be ruled out. More often, however, it appears after a few weeks of therapy on standard regimens of gradually increasing doses—that is, 0.1 g. twice weekly for three to four weeks, rising to 0.2 g. and then to 0.3 g. for similar periods, before attaining a maximum of 0.4 g. twice weekly for a patient weighing over 140 lb. (63.5 kg.).

Parallergetic dermatitis may occur in which a closely related compound—for example, diamino-diphenyl sulphoxide (Browne and Davey, 1961) or a sulphonamide—is implicated; more rarely, a chemically unrelated compound used in leprosy treatment—for example, thiambutosine or ditophal—or even a barbiturate or an antihistaminic, may provoke an immediate recurrence of generalized dermatitis in a patient primarily sensitized by dapsone.

When sensitivity to dapsone takes the form of the classical "fixed eruption," with one or more hypermelanotic macules of skin and, rarely, of mucosae (labial, nasal, buccal, urethral, conjunctival), continued medication may not always result in exacerbation of the individual lesions, and anti-leprosy treatment may be continued without danger or inconvenience. In such cases there may be a "hardening" or a reduction in sensitivity similar to that reported by Hellier (1958) in sensitization by contact, and capable of mechanical or immunological explanation, possibly with a psychological component.

Recourse may sometimes be had successfully to a second-line drug, such as thiambutosine (a diphenylthiourea) or thiacetazone (a thiosemicarbazone), to which the patient may prove to be non-sensitive.

The Literature

Opinion regarding desensitization in patients sensitive to sulphonamides is divided. Tate and Klorfajn (1944a, 1944b) reported some successful attempts, but were unable then to assert that their results were permanent or that the procedure used could be generally adopted. In the same year Park (1944a, 1944b) also reported successful desensitization of two patients, in one of whom, however, partial sensitivity returned. In the experience of some subsequent workers such methods of slow desensitization for sulphonamide sensitivity may be successful, but others agree with the conclusion expressed by Goodman and Gilman (1955) that "effective desensitization procedures are unknown." Attempts to achieve desensitization may

be nullified by repeated recurrences of skin rashes, and apparent desensitization—even when achieved—is apt to be impermanent.

In the case of patients sensitive to dapsone, especially when this sensitivity is shown by a generalized papular pruritus followed by furfuraceous desquamation or by exfoliative dermatitis, it has been found that desensitization is in the great majority of cases both possible and permanent. Lowe and Smith (1949) and Lowe (1951) achieved such desensitization by giving injections of increasing amounts of a soluble sulphone. Since dapsone itself is almost insoluble in water, an aqueous solution of solapson was employed, at first parenterally and later orally. It was suspected that the desensitizing effect was due to small amounts of dapsone either present in commercial solapson or formed on hydrolysis or after chemical degradation in the liver. This procedure has its parallel in the desensitization carried out successfully in patients sensitive to such drugs as P.A.S., isoniazid (Veterans Administration, 1961; Smith and Zirk, 1961), chlorpromazine ("largactil"), etc., sometimes under corticosteroid cover.

Present Series

Fifty-two patients under treatment for leprosy (the majority being out-patients at distant segregation villages or district clinics) have within recent years been admitted to the Uzuakoli Leprosy Settlement for desensitization in accordance with the above schema; these patients represent about 2% of all cases newly placed on treatment during these years. The criterion for selection was a generalized papular dermatitis precipitated by dapsone, accompanied or not by the other evidences of sensitivity enumerated above. Where any doubt existed about the role of dapsone, a small test dose of the drug was given orally to the patient. In all cases a flare-up occurred. There were 30 males and 22 females. All age-groups were represented, approximately in the same proportions as in patients under treatment. All the main varieties of leprosy were included.

Sensitizing Drug

Some patients who had been primarily sensitized by dapsone were subsequently found to be sensitive to other anti-leprosy drugs; thus three were also sensitive to thiacetazone; one to diamino-diphenyl sulphoxide; one to thiambutosine; one to diamino-diphenyl sulphoxide and to ditophal; one to thiambutosine and to ditophal; and one to the latter two drugs and also to barbiturates and antihistaminics. Some of the patients sensitive to dapsone might have proved to be sensitive also to other anti-leprosy drugs had these been given.

The dose of dapsone taken immediately preceding the appearance of dermatitis was 0.1 g. or less in half the patients, 0.2 g. in one-quarter, 0.3 g. in one patient, and 0.4 g. in the remainder.

The total amount of dapsone ingested before the dermatitis appeared was 0.1 g. or less in two-fifths of the patients, between 0.3 and 1.2 g. in another two-fifths, and higher amounts in the remainder. In a mistaken attempt to expedite their cure, four of the patients confessed to having taken, in addition to the prescribed doses, dapsone tablets bought clandestinely.

Method of Desensitizing

To effect slow desensitization, an aqueous solution of solapson is prepared by dissolving one tablet (0.5 g.) of the drug in 200 ml. of water, giving a concentration of 12.5 mg. in 5 ml. The initial oral dose is 5 ml., and subsequent

doses are given twice weekly, each dose being 5 ml. greater than the preceding one. After the 20th dose (100 ml., containing 250 mg. of solapson) the solid drug in tablet form is given orally twice weekly in gradually increasing amounts. Dapsone is then substituted twice weekly for solapson, the initial dose being 25 mg. The amount is gradually and cautiously increased until the full standard dose, depending on the body weight, is attained. (Some workers have advocated lower initial doses of both solapson and dapsone, the increments being proportionally smaller and given at longer intervals.)

In centres where apothecaries' measures are employed, the solapson solution is made by dissolving one tablet of the drug (0.5 g.) in 5 oz. of water, and giving a first dose of 1 dr. (which contains 12.5 mg. of solapson) and increasing by increments of 1 dr. until at the 20th dose (10th week) the quantity of solapson given (in 20 dr.) is 250 mg. Solid solapson is then prescribed, as above.

Thus, the dose of 100 mg. of dapsone is reached in about 15 weeks in an uncomplicated case, and the full dose after a further variable period. The total time necessary for desensitization may be prolonged by recurrence of symptoms of sensitivity.

Results

Of the 52 patients in whom desensitization was attempted, one absconded for personal reasons; 22 completed the prescribed course of desensitization without interruption and without recurrence of the dermatitis; 26 completed the course eventually after recurrences of signs of sensitivity (eight after a single recurrence, four after two recurrences, five after three, three after four, four after five or more recurrences, and two after more than 10 recurrences).

In only three cases was it impossible to render the patient non-sensitive to dapsone: in two of these, persistent severe dermatitis resistant to all treatment recurred after every dose of solapson solution, however small; in the other case failure was due to the concurrence of sensitivity to the products of mycobacterial breakdown, as shown by persistent severe erythema nodosum leprosum and progressive lepra reaction.

Two patients whose uncomplicated progress was suddenly halted by severe dermatitis were found to have taken tablets of dapsone purchased illicitly.

The recurrences were seen at any stage of the desensitizing procedure, but were particularly frequent at the beginning of desensitization and after the first dose or doses of dapsone. Such recurrences were of all degrees of severity, from slight subjective pruritus with no rash to "drug fever" with severe systemic symptoms and generalized papular dermatitis.

The recurrences usually yielded to immediate suppression of the desensitizing drug and to antihistaminics. The desensitizing procedure was resumed after a period that varied according to the rapidity of response to these measures. The maximum tolerated dose on resumption was found to be at most one-half of that given immediately before the recurrence. In the more severe cases the recommencing dose given was much lower than this, and successive increments were made cautiously and at longer intervals than usual. Small doses of prednisolone given over a short period appeared sometimes to facilitate resumption in more serious recurrences.

Permanence of the Desensitized State

Of the 48 patients successfully desensitized, 43 received thereafter standard dapsone therapy, in doses dependent

on the body weight and for a variable period dictated by clinical and bacteriological progress. Four patients, having been successfully desensitized against dapsone, received standard courses of thiacetazone on return to distant leprosy clinics. One of them, after following this treatment for 30 months, was given 25 mg. of dapsone; dermatitis resulted within a few hours. Another, who had been sensitive to both dapsone and thiacetazone, took thiacetazone for nine months and then standard doses of dapsone, with no recurrence of the dermatitis. The remaining patient of the 48 successfully desensitized was given thiambutosine for 30 months; he then took a single dose of 100 mg. of dapsone, and immediately experienced a recurrence of dermatitis.

Four desensitized patients, after variable periods of treatment with dapsone, returned to Uzuakoli suffering from a recurrence of dapsone sensitivity. A second attempt at desensitization was made, which was successful in each case.

Summary

In an attempt to desensitize 52 patients under treatment for leprosy who had developed sensitivity to dapsone (as shown by generalized dermatitis), aqueous solapsone was given orally in increasing doses, followed by solapsone in tablet form and then by dapsone. Forty-eight of them were successfully desensitized, 26 having recurrences of

dermatitis during the desensitizing course, which prolonged its duration.

The desensitized state was apparently permanent in 43 patients. Four of the remaining five experienced recurrence of sensitivity and were successfully desensitized again by the same procedure as before.

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Preliminary Communications

A Study of Human Colonic Muscle *in Vitro*

There has been little direct investigation of the physiology of human colonic muscle. Radiological techniques and pressure-recording studies tell us only indirectly of the behaviour of the muscle cells. Much of our knowledge of colonic physiology comes from animal experimentation, but, as is well known, the behaviour of the intestines varies from species to species. This is a preliminary report of investigations carried out *in vitro* on human colonic muscle strips from over 50 subjects.

METHOD

Healthy muscle is obtained from post-operative specimens removed for carcinoma of the large intestine. Any bowel with obstruction is excluded. All "healthy" specimens are normal macroscopically and histologically. Several inches of colon are collected in Krebs's solution immediately after resection. Muscle strips about 20 mm. long by 2 mm. wide by 2 mm. thick are removed, the mucosa and submucosa being dissected off. Most of the work has been done with circular muscle taken from between the taeniae.

The muscle strip is set up under a tension of about 3 g. in an isolated organ bath at 37° C. in Krebs's solution equilibrated with 95% O₂ and 5% CO₂. Recording is made on a smoked drum. It is left for about 20 minutes before recording begins.

RESULTS

Spontaneous Activity.—Normal colonic circular muscle exhibits rapid spontaneous contraction and relaxation with a steadily maintained tone.

Acetylcholine and Noradrenaline.—The response to acetylcholine and noradrenaline is as expected. Acetyl-

choline in doses of 10 mμg./ml. upwards evokes a contraction, while noradrenaline in doses from 100 mμg./ml. upwards causes relaxation. The acetylcholine contraction is potentiated by physostigmine and blocked by atropine. The catechol amine inhibition is sometimes blocked by the beta-receptor blocker dichlorisoprenaline (20–50 μg./ml.).

Nicotine.—Nicotine (1–10 μg./ml.) regularly causes relaxation of the muscle (Fig. 1). Doses below this range have no effect and doses greater than 10 μg./ml. cause maximal relaxation. The inhibition is blocked by hexamethonium and by dichlorisoprenaline.

FIG. 1.—Nicotine inhibition of sigmoid circular muscle and its blockade by hexamethonium. S=1 ml. normal saline. N=10 μg. nicotine/ml. He=50 μg. hexamethonium/ml. Strip length 15 mm. Lever magnification $\times 7$. Time interval 75 secs.

Histamine.—Histamine, which is classically described as causing contraction of gut smooth muscle, usually causes a biphasic response in human colonic circular muscle. In doses from 0.5 to 10 μg./ml. circular muscle relaxes initially with complete inhibition of spontaneous activity