

### Summary

Hydroxydione is a steroid anaesthetic which, when injected intravenously, enables interviews to be conducted in a setting free from tension and anxiety and confers on the patient a feeling of well-being.

Biochemical investigations and electroencephalographic patterns are discussed.

In a controlled investigation on 20 patients the action of the drug was compared with that of amylobarbitone sodium.

The indications for the administration of this drug in psychiatric patients are discussed.

I thank Dr. Linford Rees for his help in the design of this experiment and for his constant encouragement. Dr. V. H. T. James, of St. Mary's Hospital, kindly carried out the estimations of 5-hydroxy-indoleacetic acid. Schering A.G. Berlin, through their subsidiary company, Pharmethicals (London) Ltd., generously provided us with supplies of "presuren" (hydroxydione).

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## THE MANAGEMENT OF RECURRENT APHTHOUS STOMATITIS

BY

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In a previous study (Sircus *et al.*, 1957) attention was drawn to the remarkable diversity of therapeutic specifics offered over the past half-century for the cure of recurrent aphthous stomatitis. These included all the vitamins, vaccinations, oestrogens, androgens, sulphonamides, arsenic, chlortetracycline, and x rays. In that study 23 cases of the major form of the disease were each treated, using a single blind procedure, with consecutive courses of folic acid, nicotinamide, riboflavine, and "becosym" (vitamin-B complex), and not a single subject benefited from any of the drugs. Likewise, ethisterone failed to influence the disorder where it appeared to have a temporal relationship to the menses. Radiotherapy administered in a careful double-blind series also had no effect in 14 cases. Oral cortisone, 50 to 75 mg. daily, did not improve any of four subjects, but one with a severely affected mouth greatly benefited from 200 mg. daily for a week.

Farmer (1958) reported apparent improvement in a similar group of cases using aneurine hydrochloride and folic acid in combination, and similar improvement with delta-hydrocortisone, topical hydrocortisone, and vaccination, but the results were assessed by the "patient's reaction to the treatment," and he concluded that "the manner with which treatment is given is probably as important as the drug used."

However, Truelove and Morris-Owen (1958) treated 22 cases of the major form of the disease with the local application of hydrocortisone hemisuccinate (2.5 mg.) linguets and reported healing of the lesions within 48 hours. On a maintenance dose of two to four linguets daily, five cases remained completely free "for some months," and "most others" were affected only by sporadic non-ulcerative "sore spots."

The social and emotional association of this disorder has been emphasized (Sircus *et al.*, 1957) and attention drawn to the beneficial effects often seen as the result of suggestion alone. The present study extends the inquiry into the management of the disease, paying regard to this observation.

### The Investigation

Thirteen consecutive subjects attending with the major form of the disease, in whom aphthous ulcers were present continuously or with not more than a few days' freedom, were placed on a double-blind treatment trial. Observations were continued for approximately 12 months in each case. One month after an initial consultation, at which were recorded the details of the history and findings on examination, each patient was given a sequence of treatment with lozenges of identical appearance and taste. These consisted of a dummy preparation without any active ingredients; an antibiotic, framycetin sulphate ("soframycin"), 10 mg.; and a combination of framycetin sulphate, 10 mg., and prednisolone, 1 mg. The sequence of the different lozenges was distributed for each patient in random fashion, using a previously arranged plan. The patients remained 28 days on each of the preparations, allowing the lozenges to dissolve in the mouth slowly six times daily. A careful diary of the date of onset and the progress of the mouth lesions was kept by each patient from the day of the original consultation and brought monthly to the clinic. Subsequently to completing the three-months double-blind trial, most of the patients also went on to 28 days' treatment with hydrocortisone hemisuccinate (2.5 mg.) linguets, six times daily, and a further month on quinalbarbitone sodium  $\frac{1}{2}$  gr. (50 mg.) twice daily. This part of the trial was open. The code of therapy for the double-blind part of the trial was not opened until the completion of the full six months of the sequence.

The mean age of the 13 patients (9 females, 4 males) was 39 years (range 28-60). The disorder was familial in three instances.

Only four patients were considered to have a stable social background and to have normal and fully adjusted personalities. One other was a partial mental defective, two showed moderate schizoid features, and three had well-developed chronic tension states associated with exogenous stress. The remaining three had moderate to severe depression of endogenous type.

The effects of management (see Table) were classified as "curative" where ulcers were absent from the mouth throughout the period of administration of the agent,

*Effects of Management*

Phase of Trial	No. of Subjects	Effects Classification		
		Curative	Helpful	Valueless
28 days after consultation . . .	13	3	3	7
28 " " on dummy lozenges . . .	13	0	6	7
28 " " antibiotic . . .	13	2	6	5
28 " " steroid + anti-biotic (prednisolone) . . .	13	6	3	4
28 days on steroid alone (hydrocortisone) . . .	11	4	4	3
28 days on sedation alone (quinalbarbitone) . . .	8	3	1	4

"helpful" where the frequency of new ulcers fell by 50% or more of the average for the three months prior to the trial, and "valueless" where the incidence of the ulcers was unchanged or fell by less than 50%.

**Results**

When, however, the results are grouped and analysed the following features emerge.

Three patients, all female, showed no response either to the consultation or to any form of treatment. Two of these were those subjects with the schizoid features, and the third was depressed.

Three patients, one male, responded only to steroids, as shown by a "curative" effect of both steroid and antibiotic combinations and of steroid alone, but with no response to antibiotic alone. The group had no common features of personality or social background.

Four patients, two of each sex, responded equally well to every phase of the trial, including the period on dummy lozenges. Of these, two had marked evidence of chronic anxiety. Three of the four had shown a "curative" response to the initial consultation.

The remaining three patients improved after the consultation, but subsequently relapsed and showed no response to any form of therapy.

It is of interest to examine briefly the background and behaviour of the individual cases, as follows:

*Case 1.*—Woman aged 44 years. Duration of ulcers, 40 years. Lesions continuously present for 10 years. Chronic exogenous tension. Mother-in-law sick and living with her. Strong familial incidence of ulcers. Effective measure: steroids reduced ulcer incidence from continuous crops to three isolated lesions a month.

*Case 2.*—Woman aged 28. Duration of ulcers 1 year and present continuously. Schizoid features. No stress. Effective measure: nil.

*Case 3.*—Man aged 33. Duration of ulcers, 10 years, in continuous crops. Partial mental defective. Smokes 60 cigarettes in a day. Effective measure: nil. Subsequent to trial the patient was persuaded to stop smoking and to remove dentures at night; the incidence of ulcers then fell from 15 in a month to three.

*Case 4.*—Woman aged 34. Duration of ulcers, three years. Averaged eight new ulcers each month. Familial. Normal personality and no stress. Effective measure: no ulcers for six months subsequent to initial consultation.

*Case 5.*—Woman aged 60. Duration of ulcers, 14 years and in continuous crops. Marked depression. Effective measure: steroids reduced new ulcers to one or two small lesions a month.

*Case 6.*—Woman aged 44. Duration of ulcers, four years, in continuous crops. Immature, obese, depressed, invalid husband and financial stress. Effective measure: ulcers reduced to one isolated lesion a month subsequent to consultation. This result, however, coincided with patient taking up employment and relieving financial anxiety in family.

*Case 7.*—Woman aged 30. Duration of ulcers, eight months and continuous. Onset coincided with serious conflict with father. They live together in tense atmosphere without conversing. Depressed, immature, tense. Through first three phases of trial had average of 15 new ulcers a month, and then suddenly went into complete remission and in subsequent five months remained totally free. Situation with father was unchanged, but remission coincided with finding a boy friend. Was seldom home, and was apparently happy.

*Case 8.*—Woman aged 46. Duration, 25 years of continuous ulcers. Tense and depressed. Worried by "low class" noisy neighbours. Effective measure: nil.

*Case 9.*—Woman aged 45. Duration, seven years of continuous ulcers. Father and husband chronic alcoholics. Mother-in-law living with her. Severe migraine. Effective measure: dramatic disappearance of ulcers soon after beginning trial, and remained clear of ulcers for nearly six months; but this effect coincided with her mother-in-law moving elsewhere and her husband's alcoholic excesses diminishing.

*Case 10.*—Man aged 29. Onset of ulcers one year before, coinciding with attack of proctocolitis. Normal personality and no stress. Effective measure: steroids.

*Case 11.*—Man aged 40. Duration of ulcers, 20 years. Three or four ulcers each week, lasting 21 days. Normal personality and no stress. Effective measure: all phases of treatment subsequent to consultation, and including dummy lozenges, reduced incidence to two ulcers a month of seven days' duration.

*Case 12.*—Woman aged 30. Duration of continuous ulcers, two years. Onset during pregnancy and immediately after the discovery of husband's infidelity. Since then, frigid, depressed; migraine. Home atmosphere very tense. Effective measure: has had only one ulcer in the six months subsequent to the initial consultation.

*Case 13.*—Man aged 52. Not more than one week free from ulcers in two years. Tense, worrying man. Frustrated by failure to buy available business employing him for last 20 years. Effective measure: all phases of treatment, including dummy lozenges, were effective. Had 10 ulcers in a month when, owing to secretarial error, he failed to receive a supply of lozenges. In subsequent four months had only two ulcers.

**Comments**

It is notable that 6 of the 13 patients showed a remarkable response to the initial consultation, and before any therapy had been instituted; three subsequently remained totally free from lesions during the nine-months follow-up. The other three relapsed after a month or two, and then proved resistant to all therapy, including hydrocortisone. Furthermore, dummy lozenges produced a reduction of over 50% in the frequency and duration of ulcers in 6 of the 13 subjects. Therapy for this remittent disorder must be set against this backdrop before judgment is made on its efficacy. Nevertheless, local application of a steroid, prednisolone or hydrocortisone, is capable in approximately a quarter of the subjects of bringing about a sustained remission from the disease where all other measures, including suggestion, appear to fail.

In the absence of any knowledge of the basic aetiology of recurrent aphthous ulceration, management must remain empirical and aimed at associated features which may be acting to effect continuity of the disease process. Thus the evidence from this and the previous study (Sircus *et al.*, 1957) suggests that the interest of the physician, sedation, and the resolving of social and emotional problems do more than any other procedures to effect control in those cases where chronic anxiety,

tension, or depression of exogenous origin is clearly evident. No such value has been shown where the abnormal states of mind appeared to be endogenous in nature. Where no such exogenous stress or endogenous abnormality is associated with the disease, then steroid therapy remains the most useful of the procedures examined. Two additional points of management may here be mentioned, though not a part of the main study.

Extremely severe and continuous ulceration of the mouth with multiple giant ulcers has been managed with bed rest and corticotrophin, 80–120 units intramuscularly daily, for five to seven days on three occasions, with complete resolution within 10 days in each case. Subsequent relapse after some months, however, has been the rule.

Infrequently occurring isolated ulcers have been most effectively controlled by instructing the patient at the first evidence of a new lesion, either the appearance of a vesicle or of a tiny painful break in the mucosa, to touch it with a small crystal of copper sulphate held in tweezers, after preliminary swabbing of the area with amethocaine solution. During the next 24 hours a lozenge of prednisolone or hydrocortisone is placed in the vicinity of the lesion every few hours and there allowed slowly to dissolve.

Unfortunately for the majority of the sufferers from the frequently recurrent or continuous form of the disease, relief must await further advances in our knowledge of the aetiology.

### Summary

Thirteen cases of severe recurrent aphthous ulceration of the mouth were subjected to a double-blind trial to determine the value of antibiotics and steroids in management.

The trial was so designed that the influence of suggestion and the interest of the physician could be appreciated and evaluated.

It has been shown that antibiotics are of no value in treatment, and that steroid hormones have a useful but limited application. Suggestion and medical interest are shown to have important effects which must be allowed for in judging therapy in this disease.

I am indebted to Dr. J. J. Segall and Roussel Laboratories Ltd. for the preparation and free supply of the identical sets of lozenges used in the trial, and to Miss Gillian Tucker for skilful assistance in the organization of the double-blind part of the study. Several of the cases were referred to me by Dr. J. W. Galloway and Dr. W. J. Baird, of the periodontal diseases department of the Edinburgh Dental Hospital, from whom I had the greatest encouragement and co-operation.

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According to records of the American Medical Association, Dr. LINDSEY S. McNEELY, who will be 99 on November 14, is the oldest practising physician in the United States. He was born in a log cabin in 1860 and had been in practice at Kirby, near Pittsburgh, for 69 years. The only 99-year-old doctor in Great Britain, Sir WILLIAM COATES, who was born in June, 1860, has retired.

## Medical Memoranda

### Blood Groups and Toxaemia of Pregnancy

The discovery that certain blood groups, especially those of the ABO system, may be associated with particular diseases is comparatively recent. In 1954 Pike and Dickins examined the frequencies of ABO groups in toxæmic and non-toxæmic women and showed that group O was significantly more frequent in toxæmic mothers than in the remainder. Further expansion of their figures, with some modification, by Dickins (1955) confirmed this. However, examination of a second series by Dickins, Richardson, Pike, and Fraser Roberts (1956) showed no significant difference between the ABO blood group frequencies in toxæmic and non-toxæmic mothers, and Pearson and Pinker (1956) also were unable to find any difference between the two groups.

In discussing some of the biometric problems involved in establishing associations between blood groups and diseases Fraser Roberts (1955) stresses the large number of cases required and the importance of adopting rigid and precisely defined criteria for including cases in a series so that it is possible to add further groups which are individually too small for analysis, and to compare results from different parts of the world.

In presenting this small series the need for comparison with former publications has been borne in mind, and it is perhaps of interest that previous series have come from areas in England near to each other.

From time to time, beginning with Dienst in 1905, it has been suggested that toxæmia of pregnancy is due to ABO incompatibility between foetus and mother, isoimmunization of the mother taking place because the red cells of the foetus bear an antigen which is absent from the mother. The published results have not convincingly supported this hypothesis: for example, Hurst, Taylor, and Wiener (1946) found a greater number of incompatible blood groups between infants and mothers in cases of toxæmia of pregnancy than in normal cases, although the difference was not significant. They also found that some mothers showed a significant rise in isoagglutinin titre and that these formed a greater proportion of the toxæmic group than the normal group, but the series were too small for any definite conclusions to be reached.

Dickins (1955) also found that predominance of group O in toxæmic mothers persisted when those who had hypertension were considered as a separate group, but this increase was present both in those in whom the hypertension was due to the toxæmia and in those in whom essential hypertension occurred during pregnancy. Maxwell and Maxwell (1955), investigating cases of essential hypertension, however, were unable to find any significant difference in the blood-group distribution. In this series hypertensive cases were also investigated as a distinct group, but it was not possible to separate from this group cases of essential hypertension.

### MATERIAL

The ABO and D blood groups of mother and infants in 1,087 pregnancies were determined; these included 149 cases of toxæmia. Apart from eclampsia, the