patients were delivered of twins. Other factors, too, would seem to aggravate or even precipitate the onset of the anaemia: diarrhoea and vomiting, debility from repeated pregnancies, infection, pre-eclamptic toxaemia, and cardiac disease were found in that order in the present series. Only one patient appeared to have had a normal pregnancy, and she had been treated for an iron-deficiency anaemia at the seventh month. With hospitalization and treatment it was possible to deal with these secondary complications and in this way remove any factors which might possibly enhance a deficiency.

Another aggravating factor which may also increase the demand for folinic acid once the upset in erythropoiesis has been established is that of more rapid blood destruction. We have been unable to demonstrate the existence of an actual haemolysin in the megaloblastic anaemia of pregnancy, but in all the buffy coats examined there is evidence of erythrophagocytosis, and Pappenheimer bodies, similar to those seen in haemolytic anaemias, are present in some of the nucleated red cells. Ungley and Thompson (1950) reported a more rapid elimination of transfused cells in one of their cases and severe haemolysis in another. With folic acid therapy they found that the haemolysis ceased and the rate of elimination of transfused cells fell to normal. In our cases the erythrophagocytosis disappeared. These findings suggest a possible increase in the rate of red cell destruction, though obviously it is not present to the same degree in all cases. Since treatment appears to reduce this process, one would expect that replacement with new cells would also fall to normal and, in this respect at least, the need for extra folic or folinic acid would be less.

Thus with treatment for both the anaemia and its complications it is possible that the demand for folinic acid may be somewhat reduced, and, with normoblastic erythropoiesis established, the pregnant woman may once more be able to keep herself in balance and maintain satisfactory blood levels. From what has been said previously, however, it is unlikely that the initial effect of folinic acid is purely one of replacement therapy. The evidence rather points to some catalytic action, and it may be that folinic acid has multiple duties, not only associated with the bone marrow, but also with those processes concerned with the production and utilization of the whole folic acid system of enzymes.

Summary

Nineteen patients with megaloblastic anaemia of pregnancy and the puerperium have been treated with folinic acid (" leucovorin ") and the results have been reviewed.

Sixteen received treatment over a limited period till the reticulocyte response reached its peak.

Eleven of these were antenatal anaemias, and though their treatment was discontinued all continued to improve. At term their average haemoglobin was 10.4 g. per 100 ml. and red cell count 3,350,000 per c.mm.

In order to produce a satisfactory response with this short-term therapy, it was found that the folinic acid had to be given in sufficiently large amounts initially (approximately 50 mg.) and that the amount necessary appeared to be independent of the degree of anaemia and the route of administration.

From these findings it seems unlikely that the megaloblastic anaemia of pregnancy is due to an absolute deficiency of folinic acid. Instead the latter would appear to act more as a catalyst at some stage in the haemopoietic process, and evidence is brought forward to show how the demand for folinic acid itself may be further reduced once normal erythropoiesis is established.

My thanks are due to Dr. A. D. T. Govan, Director of Research, for his help in the preparation of this paper, and to Lederle Laboratories Division for supplies of leucovorin used in the trial.

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RECTAL HYDROCORTISONE

BY

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Local administration of hydrocortisone in the treatment of ulcerative colitis was mentioned by Truelove and Witts (1955) and by Park (1955). For this purpose the steroid may be given as an ester—acetate or hemisuccinate—or as the free alcohol. The esters may well be inactive until hydrolysed to free steroid, and it is not known whether the large bowel contains suitable enzymes. Enemata of hydrocortisone and its esters could be dispensed as solutions or suspensions, but the free steroid is only sparingly soluble in water. Truelove (1956) used a solution containing 50 mg. of hydrocortisone per 100 ml. of 4.5% alcohol in saline; apparently this concentration of alcohol did not cause any local discomfort, but we preferred to avoid any solution that might aggravate the inflammation of the colonic mucosa. As 1% solutions of hydrocortisone have been used extensively in dermatological practice and the solvent does not seem to irritate acutely inflamed skin, we have used diluted 1% hydrocortisone skin lotion for these studies. A further aspect of the problem about which there is very little information is the extent to which hydrocortisone is absorbed from the bowel. Liddle (1956) has reported 26% absorption of hydrocortisone acetate administered per rectum as suppositories or in an ointment.

We have studied the absorption of various preparations of hydrocortisone administered locally in five patients with ulcerative colitis. We are not in a position to offer any opinion about the value of this form of treatment; this report is concerned mainly with its endocrine implications.

Methods.—The patients were men with mild or moderately severe ulcerative colitis, thought to be suitable for steroid therapy. Daily urine collections were made from 6 a.m. to 6 a.m. Excretion of hydrocortisone and its metabolites was estimated by the total 17-

hydroxycorticosteroid method of Appleby *et al.* (1955), using modifications described elsewhere (Moxham and Nabarro, 1956). Urinary 17-ketosteroids, sodium, potassium, and creatinine were also estimated by standard methods.

Results

The first two patients studied were given 20 ml. of 1% hydrocortisone skin lotion* containing 200 mg. of steroid made up to 120 ml. with saline. The fluid was run into the rectum in about 15 minutes, starting at 9 p.m., and the patient was encouraged to retain it as long as possible. The urinary steroid excretions are shown in Fig. 1. Case 1 was treated in this way for 14 days and received 100 mg. daily for a further three days. The hydrocortisone solution was poorly retained, but despite this there was an increase of urinary steroid excretion. Case 2 was an in-patient at the Central Middlesex Hospital, and urine samples were made available through the kindness of Dr. F. Avery Jones. This patient retained the hydrocortisone well and there was a striking increase of urinary total 17-hydroxycorticosteroids; on a subsequent occasion 200 mg. of hydrocortisone was given by mouth with only a slightly higher figure for steroid excretion.

Studies in greater detail were made in Cases 3 and 4. Case 3 was referred by Mr. O. V. Lloyd-Davies. The patient started to improve during the control period and continued to do so steadily while steroids were being given. There was no evidence that the rectal steroids influenced the process. The hydrocortisone acetate and alcohol suspensions and the skin lotion were diluted to 120 ml. and given as in Case 1 above. Five hydrocortisone suppositories, each containing 40 mg. of the alcohol, were given over the 24-hour period. At least two days elapsed between each form of treatment. This patient retained the enemata well, and unexpectedly good absorption of hydrocortisone from the skin lotion was observed (Fig. 2).

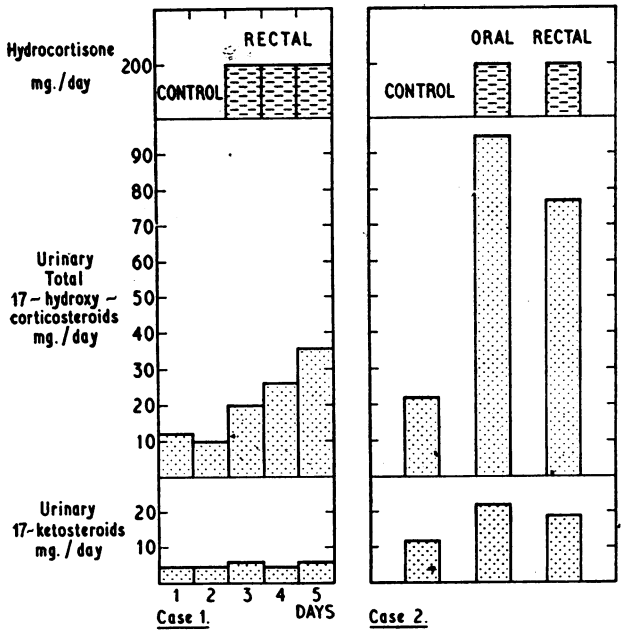

FIG. 1.—Urinary steroid excretions in Cases 1 and 2.

We are indebted to Dr. G. D. Hadley for being allowed to study Case 4. This patient's ulcerative colitis was moderately severe; he improved throughout the period of treatment, although the change was greater with hydrocortisone alcohol suspension and solution. The clinical improvement was reflected in the sigmoidoscopic changes (Mr. J. H. Lees Ferguson). In this case the steroid suspension or solution was diluted to 100 ml. and given by slow rectal drip lasting approximately two hours. The enemas were retained for 20–160 minutes (acetate suspension), 100–120 minutes (alcohol suspension), and 120–240 minutes (solution). As judged by steroid excretion, absorption was poor, although it improved at the end of study when the patient was given the suppositories (Fig. 2). At this time he was symptom-free.

Case 5 received hydrocortisone alcohol suspension, hydrocortisone hemisuccinate solution, and the hydrocortisone alcohol solution used in the previous cases. With each preparation 200 mg. of hydrocortisone was given in 120 ml. of fluid over a period of 15 minutes. This patient was able to retain the enemata for about 12 hours. The alterations of steroid excretion are shown in Fig. 3. The most striking finding is the increase of 17-ketosteroid excretion.

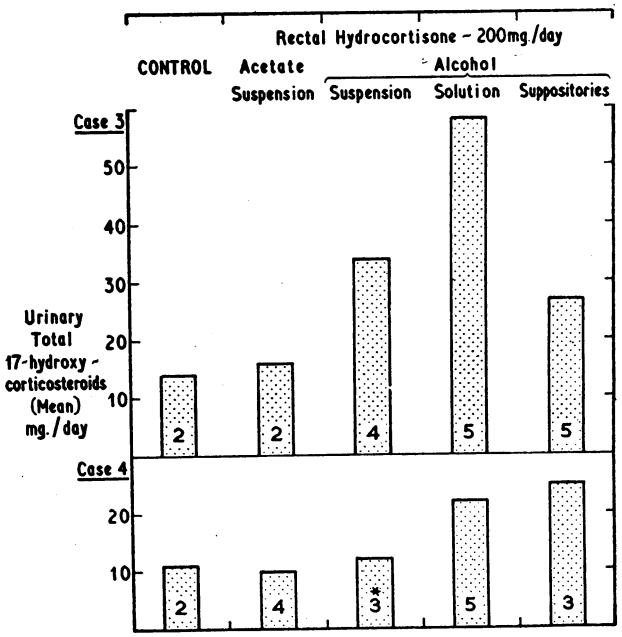

FIG. 2.—Urinary excretion of hydrocortisone and metabolites in Cases 3 and 4. Figures in the columns indicate the number of days on which the particular form of treatment was given. *250 mg. hydrocortisone alcohol.

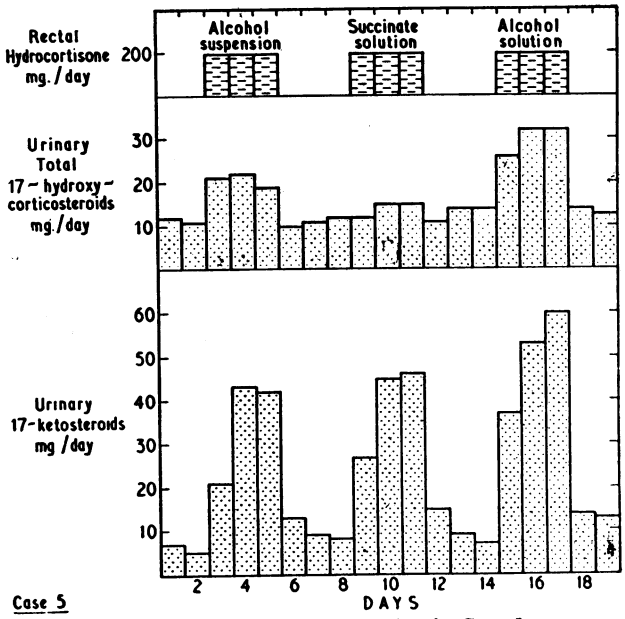

FIG. 3.—Urinary steroid excretion in Case 5.

*Roussel Laboratories Ltd.; the solvent of hydrocortisone free alcohol in this lotion is a mixture of glycols.

Discussion

Oral hydrocortisone is rapidly and almost completely absorbed. Urinary 17-hydroxycorticosteroid excretion in adrenalectomized patients receiving oral cortisone acetate amounts to about 36% of the dose in mg. (Moxham and Nabarro, 1956). Results with patients given hydrocortisone are comparable. From these figures it is possible to assess the approximate absorption of steroid administered per rectum. If, however, treatment is given to patients with intact adrenals there may be no increase in urinary steroid excretion because of suppression of endogenous steroid secretion. The short periods of treatment used in Cases 3, 4, and 5 minimize this difficulty, and the increase of urinary total 17-hydroxycorticosteroid output over the control figure may be taken as approximately one-third of the steroid absorbed. There was no evidence of absorption of hydrocortisone when given as a suspension of the acetate. Up to 30% of the free alcohol was absorbed from a suspension or suppositories. Hydrocortisone absorption from the skin lotion was considerable in Cases 2 and 3 (83% and 66% respectively), but much less in the other three (16%, 30%, and up to 36% in Cases 4, 5, and 1 respectively).

The fact that significant absorption of the steroid can occur raises a number of problems. It is important to ascertain whether the hydrocortisone is absorbed in a physiologically active state or whether it is reduced to inactive metabolites prior to absorption; in the latter case a high urinary steroid figure might still be obtained. Case 3 showed marked sodium retention and potassium diuresis with the free alcohol suspension, solution, and suppositories, and corresponding changes on stopping them. Similar alterations of electrolyte excretion were noted when Case 4 was given solution and suppositories and when Case 5 was given the free alcohol solution. There seems, therefore, to be little doubt that hydrocortisone is physiologically active when absorbed from the rectum. The greatly increased 17-ketosteroid excretion in Case 5 may be the result of bacterial modification of the hydrocortisone in the colon.

The hydrocortisone that is absorbed may produce undesirable side-effects. An important possibility is adrenal cortical suppression with liability to acute adrenal insufficiency following stress, including surgery. Steroid therapy was given intermittently in Cases 3 and 4, but Case 1 had 17 days' treatment with only moderate absorption; despite this there was a significant fall of urinary steroid output when treatment was stopped (Fig. 4). The fact that rectal steroid therapy leads to suppression of the patient's adrenal glands is further confirmation that the hydrocortisone is absorbed in a physiologically active state, and it also means that there are potential dangers in prolonged pre-operative preparation with rectal steroid therapy.

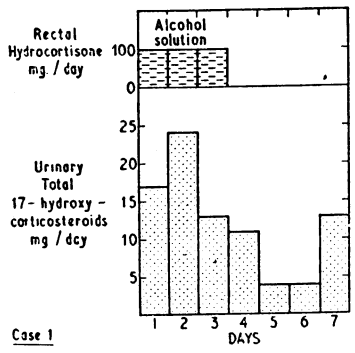

FIG. 4.—Case 1, urinary steroid excretion at the end of treatment; prior to this, 200 mg. rectal hydrocortisone had been given daily for 14 days.

Summary

The absorption of hydrocortisone administered by retention enemata in ulcerative colitis has been studied in five cases.

There was no evidence that hydrocortisone was absorbed from a suspension of the acetate. Absorption occurred when hydrocortisone (free alcohol) was given as a suspension or in suppositories, and to a slight extent with an aqueous solution of hydrocortisone hemisuccinate. Significant absorption was found when hydrocortisone skin lotion was used; in one patient it was estimated as 80%. One of the patients had a considerable increase of urinary 17-ketosteroid excretion while receiving rectal hydrocortisone.

Rectal steroid therapy may suppress the patient's adrenal glands and, if used pre-operatively, result in acute adrenal insufficiency in the immediate post-operative period.

We are indebted to Dr. A. E. Gremeaux, of Roussel Laboratories Ltd., for the preparation of hydrocortisone acetate and alcohol suspensions given to Cases 3 and 4, and for information about the solvent used for the hydrocortisone alcohol solution. We are grateful to Glaxo Laboratories Ltd. for supplying the hydrocortisone hemisuccinate, and to Mr. G. Bryan, chief pharmacist to the Middlesex Hospital, for preparing the suppositories. We wish to thank the Clinical Research Committee for laboratory facilities in the Institute of Clinical Research of the Middlesex Hospital Medical School, and for a personal research grant to one of us (J. D. N. N.). The figures were prepared by Mr. V. K. Asta.

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FINGERPRINT SWEAT TEST IN FIBROCYSTIC DISEASE OF PANCREAS

PRELIMINARY COMMUNICATION

BY

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The diagnosis of fibrocystic disease of the pancreas is rapidly becoming more frequent as a result of the more general appreciation of the clinical picture and greater reliability of the laboratory tests confirming it. Recent reports seem to indicate that estimation of the sweat electrolytes is the most reliable of the many tests employed by the laboratory. The performance of this test offers few technical difficulties, but there is concern about its possible dangers, especially when applied to small infants. Many infants do not develop the ability to sweat perceptibly until the age of 6 weeks to 3 months, and, since the test implies wrapping up the infant in a plastic bag and, if necessary, applying external warmth, it can produce a dangerous rise in the body temperature. We have noticed that some small babies, especially where there is severe pulmonary involvement, rapidly become tachypnoeic and pyrexial. Careful supervision is necessary, and, since no untoward effects are produced in the vast majority of cases, this care is too easily relaxed. To our knowledge two infants have died as a result of the test.