PAPERS AND ORIGINALS

Liver Damage due to Methotrexate in Patients with Psoriasis

M. G. C. DAHL, M. M. GREGORY, P. J. SCHEUER

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Summary

Liver function and histological changes in liver biopsies were studied in 37 patients who had been treated for psoriasis with methotrexate. Cirrhosis was found in seven (19%) and hepatic fibrosis of varying severity in 10 (27%). Minor abnormalities in another 17 (46%) consisted of fatty change, round cell infiltration, and extensive vacuolation of liver cell nuclei. In only three (8%) was hepatic histology entirely normal. The severity of liver damage was related to the duration of methotrexate treatment. Minor abnormalities of liver function tests and liver histology were also found in eight control psoriatic patients. Standard liver function tests were of little value in predicting the degree of liver damage. It appears that methotrexate, in the doses normally used to control psoriasis, may cause cirrhosis if treatment is prolonged and that liver biopsy is necessary for evaluation of liver damage in these patients.

Introduction

Abnormal liver function tests are often encountered during the treatment of psoriasis with methotrexate. The incidence of these abnormalities varies widely in individual series, but in the short term changes are reversible (Ryan *et al.*, 1964). There is less information available about the long-term effects of methotrexate on liver function and histology (Baker and Dahl, 1969).

Though folic acid antagonists were introduced in the treatment of psoriasis in the early 1950s (Gubner *et al.*, 1951; Rees *et al.*, 1955), it was not until 1964 that a psoriatic patient was first reported with liver disease attributable to methotrex-

ate (O'Rourke and Eckert, 1964). More recently six further cases of cirrhosis have been recorded (Coe and Bull, 1968; Muller *et al.*, 1969; Epstein and Croft, 1969). Changes in hepatic histology attributed to folic acid antagonists have also been reported in leukaemia (Colsky *et al.*, 1955; Hutter *et al.*, 1960; Taft, 1965; Hersh *et al.*, 1966; Talerman and Thompson, 1966; Sharp *et al.*, 1969), histiocytosis X (Taft, 1965; Sharp *et al.*, 1969), and benign ocular diseases (Hersh *et al.*, 1966).

The frequency and rapidity with which methotrexate-induced liver damage occurs in psoriatic patients is not known. We have obtained liver biopsies from a group of psoriatic patients treated with methotrexate and have attempted to correlate the histological findings with duration of treatment, dose, and clinical features. Biopsy specimens have also been obtained from a few psoriatic patients who had not been treated with folic acid antagonists.

Patients and Methods

Forty five patients were studied, 37 of whom were being or had been treated with methotrexate. The age range for the treated group was 18-72 (mean 52) years, and in the untreated group it was 30-72 (mean 59) years. All patients in the treated group had severe and resistant psoriasis before methotrexate treatment was started. The eight patients in the untreated group all had active psoriasis requiring inpatient treatment at the time of study. The duration of treatment with methotrexate was 3 to 73 months.

None of the patients habitually drank spirits, but three drank between 6 and 12 pints (3.4 and 6.8 litres) of beer every week. Two patients with cirrhosis were excluded from the study because alcohol was considered to be an important aetiological factor, and a further patient with cirrhosis was excluded because of unequivocal cutaneous evidence of arsenic toxicity. Only one patient gave a history of previous infectious hepatitis in childhood. There were no clinical signs to suggest liver disease in any of the patients before treatment with methotrexate, though in five there were minor laboratory abnormalities of liver function tests which are discussed below. Systemic corticosteroids had previously been given to seven patients. One of these was still taking steroids at the time of liver biopsy but in all the others steroids had been

Department of Dermatology, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP

M. G. C. DAHL, M.B., M.R.C.P., M.R.C. Research Fellow

Department of Pathology, Royal Free Hospital School of Medicine, London W.C.1

M. M. GREGORY, M.B., B.Sc., Lecturer in Morbid Anatomy
P. J. SCHEUER, M.D., M.R.C.PATH., Reader in Morbid Anatomy

discontinued at least six months previously. No patient was known to have diabetes mellitus. Corticosteroid-induced glycosuria had been present in one patient 18 months previously but none had glycosuria at the time of liver biopsy. None of the patients was grossly obese.

Several different dosage schedules for methotrexate were used. Two broad categories could be distinguished; firstly, a "continuous low dose" regimen, in which 2.5 mg was taken orally on two to five days every week or daily on alternate weeks; and, secondly, an "intermittent" regimen, in which 5-45 mg was given orally or intramuscularly in a single dose every one to four weeks. For all patients the dose was continuously adjusted according to the clinical response, and many were treated by both regimens at different times. Nevertheless, 22 patients received predominantly "continuous low dose" treatment, 11 received predominantly "intermittent" treatment, and in 4 both regimens were used for about equal periods.

Except in one case, liver function tests were carried out before methotrexate treatment was started, and in all patients they were repeated at intervals during therapy. Liver function tests included serum bilirubin, alkaline phosphatase, aspartate aminotransferase, and in some cases alanine aminotransferase. Bromsulphthalein retention tests were performed in 30 of the 37 patients treated with methotrexate and in all eight of the untreated patients immediately before liver biopsy.

The patients attended several different hospitals in Newcastle upon Tyne and London. To achieve uniformity the following names, units, and normal ranges were adopted and conversions made where necessary; serum bilirubin, 0.1-0.9 mg/100 ml; alkaline phosphatase, 20-85 IU/100 ml; aspartate aminotransferase, 4-20 IU/100 ml; and alanine aminotransferase, 4-20 IU/100 ml. Bromsulphthalein retention tests were performed with a dose of 5 mg/kg. Blood samples were taken 45 minutes after injection, and the upper limit of normal was taken as 6%.

Liver biopsy specimens were obtained by the Menghini (1958) technique and fixed immediately in formol-saline. Specimens were processed routinely and 5- μ sections cut from paraffin blocks. All sections were stained with haematoxylin and eosin. Reticulin fibres were demonstrated by the silver impregnation method of Gordon and Sweet and iron by Perl's Prussian blue method.

Of the 37 patients treated with methotrexate, nine were initially investigated because liver damage was suspected clinically. Obviously this selection would have tended to bias the results towards an increased incidence of liver disease. At Newcastle an attempt was made to study all patients treated for psoriasis with methotrexate, regardless of whether or not liver damage was suspected. This group of 28 patients is therefore unselected and the results for this group are considered both with the others and separately.

Results

There were no consistent clinical features indicative of liver disease in the methotrexate-treated patients. Hepatomegaly was found at the time of biopsy in 7 out of 17 who were subsequently shown to have cirrhosis or hepatic fibrosis. Splenomegaly occurred in three patients with cirrhosis and in one patient with fibrosis. Ascites was found in two of the cirrhotics.

Abnormal liver function tests were found in five patients before methotrexate was started. In two the aspartate aminotransferase levels were slightly raised to 21 IU/100 ml, but subsequently were within normal limits. Raised alkaline phosphatase levels of 98 to 127 IU/100 ml were found in the other three. No cause was established for these findings and in two the levels fell to normal during treatment with methotrexate.

In all patients who developed cirrhosis or hepatic fibrosis abnormal liver function tests were recorded at some time during treatment. In several patients, however, these abnormalities were slight and often transitory in spite of continued treatment. Similar abnormalities were found in several patients who showed only non-specific reactive hepatitis on liver biopsy, and one patient with a histologically normal liver had previously been found to have raised aspartate aminotransferase levels of up to 57 units over a period of three months during treatment. Raised alkaline phosphatase levels occurred in seven patients, six of whom were subsequently shown to have hepatic fibrosis or cirrhosis. Low prothrombin times were found in three patients. There was a rapid response in two to the administration of parenteral vitamin K. One of these was shown to have steatorrhoea associated with erythroderma (Shuster and Marks, 1970). In the other patient there was no response to vitamin K, and established cirrhosis was subsequently found.

Abnormal bromsulphthalein retention was found in 19 out of 30 methotrexate-treated patients (Fig. 1). There was, however, little correlation between percentage retention and the severity of liver damage subsequently found at biopsy. Bromsulphthalein retention was, however, normal in some patients with considerable liver damage.

In the group of 37 patients treated with methotrexate histological evidence of established or developing cirrhosis was present in 7 and varying degrees of hepatic fibrosis were seen in another 10. Among the other 20 patients non-specific reactive hepatitis was seen in 17 the remaining 3 being normal. Of the group of 28 patients investigated regardless of whether or not liver disease was suspected clinically 3 had cirrhosis, 9 showed hepatic fibrosis, 14 showed non-specific changes, and 2 were normal.

The type of cirrhosis varied. Active micronodular cirrhosis with inflammation and piecemeal necrosis blurring the septal-parenchymal junction (Fig. 2) was found in four cases while one other case showed features of severe chronic aggressive hepatitis. In another patient who had discontinued methotrexate four months previously there was a mixed micronodular and macronodular cirrhosis which appeared inactive (Fig. 3). Varying degrees of fatty change and prominent nuclear vacuolation were present in all cases.

Fibrosis, mainly portal in distribution, was seen in another 10 patients. Mild cases showed short septa extending around the lobules (Fig. 4) while in others there was moderately severe portal and intralobular fibrosis with considerable distortion of the hepatic architecture. Nuclear vacuolation was a

FIG. 1—Bromsulphthalein (BSP) retention in psoriatic patients. Left-hand column indicates patients who had never been treated with methotrexate (MTX). Open circles in methotrexate-treated groups indicate patients who had discontinued treatment at least three months before investigation.

FIG. 2—There is active cirrhosis with blurring of the septal-parenchymal junction by piecemeal necrosis, and pronounced swelling of adjacent liver cells. The connective tissue is heavily infiltrated with inflammatory cells, and striking ductular proliferation is seen. (Haematoxylin and eosin. $\times 125$)

FIG. 3—There is established cirrhosis. The nodule seen is well demarcated by fibrous connective tissue infiltrated with mononuclear cells. There is variation in the size of liver cells and their nuclei, and a moderate degree of fatty change is present. (H. & E. $\times 113$)

FIG. 4—Normal architecture is preserved but short fibrous septa are seen extending from a portal tract around the lobules. A moderate degree of fatty change is present. (H. & E. $\times 125$)

constant feature, and fatty change was present in nine cases. Moderate siderosis was present in one case in this group but no significant stainable iron was found in any of the other 36 biopsies.

Non-specific changes only were found in 17. In nine there was a variable degree of non-specific inflammation with mononuclear cell infiltration in both portal tracts and parenchyma. Small focal necroses were occasionally found, and in two cases the presence of acidophil bodies indicated recent liver cell damage. In 12 cases there was mild to moderately severe fatty change, and nuclear vacuolation of varying degree (Fig. 5) occurred in 13.

The severity of liver damage correlates with the duration of methotrexate treatment (Fig. 6). The patients have been considered in three groups according to the liver biopsy findings. In those showing either normal liver histology or non-specific changes the mean duration of treatment was 17.7 ± 3.4 months ($\pm$ S.E.). In the group with fibrosis the duration was 32.9 ± 6.6 months. The difference between these values is significant ($P < 0.05$). In the group with cirrhosis the mean duration was 46.9 ± 4.9 months. The difference between this value and that for the normal and non-specific group is highly significant ($P < 0.001$) but compared with the fibrosis group the difference does not reach statistical significance. If the 28 unselected patients from Newcastle are considered separately the corresponding values for the three groups are 19.6 ± 4.1 , 35.2 ± 7.0 , and 48.7 ± 5.9 months respectively. The value for the cirrhosis group differs significantly from that for the normal and non-specific group ($P < 0.02$) but the other values do not differ significantly.

The prevalence of fibrosis and cirrhosis rises steadily as the duration of methotrexate treatment increases (Fig. 7). If the unselected group of patients from Newcastle is considered separately the same upward trend is found.

The dose of methotrexate in each group of patients is shown in Fig. 8. Because of the wide variation in dose regimens and dose levels, an average value, expressed as mg/month, has been calculated for each patient. The mean of these values was 41.3 ± 2.6 mg/month in the normal and non-specific group, 41.2 ± 4.1 mg/month in the fibrosis group, and 51.8 ± 7.9 mg/month in the cirrhosis group. There is no significant difference between the values for any of these groups.

In the small group of eight patients who had not been treated with methotrexate no clinical abnormalities suggestive

FIG. 5—Hepatic architecture is normal. The portal tract seen shows a mild mononuclear inflammatory infiltrate. Nuclear vacuolation is prominent and there are occasional fat vacuoles. (H. & E. $\times 130$)

FIG. 6—Severity of liver damage in relation to duration of methotrexate treatment. The difference in values between the cirrhosis group and the normal and non-specific group is highly significant ($P < 0.001$). The difference between the fibrosis group and the normal and non-specific group is significant ($P < 0.05$).

FIG. 7—Prevalence of hepatic fibrosis and cirrhosis in relation to duration of methotrexate treatment. Solid blocks represent figures for all patients investigated. Hatched blocks represent Newcastle patients only. Figures indicate numbers of affected individuals and totals in each group.

of liver disease were found. Several of them, however, had minor abnormalities of liver function tests and abnormal bromsulphthalein retention of up to 9% at 45 minutes. There was a fairly constant histological picture of mild non-specific reactive hepatitis with fatty change and nuclear vacuolation but the changes were less severe than in the methotrexate-treated patients. One of the group showed mild portal fibrosis and another evidence of recent mild liver cell necrosis. No significant stainable iron was found in any of this group.

Discussion

It was not possible to make an adequate analysis of liver function tests during methotrexate treatment. It is known that abnormalities of bromsulphthalein retention and serum transaminases may be very transitory following the administration of methotrexate (Ryan *et al.*, 1964). The time relationship of liver function test estimations to the dose of methotrexate was not standardized in these patients, thus making comparison impossible. The inadequacy of regular liver function tests, however, was shown by several of the patients. One had received 10-25 mg of methotrexate intramuscularly every one to two weeks for 73 months. During this time liver function tests were estimated on 41 occasions. The only abnormality recorded was a marginal rise of serum alkaline phosphatase to 87 IU on two occasions. A liver biopsy, however, showed liver cell necrosis, fatty change, and fibrosis.

FIG. 8—Severity of liver damage in relation to dose level of methotrexate. There is no significant difference between the levels in any of the groups.

There is evidence that a raised serum alkaline phosphatase level is usually associated with considerable liver damage. Hepatic fibrosis or cirrhosis was found in six out of seven patients who had previously shown raised alkaline phosphatase levels during treatment. It must be emphasized, however, that the converse is not true, and cirrhosis was found in several patients in whom alkaline phosphatase levels had been consistently normal.

The inadequacy of bromsulphthalein retention as a diagnostic test when assessing the degree of liver damage is shown in Fig. 1. Even though most of the more severely affected patients showed abnormal bromsulphthalein retention the degree of abnormality was in many cases no greater than in patients with only minor liver damage histologically. One patient who had discontinued methotrexate four months previously showed normal bromsulphthalein retention (4%) but established cirrhosis on liver biopsy. Normal bromsulphthalein retention does not exclude gross anatomical changes within the liver, especially if treatment has been previously discontinued.

It is likely that most of the severe histological liver changes seen in psoriatic patients treated with methotrexate were due to the treatment. Biopsy specimens from eight patients who had not been treated with methotrexate showed mild non-specific changes and one showed mild portal fibrosis. In a recent study (Berge *et al.*, 1970) of 32 patients with psoriasis who had never been given methotrexate, 16 were found to have fatty liver and two had cirrhosis, but obesity and abuse of alcohol were common in this series and may well have been partly responsible for these findings. Of our patients treated with methotrexate, on the other hand, nearly half had hepatic fibrosis or cirrhosis (46%) and in all but two of these there was also mild to moderately severe fatty change. This combination is uncommon in the U.K. except in alcoholic liver disease. In none of our patients, however, was there a history of alcoholism, and histological features of alcoholic hepatitis such as Mallory's hyaline, single-cell necrosis, and neutrophils were constantly absent. The changes observed are similar to those previously attributed to methotrexate both in psoriasis (O'Rourke and Eckert, 1964; Coe and Bull, 1968; Muller *et al.*, 1969) and in other conditions (Colsky *et al.*, 1955; Hutter *et al.*, 1960; Taft, 1965; Hersh *et al.*, 1966; Talerman and Thompson, 1966).

Arsenic has been cited as a cause of cirrhosis in the older literature (Rolleston and McNee, 1929), but this is currently regarded as unproved (Sherlock, 1968). Treatment of psoriasis with Fowler's solution (potassium arsenite) and other arsenicals was frequent in the past. Several patients in this series admitted to previous treatment with arsenicals and others were uncertain. Though one patient was excluded

because of evidence of arsenic toxicity none of the patients included for analysis here had any evidence of arsenic toxicity. Arsenic does not seem to have played a significant part in the aetiology of liver disease in these patients.

Of the 20 patients treated with methotrexate who had neither cirrhosis nor hepatic fibrosis all but three showed more severe fatty change, nuclear vacuolation, and inflammation than the untreated group. In the absence of recognized causes of fatty liver such as malnutrition, alcoholism, obesity, diabetes mellitus, and systemic steroid therapy it is likely that these abnormalities were due either to the more severe degree of psoriasis in these patients, or to treatment with methotrexate, or to a combination of both these factors.

In order to determine the significance of the prevalence of cirrhosis (19%) found in the patients treated with methotrexate, the overall prevalence of cirrhosis both in the general population and in psoriatics is relevant though difficult to assess. The prevalence of cirrhosis varies in different parts of the world and this must be taken into consideration when comparing data from different countries. In a survey of 15,000 unselected patients admitted to a general hospital in Birmingham between 1959 and 1964 the incidence of all types of cirrhosis was 0.17% (Stone *et al.*, 1968). Between 1 and 2% of the U.K. population are affected by psoriasis (Ingram, 1954), but only a small fraction are as severely affected as the group of patients we have investigated. Psoriasis is not known to predispose to cirrhosis, though liver biopsy abnormalities have previously been reported (Dogliotti *et al.*, 1955; Huriez *et al.*, 1957). Of 40 psoriatics who had not had methotrexate, (the 32 reported by Berge *et al.* (1970) and the eight studied by ourselves) two had cirrhosis and one showed fibrosis. Though this cannot be regarded as a satisfactory control group the figures indicate that the prevalence and severity of the liver damage in the methotrexate group, in which 7 (19%) had cirrhosis and 10 (27%) had fibrosis, is of a totally different order from that seen in the untreated group.

The dosage schedule and route of administration of methotrexate in our series of patients was determined mainly on the grounds of effectiveness, freedom from overt side effects, and convenience. In general, the minimum dose which would keep the patient reasonably free of psoriasis was used. Various other factors which we have not been able to analyse may be important when considering the toxic effects of methotrexate, and these include individual variations in drug metabolism and possible potentiation by other drugs. About two-thirds of the patients in this series were treated with "continuous low dose" methotrexate, and preliminary data suggest that the incidence of severe liver damage may be less in patients treated with "intermittent" dosage. Further investigation is in progress and we hope to report on this aspect shortly. Nevertheless, despite the heterogeneity of this group of patients the severity of liver damage correlates well with the duration of methotrexate treatment (Fig. 6). Since these were the minimum effective dose levels which controlled the patient's psoriasis, the hazards of long-term treatment are obviously considerable. It is possible that we have underestimated the incidence of cirrhosis by excluding three patients in whom the aetiology was disputed.

In a recent study of 20 psoriatic patients (Shapiro *et al.*, 1970) no significant differences in liver function tests or liver biopsy findings could be found between the nine who had received methotrexate and the others who had received topical treatment only. Minor abnormalities, including mild hepatic fibrosis were, however, common in both groups. A "continuous low dose" schedule of methotrexate was used in dose levels similar those given to the patients we have studied but the duration of treatment was only 3 to 30 months. Our data indicate that most of the more severe liver changes occur after longer periods at this dose level. This, together with the smaller number of patients investigated, seems to explain the discrepancies between the two studies. Of the 14 patients in our series who received methotrexate for more than 30

months, six had cirrhosis and another five showed fibrosis, which in some cases was severe.

Conclusion

Methotrexate is known to be hepatotoxic when given in high dosage. In the doses generally used for treating psoriasis liver damage has only recently been recognized as a serious problem. In the patients we have studied hepatic fibrosis has developed after as little as one year's treatment with methotrexate, and after three years' treatment cirrhosis or some degree of hepatic fibrosis was present in about 50% of cases. Unlike many of the other side effects of methotrexate, hepatic fibrosis is potentially irreversible and may progress to cirrhosis.

Liver function tests are of little value in predicting the degree of hepatic damage, though raised alkaline phosphatase levels may suggest fibrosis or cirrhosis. The clinical observation of hepatomegaly during treatment was associated in all cases with considerable hepatic fibrosis or cirrhosis. Liver biopsy is the only investigation in this study which has proved a reliable method of assessment both during and after treatment. The possibility that "intermittent" dosage is less hepatotoxic than "continuous low dosage" requires urgent clarification.

These findings indicate that long-term suppression of psoriasis with methotrexate should be undertaken with the greatest caution. Regular investigation of these patients by liver biopsy at intervals of 6 to 12 months would probably give adequate warning of the onset of irreversible liver damage.

Addendum.—Since submission of this paper it has become quite clear that the hepatotoxicity of methotrexate is much greater when the drug is given by the "continuous low-dose" schedule compared with similar amounts given "intermittently." It should be emphasized that most of the patients considered in this paper were treated by the continuous low-dose schedule. We hope shortly to publish a comparative study between these two regimens.

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Requests for reprints should be addressed to Dr. M. G. C. Dahl.

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Hypothalamic-pituitary-adrenal Function in Patients Treated with Long-term Depot Tetracosactrin

W. J. IRVINE, D. R. CULLEN, S. A. KHAN, J. G. RATCLIFFE

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Summary

Four patients treated with depot tetracosactrin for 10 to 18 months maintained normal hypothalamic-pituitary-adrenal function assessed by the nyctohemeral variation of plasma corticosteroids and by the responses of plasma corticosteroids to insulin-induced hypoglycaemia, lysine-vasopressin, and depot tetracosactrin. The pituitary component of the response was analysed by measuring plasma immunoreactive ACTH levels. Three patients showed a nyctohemeral ACTH rhythm and normal ACTH responses to insulin-induced hypoglycaemia. Consistently undetectable morning plasma ACTH levels were found in the fourth patient, who also showed an unusually delayed rise in both ACTH and corticosteroid levels in response to insulin-induced hypoglycaemia, though the peak values attained were normal.

The lack of suppression of hypothalamic-pituitary-adrenal function together with the good clinical response in these four patients suggests that treatment with depot tetracosactrin should be considered when long-term corticosteroid therapy is required.

Introduction

It is well established that the administration of synthetic or natural corticosteroids over a prolonged period may be followed by suppression of hypothalamic-pituitary-adrenal function. Basal plasma ACTH levels, measured by bioassay (Graber *et al.*, 1965) and radioimmunoassay (Besser *et al.*, 1971), and corticosteroid levels are low initially after steroid withdrawal. An impaired corticosteroid response to insulin-induced hypoglycaemia is also commonly found (Daly *et al.*, 1967; Plumpton and Besser, 1969; Malone *et al.*, 1970). In the latter studies, however, the distinction between a pituitary

and an adrenal defect could not always be made in the absence of plasma ACTH measurements.

Reports on the effect of long-term porcine corticotrophin therapy on hypothalamic-pituitary-adrenal function (Bacon *et al.*, 1968; Carter and James, 1970) have shown that most patients maintain normal or only marginally subnormal corticosteroid responses to insulin-induced hypoglycaemia and that prolonged daily corticotrophin therapy may offer a significant advantage over prolonged corticosteroid treatment.

The present paper reports hypothalamic-pituitary-adrenal function (assessed by nyctohemeral variation, insulin-induced hypoglycaemia, lysine-vasopressin, and tetracosactrin stimulation tests) in four patients treated with long-term depot tetracosactrin. Both plasma immunoreactive ACTH and fluorogenic corticosteroids were measured to analyse the hypothalamic-pituitary-adrenal response in terms of the pituitary as well as the adrenal components.

Patients studied

The clinical data and therapeutic history of the four patients studied are summarized in Table I. All four patients had an excellent clinical response to depot tetracosactrin (Synacthen Depot) (tetracosactrin adsorbed on to an inorganic zinc complex) treatment, and complications (pigmentation and fluid retention) occurred only with doses of 1 mg twice weekly or greater. Local pain was experienced with subcutaneous but not with intramuscular injection. One patient (Case 3) was well controlled on prednisolone 30 mg/day but developed hypertension, a Cushingoid appearance, and multiple vertebral fractures. Following the change to depot tetracosactrin there was some evidence of healing of the fractures. Case 4 was not controlled on betamethasone 2 mg/day for two and a half years or corticotrophin gel 60 IU intramuscularly weekly for seven months.

Methods

Insulin-induced hypoglycaemia tests were performed four to six days after an injection of depot tetracosactrin by giving 0.15 unit of soluble insulin per kg body weight by rapid intravenous injection through an indwelling forearm cannula, a continuous slow intravenous infusion of saline having been set up one hour previously. Samples of blood were obtained via the cannula at -30, 0, +30, +60, +90, and +120 minutes relative to the insulin injection, for determination of

Departments of Endocrinology and Therapeutics, Royal Infirmary, Edinburgh, and M.R.C. Clinical Endocrinology Unit, Edinburgh

W. J. IRVINE, B.SC., F.R.C.P.ED., Consultant Physician

Royal Infirmary, Edinburgh

D. R. CULLEN, M.B., M.R.C.P., Senior Registrar in Medicine
S. A. KHAN, M.R.C.P.ED., D.T.M.&H., Senior Registrar in Dermatology

St. Bartholomew's Hospital, London E.C.1

J. G. RATCLIFFE, M.SC., B.M., Lecturer in Chemical Pathology