

Clinical Reports

Effect of Adrenal Steroids and of Gluten upon Malabsorption Induced by Neomycin

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THE specific defects responsible for the development of primary enteric malabsorption remain obscure. Nevertheless, considerable success in reversing the severe symptom complex of sprue-like states has been achieved through the use of gluten-free diets^{1,2} and adrenal steroids.³

Recently an experimental malabsorption syndrome induced by the oral administration of large doses of neomycin has been described which is reversible upon withdrawal of the drug.⁴⁻⁶ In an attempt to investigate further the similarities between this and the naturally occurring malabsorptive states, the effect of adrenal steroids and of gluten in subjects receiving neomycin has been studied.

METHODS

Thirteen patients served as subjects for this study. Their clinical diagnoses included Laennec's cirrhosis (five patients), cerebral thrombosis (two patients), acute alcoholism (two patients), myocardial infarction, Parkinsonism, cervical disc and diverticulosis. Two of the cirrhotic patients were found to have mild steatorrhea.

One patient (J. Z.) was studied during periods of

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control, neomycin sulfate§ (4 gm. three times daily), and post-drug control, each period being of 6 to 8 days duration. Ten thousand units of supplemental beta carotene were supplied daily to produce rising plasma carotene levels during the study. Serial plasma carotene determinations were obtained on alternate days using the method of Yudkin.⁷ Urinary excretion of d-xylose for a five hour period following a 25 gm. oral load was determined during each study period.⁸

Two patients (W. C. and J. N.) were studied during six to eight day periods of control, neomycin, and neomycin plus cortisone (100 mg. daily). Supplemental doses of beta carotene were given throughout. Again, the absorptive parameters were serial plasma carotene concentrations and urinary excretion of d-xylose.

Biopsy specimens of jejunal mucosa were obtained from one subject (H. M.) during successive periods of control, neomycin, control, and neomycin plus cortisone. Jejunal mucosal biopsy specimens were obtained by the use of the Crosby peroral biopsy capsule.⁹ In this subject urinary excretion of d-xylose was determined during each period.

In three patients (C. R., D. M. and M. H.) plasma carotene levels were determined during five to thirteen day periods of control, cortisone or hydrocortisone (60 mg. daily), and post-steroid control. Three thousands units of beta carotene were administered daily to these subjects in an attempt to produce stable or gradually rising plasma carotene levels in contrast to the sharp increases noted with large doses.

In four subjects (J. L., J. P., H. S. and J. M.) the effect of a gluten-free diet on the malabsorption induced by the administration of neomycin was studied. Serial plasma carotene concentrations

§ Generously supplied by The Upjohn Company, Kalamazoo, Michigan.

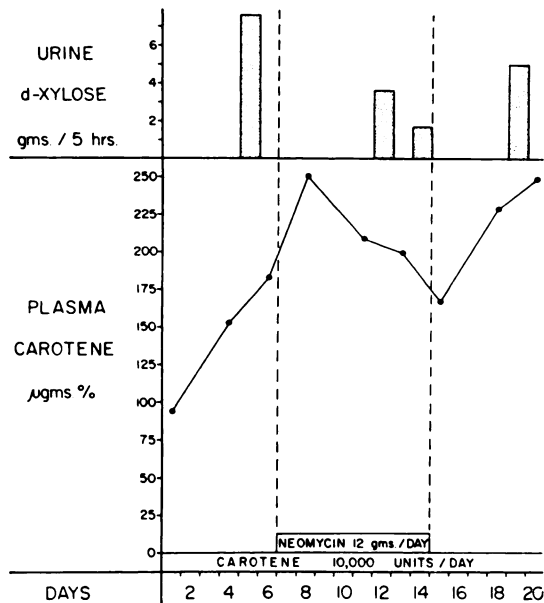


FIG. 1. J. Z. Effect of neomycin upon plasma carotene levels and d-xylose absorption.

were obtained on all four patients and fecal fat and urinary excretion of d-xylose were determined in two subjects (H. S. and J. M.). Following six day periods of control and neomycin these subjects received a gluten-free diet similar to that outlined by Schwartz et al.² Dietary fat was kept constant (102.5 gm. per day) in all three periods. Stools were collected by the use of carmine red markers, and total fecal fat was determined by the "wet" method of Fowweather et al.¹⁰

In two patients (J. H. and J. S.) the specific effect of gluten administration was compared with the effect of neomycin administration. Fecal fat analyses were obtained during successive six day intervals of control, supplementary gluten (12 gm. per day), control, neomycin (6 or 12 gm. per day), and control. These subjects were maintained on a constant diet containing gluten throughout the study. Again, fat intake was uniform throughout (80.5 gm. per day).

RESULTS

Neomycin and Steroids

The typical depressant effects of neomycin on plasma carotene values and urinary excretion of d-xylose occurred in one patient (J. Z.) (Fig. 1). There was a fall in carotene values when neomycin was given despite the supplemental

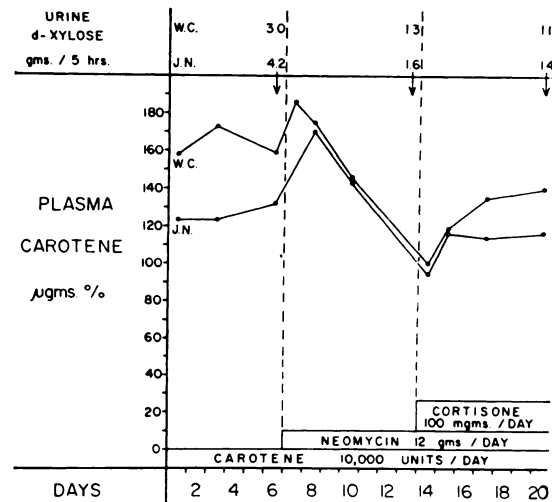


FIG. 2. W. C. and J. N. Effect of cortisone upon plasma carotene level and d-xylose absorption during administration of neomycin.

administration of carotene. When neomycin therapy was withdrawn, the carotene concentration and d-xylose values rose toward the levels that existed before neomycin was administered.

In a similarly designed study, cortisone given with the neomycin yielded apparent reversal or neutralization of the depressant effect of neomycin on the plasma carotene concentrations (Fig. 2). However, the d-xylose values did not parallel the carotene changes, and no reversal of the depressed excretion of d-xylose occurred with cortisone.

The jejunal mucosal biopsy specimens from a single subject during two periods of no medication and periods of neomycin administration and of neomycin plus cortisone administration showed changes which have been described following the administration of neomycin.⁵ These consisted of lymphocytic infiltration, edema of the lamina propria and clubbing of the villi (Fig. 3). These changes were not seen in either of the biopsy specimens obtained during the control period, but were present during each neomycin period and were unaltered by the administration of cortisone. The d-xylose values correlated well with the histologic findings, being 3.9 and 4.7 gm. in the specimens taken during the control periods, 2.2 gm. in the neomycin period, and 2.6 gm. in the

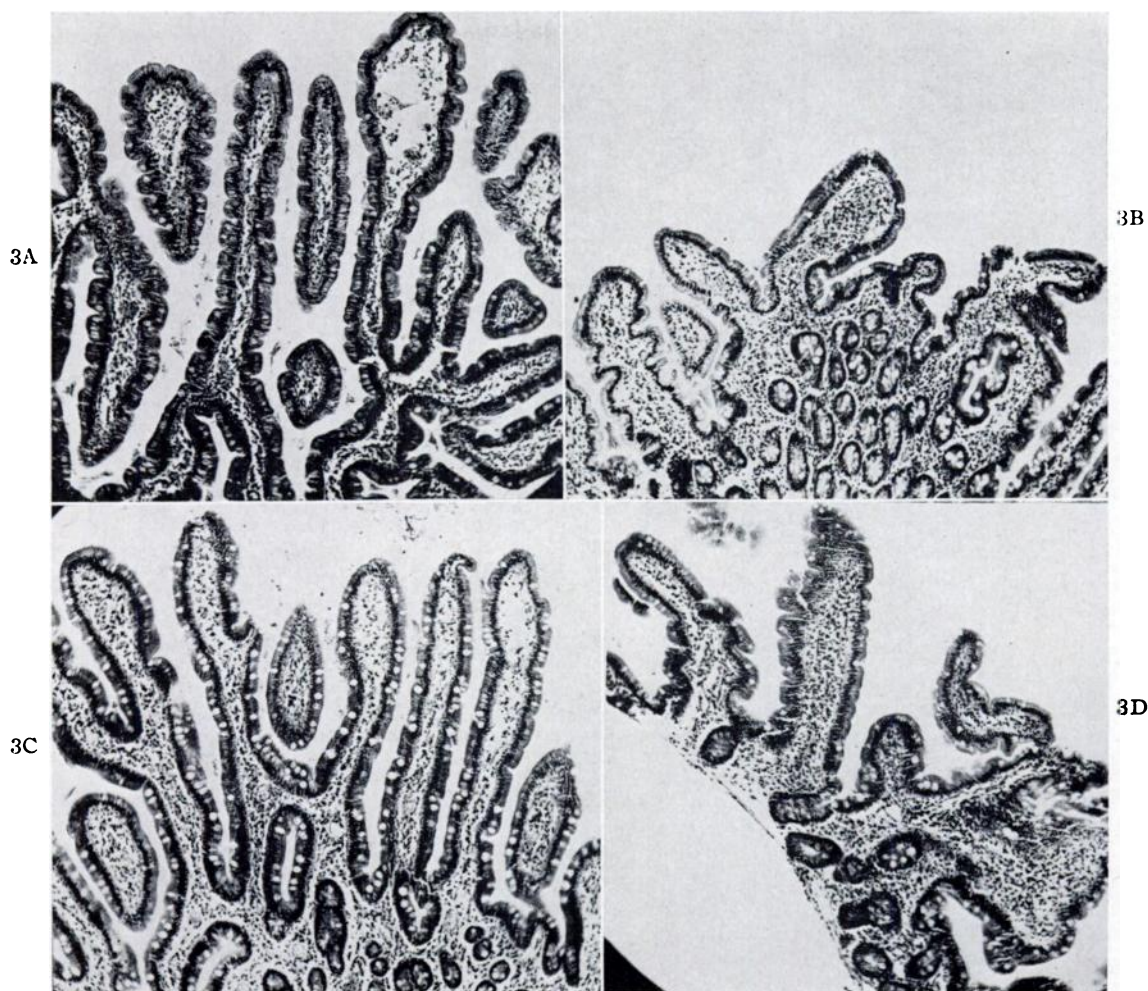


FIG. 3. H. M. Four successive biopsy specimens (hematoxylin and eosin stain, original magnification $\times 90$) from the same subject taken during periods of (A) control, (B) neomycin (12 gm. per day), (C) control and (D) neomycin plus cortisone (100 mg. per day). The changes induced by neomycin, namely, round cell infiltration and edema of the lamina propria and clubbing of the villi are also seen during the period when both neomycin and cortisone were given. Urinary excretion values of d-xylose for the four periods were, respectively, 3.9, 2.2, 4.7 and 2.6 gm.

period when both neomycin and cortisone were administered.

Effect of Steroids upon Plasma Carotene Concentrations

The disparity between the apparent effect of cortisone on carotene values and the lack of effect upon d-xylose and biopsy findings during neomycin administration was investigated further. Of the three subjects studied during the administration of adrenal steroids, a rise in serial plasma carotene values when steroid was given and a subsequent fall to control levels when the steroid was withdrawn was observed

only in one subject (M. H.) (Fig. 4). No significant change attributable to adrenal steroids could be observed in the other two subjects.

Neomycin and Gluten-Free Diet

The removal of gluten from the diet during a prolonged period of neomycin administration appeared to arrest the decline in carotene concentration (Fig. 5). In these studies, however, the carotene levels may have begun to stabilize at a low level during neomycin administration before the gluten was withdrawn from the diet. In the two subjects (H. S. and

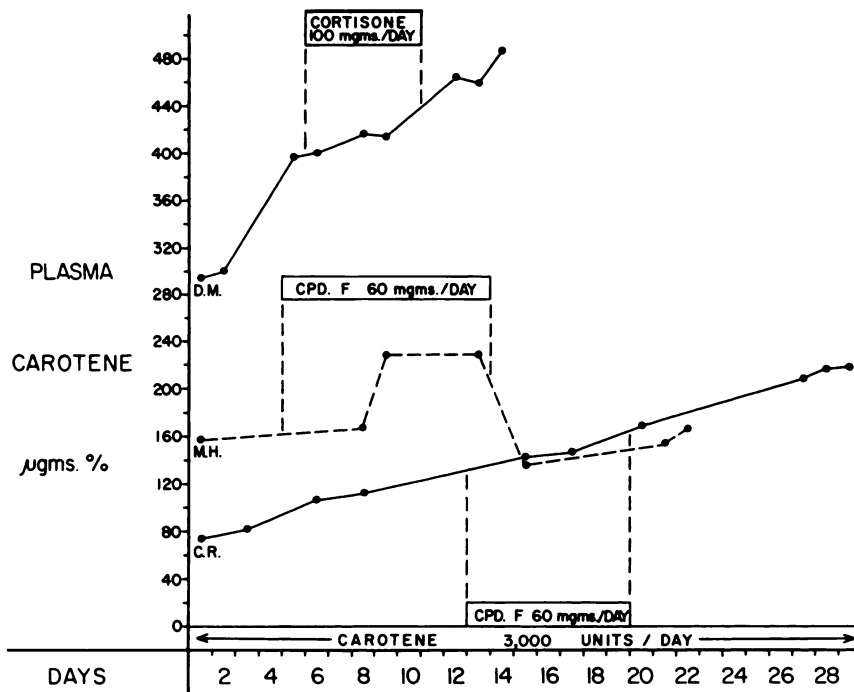


FIG. 4. Effect of steroids alone upon plasma carotene levels.

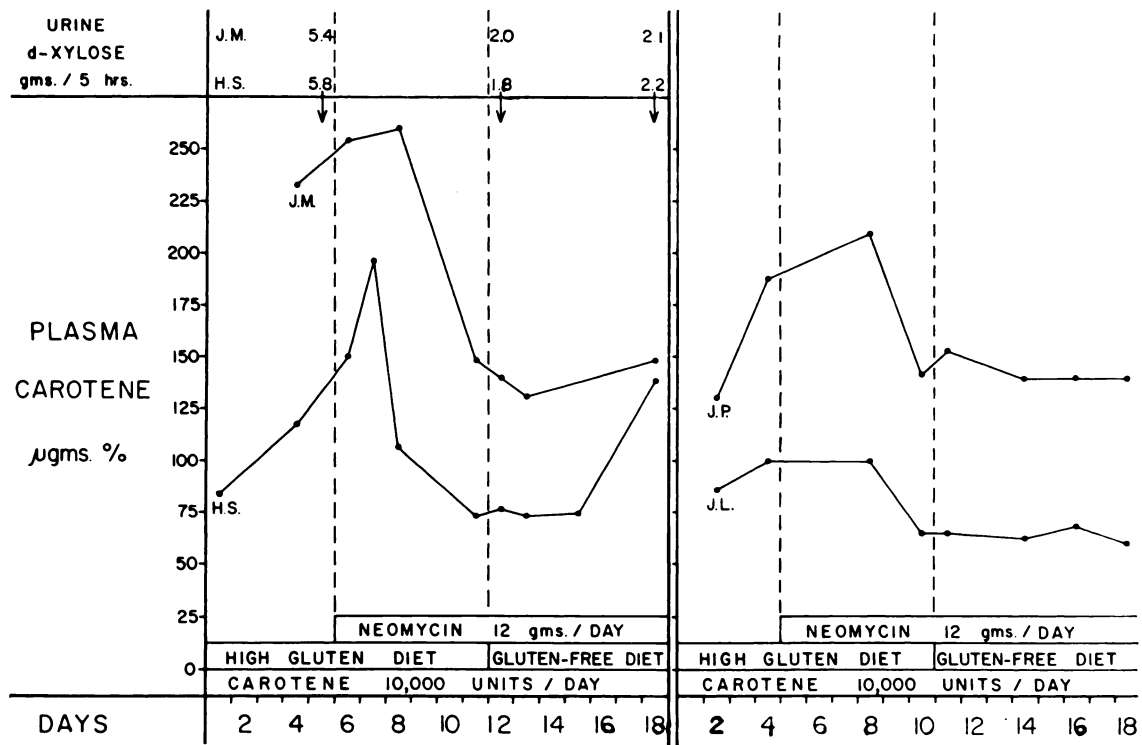


FIG. 5. Effect of removing gluten from the diet upon plasma carotene level and d-xylose absorption.



TABLE I
Fecal Fat Excretion During Neomycin Administration with and without Dietary Gluten (Fat Intake 102 gm. Daily)

Period	Total Fecal Fat (gm./day)	
	H. S.	J. M.
Control (normal diet).....	20.1	15.9
Neomycin 12 gm./day (normal diet).....	37.8	27.3
Neomycin 12 gm./day (gluten-free diet).....	37.7	26.3

J. M.) in whom d-xylose excretion studies were made, the gluten-free diet had no appreciable effect in restoring these values to control levels. Similarly, analyses of fecal fat in two subjects (H. S. and J. M.) revealed that the total quantity of fat excreted during neomycin administration was not reduced by the gluten-free diet (Table I).

Neomycin and Gluten

Despite the inability of the gluten-free diet to

influence the malabsorption induced by neomycin, further studies of the role of gluten were attempted by determining the effect of adding gluten to a normal diet. Twelve grams of supplemental gluten provided each day over six-day periods did not alter either the total fat output or the pattern of fat fractions excreted when contrasted with control measurements (Fig. 6). By comparison, 6 gm. of neomycin given daily doubled the fecal fat loss while 12 gm. daily produced a fourfold increase in total fat excretion. The increase in fecal fat with neomycin was primarily accounted for by increments in free fatty acid and soap.

COMMENTS

The inability of orally administered cortisone to reverse the malabsorption induced by neomycin may have been due to the relatively brief periods employed. However, on the basis of the data obtained, it appears that the sprue states and the neomycin "syndrome" are different in regard to the response to cortisone.

The ability of adrenal steroids to stabilize or even raise serum carotene concentration despite

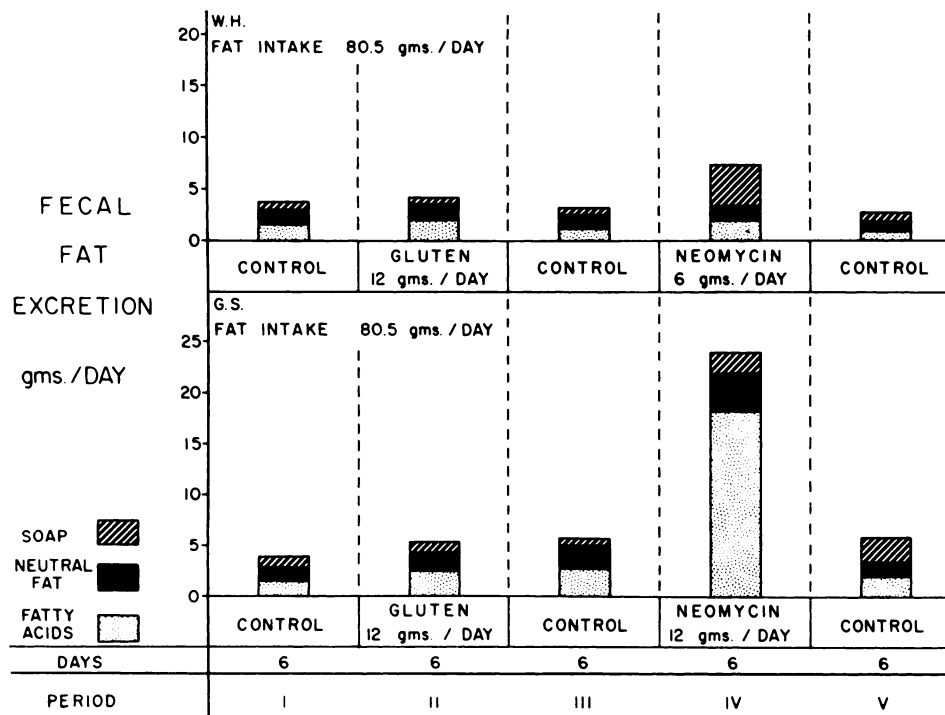


FIG. 6. Comparison of effect of added gluten and of neomycin upon fecal fat excretion. Both subjects received 80 gm. of dietary fat daily.

other evidence of continuing malabsorption suggests that carotene may not be a reliable parameter of improved absorption with such therapy. By contrast, it appears that the results of neither d-xylose test nor the jejunal biopsy are affected by the administration of steroids. This observation in regard to d-xylose confirms the report of Finlay and Wightman.¹¹ Such a finding might also be correlated with the observations of Butterworth and his co-workers¹² which suggest that d-xylose absorption is improved but not returned completely to normal with folic acid treatment in tropical sprue. Similarly, these investigators have reported depression of d-xylose absorption in dogs given aminopterin. The d-xylose test and jejunal biopsy would, therefore, appear to be more reliable parameters of improvement than plasma carotene levels in patients receiving therapy. Under ordinary conditions, however, our experience and that of others¹³ indicate that carotene levels are an excellent parameter of absorption, particularly during carotene loading.

The data obtained also indicate that in contrast to neomycin, gluten does not produce steatorrhea in normal subjects over short periods such as those used in this study. Conversely, the deletion of gluten from the diet for brief periods does not ameliorate the effect of neomycin under the conditions of this study. The observations with the gluten-free diet, however, cannot be considered conclusive in view of the fact that naturally occurring non-tropical sprue is frequently not improved for several weeks or longer when a gluten-free diet is introduced.

SUMMARY

The effect of adrenal steroids and of the gluten-free diet upon the malabsorption syndrome induced by the administration of neomycin has been studied. The parameters employed in this study included serial plasma carotene concentrations, urinary excretion of d-xylose, jejunal mucosal biopsy and fecal fat analysis. The effect of the addition of gluten to a normal diet was compared with the effect of neomycin in equal dosage.

The malabsorption induced by the adminis-

tration of large doses of neomycin was not reversed by the administration of adrenal steroids or the administration of a gluten-free diet as judged by d-xylose excretion, jejunal biopsy or fecal fat excretion. Plasma carotene concentration, however, showed no further decline with neomycin when either cortisone or a gluten-free diet was superimposed. Administration of cortisone or hydrocortisone alone did not consistently alter plasma carotene. The addition of gluten to normal diets did not induce steatorrhea in normal subjects.

The results suggest that under the conditions imposed, using brief periods of study, the malabsorption syndrome induced by the administration of neomycin differs from naturally occurring sprue-like states in the response obtained with the use of adrenal steroids or a gluten-free diet.

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