cant delay in estrogen-withdrawal bleeding when given in doses ranging from 5 to 200 mg daily. The failure of ethisterone to produce a delay in the onset of bleeding in the rhesus monkey is noteworthy in view of the demonstration of progestational activity in women of an oral dose of ethisterone 6 to 8 times that of the effective intramuscular dose of progesterone(7,8). In addition, ethisterone has been shown to have marked progestational activity in the rabbit(4,9).

Hertz *et al.* have reported that norethisterone is about 4 times more active than ethisterone in the production of progestational changes of the endometrium in women(10). From the data presented here it appears that norethisterone given orally in the monkey has approximately 40% of the activity of progesterone given by the subcutaneous route.

Summary. Two 19-nor steroids have been tested for progestational activity, as measured by inhibition of uterine bleeding following estrogen-withdrawal in the rhesus monkey. 19-norprogesterone was found to be 8 to 16 times as active as progesterone when administered parenterally. Orally administered 17α-ethinyl-19-nortestosterone was active at 2.5 mg daily whereas 17α-ethinyl testosterone was inactive in a range of dosages from 5 mg to 200 mg.

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Elevated Chylomicron Index in Multiple Sclerosis and Its Response to Digestive Enzyme Therapy.* (22928)

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The possibility of an altered lipid metabolism in multiple sclerosis has been suggested by the observations of several groups of investigators. Swank(1) found that a low-fat diet appears to reduce frequency and severity of exacerbations of this disease. Roboz, *et al.* (2) have shown by paper electrophoresis a tendency for greater variability in serum lipoprotein patterns of a series of multiple sclerosis patients than in those of normal individuals; this increased variability appears to be associated with a trend toward increased alpha-1 lipoprotein and corresponding decrease in the lipids of the "gamma" region. Aird, *et al.*(3) produced preliminary evidence which indicates that the relative concentration of the Sf(12-20) serum lipoproteins is elevated in those cases of multiple sclerosis graded "rapidly progressive." Zinn and Griffith(4) have demonstrated that in two conditions in which there exists an altered lipid

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metabolism, atherosclerosis and diabetes mellitus, the chylomicron index is elevated. The chylomicron index is the percentage of serum fat particles which appear by dark-field microscopy to be approximately 0.5 μ or greater in diameter.

This report presents evidence of an elevated chylomicron index associated with multiple sclerosis and a means whereby this symptom may be reversed toward or into the normal range.

Methods. Blood samples were obtained from subjects at approximately 9:00 a. m. after a fast period starting after lunch the day before. From noon until 10:00 p. m. of day of fast, the subjects were strictly limited in their fat consumption. They were allowed only plain jello, black coffee, tea, citrus and pineapple juice, and water. From 10:00 p. m. until the sample was taken the next morning, the subject was allowed nothing to eat or drink and was not permitted to smoke. Blood was drawn from puncture wound in the side of finger into several capillary tubes of approximately 1 mm bore. These tubes were fire-sealed at the clean end, and after clot had formed and retracted, they were centrifuged at 1,000 r.p.m. for 10 minutes to separate serum from clot. The serum was then transferred to a clean glass slide, and a cover slip placed on the serum. Dark-field examination of fat particles of the serum was made at 1940x magnification. A net micrometer in the 20x ocular was used to estimate particle size. A count was then made to estimate total number of particles and number of particles of a diameter of 0.5 μ or greater which were visible at one level of focus in 2 large squares of the net micrometer. One large square of the net micrometer included an area of 25 μ^2. This counting procedure was repeated at 50 locations on the slide so that an area of 2,500 μ^2 was examined. In all cases duplicate serum samples were similarly counted. The chylomicron index was then calculated. Initially, following determination of chylomicron index before treatment, patients were paired according to severity of condition into a placebo group and a group which received a commercial preparation containing 150 mg of bile salts and 300 mg of pancreatin in an enteric coating around which is a shell of 250 mg of pepsin bearing a water soluble coating (Entozyme).† The placebo tablets simulated the Entozyme tablets in appearance and neither the patient nor the observers knew which preparation was being administered until after all tests of the treated patients had been made. The subjects were required to take 3 tablets 3 times a day after meals. At times varying from 1 to 18 months after patients began taking the tablets, their chylomicron indices were again determined. More recently a third group has been included. They received 300 mg of triple strength pancreatin as an enterically coated tablet‡ 3 times a day and are being studied in the same manner as those receiving either placebo or Entozyme. This group has varying degrees of severity as the other 2 treatment groups. Age of the patient was not considered in assigning patients to the 3 groups. However, the age ranges for the multiple sclerosis groups and the control group of 12 presumably healthy volunteers were similar in that they all included individuals varying in age from the mid-twenties to the mid-sixties.

Results. Pretreatment chylomicron indices have been obtained on 95 multiple sclerosis patients. Of this number, 28 have not been retested after beginning treatment. Of the remaining 67 patients, 21 received placebo, 34 received Entozyme, and 12 received pancreatin. The results of this study are summarized in Table I. The chylomicron index values of Entozyme treated patients are arranged in this table according to the time interval after initiation of treatment at which they were obtained; therefore, in some cases the subjects included in the 1-2 month group are included also in the 2-3 month and/or in the 5-18 month group. Statistical significance of the differences of the means was determined by the formula $CR = \frac{\overline{X}_1 - \overline{X}_2}{\sqrt{(SE)_1^2 + (SE)_2^2}}$. CR must

† A. H. Robins Co., Inc.

‡ Wilson Laboratories.

TABLE I. Effect of Placebo, Pancreatin, and Entozyme Treatment on Chylomicron Index in Multiple Sclerosis.

	Normal control	M.S. pre-treatment	M.S. placebo treated	M.S. Entozyme treated 1–2 mo	M.S. Entozyme treated 3–4 mo	M.S. Entozyme treated 5–18 mo	M.S. pancreatin treated, 1–2 mo
No. cases	12	95	21	14	18	16	12
Mean & S.D.	34 ± 4.92	55 ± 5.04	55 ± 5.55	37 ± 6.96	34 ± 5.30	37 ± 7.94	41 ± 11.92
Index range	26–41	37–63	45–62	25–57	26–48	23–52	29–61

have a value of 2 or more for the difference of 2 mean values to be significant. By this standard there is no difference between the values for untreated and placebo-treated multiple sclerosis patients, but a significant difference does occur between these and the values for normal subjects. Entozyme treated patients and pancreatin treated patients, respectively. No correlation was found between chylomicron responses and age of the patient. The normal control group was small in number (12 subjects). However, a much larger number of normal cases has been tested by one of us (RGS) but at a different time and in a different laboratory and are therefore not included in Table I. The values were similar to those of the present 12 cases and to those reported by Zinn and Griffith(4) whose control group had an average chylomicron index of 28% ± 6.5%.

Of additional interest are 2 patients who, having been on Entozyme for over a year, voluntarily ceased therapy. Just before cessation of therapy, one of these patients had a chylomicron index of 33%; 3 months later, the index had not changed, but at 5 months after cessation of therapy, the chylomicron index was elevated to 57%. The other patient's chylomicron index was found to have increased from 32%, the value immediately before the Entozyme was stopped, to 63% four months later. One month after therapy was reinstituted, both patients again had chylomicron indices within the normal range, 39% and 36% respectively.

Comments. In multiple sclerosis, the chylomicron index is significantly elevated (55%) and is similar to that found by Zinn and Griffith(4) to be associated with atherosclerosis and diabetes, 55% and 52% respectively. However, whether or not the mechanism producing the elevated chylomicron index in multiple sclerosis is in any way related to that of either atherosclerosis or diabetes is a question which cannot be answered at this time.

The elevated chylomicron index may be considered a symptom of multiple sclerosis. The alleviation of this symptom may or may not reflect a beneficial effect in the patient. In this respect, the evaluation of digestive enzyme therapy in multiple sclerosis must await long term clinical evaluation.

Summary. The chylomicron index is above normal in multiple sclerosis. The oral use of a preparation of pepsin, pancreatin, and bile salts lowers the chylomicron index to normal. Pancreatin alone appears to have a similar effect although, as judged by the standard deviations, less regular than the pepsin, pancreatin and bile salts combination. No response was shown by the group which received placebo.

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