of the animal. Since it has been reported that periodic increases in DNase II activity, as well as that of other acid hydrolases in actively regenerating tissue, are synchronized with the cycles of mitotic division(18), the high levels of DNase II, in dystrophic muscle, may indicate attempts of damaged muscle to regenerate. Perhaps a more important source of increased DNase II activity, as well as that of other hydrolytic enzymes, is an actual increased synthesis of lysosomes by the muscle cell. An increase in number of lysosomes and in activity of acid phosphatase has been reported in the renal papillae of potassium-deficient rats(19).

Summary. Determinations carried out in dystrophic muscle from the mouse and chicken with hereditary dystrophy, and from the Vit. E-deficient rabbit, revealed a 5- to 10-fold increase in activity of acid deoxyribonuclease when compared with controls. Noncollagen protein nitrogen content of dystrophic chicken breast muscle was 20% less than that of controls.

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Reduction of Serum Cholesterol Concentrations by Paromomycin in Patients with Arteriosclerosis.* (29017)

PAUL SAMUEL, OLYA B. SHALCHI AND CHARLES M. HOLTZMAN
(Introduced by L. G. Parmer)
Department of Medicine, Long Island Jewish Hospital, New Hyde Park, N. Y.

It has been reported from this laboratory that oral administration of 1.5 to 2 g of neomycin sulfate reduced significantly the concentration of serum cholesterol in patients (1,2,3). Following this finding the effect of oral administration of 15 additional antibacterial drugs on human serum cholesterol levels has been studied(3). Oral para-aminosalicylic acid (8 to 12 g daily) reduced serum cholesterol concentrations comparably to neomycin, and oral administration of kanamycin and chlortetracycline (1 to 2 mg daily) resulted in significant but less marked reduction of serum cholesterol levels(3). All other assayed antibacterial substances had no discernible effect on serum cholesterol(3).

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TABLE I. Effect of Oral Administration of Paromomycin (2 g Daily) on Average Total Serum Cholesterol Concentration (and Standard Deviation) of 10 Patients.

Patient, age, sex	Diagnosis	Avg control total serum cholesterol, mg %	Wk*	Paromomycin avg total serum cholesterol, mg %	% fall	p
J.C. 42 ♂	Cerebral vascular accident	287 ± 12	16	238 ± 14	17%	<.001
D.B. 42 ♀	Essential hypertension	229 ± 17	13	177 ± 19	23%	<.001
J.L. 47 ♂	Coronary artery disease	327 ± 12	11	248 ± 18	24%	<.001
A.K. 12 ♂	Familial hypercholesterolemia	816 ± 48	11	727 ± 46	—	>.01
H.F. 46 ♂	Coronary artery disease Cerebral vascular accident	322 ± 14	9	273 ± 14	15%	<.001
A.F. 44 ♀	Peripheral vascular disease	264 ± 14	9	233 ± 17	12%	<.005
C.S. 43 ♀	Coronary artery disease	344 ± 11	8	350 ± 19	—	>.4
H.Z. 42 ♀	Coronary artery disease Familial hypercholesterolemia	579 ± 17	8	469 ± 14	19%	<.001
A.M. 78 ♀	Coronary artery disease	238 ± 13	8	219 ± 21	—	>.05
E.A. 55 ♀	Coronary artery disease	206 ± 13	5	179 ± 8	13%	<.01

* Weeks on paromomycin.

In the present paper the effect of paromomycin, not available during the previous studies, on total serum cholesterol concentration of patients is reported.

Material and methods. Ten patients, 4 males and 6 females, aged 12 to 78 years, were studied Food intake of the patients was uncontrolled, but they were instructed to adhere to their customary diets. Medications known to influence serum cholesterol concentrations or other antibacterial drugs were not given. Patients were weighed weekly, and blood counts, tests of urine, blood urea nitrogen, serum bilirubin and cephalin flocculation were carried out periodically.

Serum cholesterol concentrations were determined once a week in the fasting state by the method of Abell *et al*(4). Control serum cholesterol levels, prior to administration of the drug, were observed for 6 weeks or longer. Serum cholesterol concentrations were determined in 9 patients for 6 to 24 weeks during a recovery period after the experimental medication was discontinued.

Paromomycin sulfate† was given orally at the daily dose of 2 g in 2 divided doses, for periods of 5 to 16 weeks.

Results. The results of oral administration of paromomycin are included in Table I. Total serum cholesterol concentrations were reduced significantly ($p<0.01$) in 7 of the 10 patients studied, by 12 to 24%. The average for the group was 18%. In the remaining 3 subjects the change in serum cholesterol levels was not statistically significant. Serum cholesterol concentrations reached a low point after 1 to 4 weeks and remained there as long as paromomycin was administered, returning to control levels 1 to 6 weeks later (Fig. 1 and 2).

No major side-effects occurred during administration of paromomycin. Three of the 10 patients developed temporary mild diarrhea, which was spontaneously controlled in a few days without changing the medication. The weights of the patients remained within 2 lb variation.

Discussion. The possible mechanisms by which neomycin lowered human serum cholesterol concentrations have been discussed (1,2,3). It was shown that intramuscular administration of the drug failed to alter serum cholesterol levels, indicating that the action of neomycin was dependent on its presence in the gastrointestinal tract. There was no demonstrable enterohepatic circulation of the drug, which excluded its direct action on the liver. Absorption of I^{131} trioleate was not different during control periods and periods of oral neomycin administration in the same patients(3). Although there is still no conclusive evidence, it was suggested that the reduction of serum cholesterol was related to modification of the intestinal bacterial flora,

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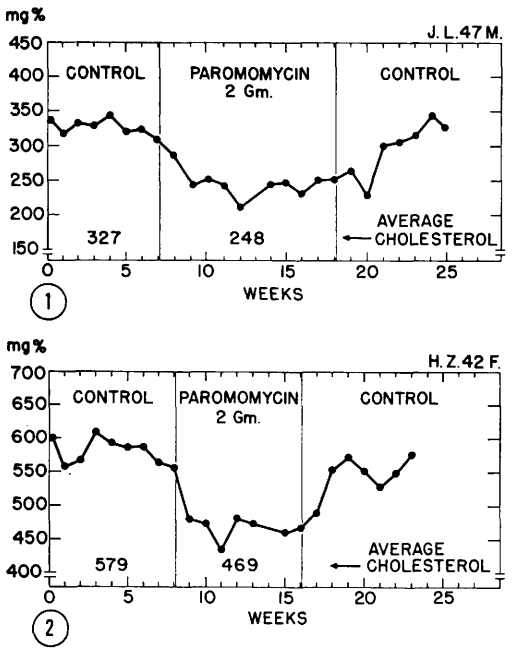

FIG. 1. Effect of daily oral administration of 2 g of paromomycin on total serum cholesterol concentration of patient J.L., 47 ♂.

FIG. 2. Effect of daily oral administration of 2 g of paromomycin on total serum cholesterol concentration of patient H.Z, 42 ♀.

and that geographic differences in serum cholesterol levels of different populations may thus be mediated through environmentally-induced differences of the character of normal intestinal bacteria(3). Subsequently an increase of fecal bile acid excretion during neomycin administration was reported(5), possibly indicating the bile acid sequestrating effect of the changing intestinal flora.

The chemical structure of paromomycin resembles closely that of neomycin, kanamycin and streptomycin(6). Its antibacterial spectrum is related to that of neomycin and kanamycin(7,8) and like the latter, it is poorly absorbed from the gastrointestinal tract in man and in animals(7,8). Its oral administration was well tolerated in this study, which is in agreement with findings of other investigators(8). In animals, when given parenterally in high doses, renal tubular and glomerular abnormalities resulted(7).

In spite of its chemical resemblance to paromomycin, neomycin and kanamycin, oral administration of streptomycin failed to influence the concentration of serum cholesterol of patients in previous studies(2,3). Kunin, Wilcox, Najarian and Finland(9) reported that kanamycin, paromomycin and neomycin had essentially the same activity *in vitro* against various Enterobacteriacae, and complete cross-resistance resulted between these 3 antibiotics from repeated subcultures in the presence of any one of them. Similar cross-resistance resulted in fecal organisms during treatment, when the antibiotics were given over a sufficient period. However, "streptomycin-resistant strains isolated from patients did not show cross-resistance to paromomycin, neomycin or kanamycin, and results obtained from the fecal strains suggested that strains resistant to the latter, when obtained from patients under treatment, did not readily acquire cross-resistance to streptomycin"(9). In the absence of direct evidence it cannot be proved that the above phenomenon is directly correlated with the action of the neomycin-related drugs on serum cholesterol concentrations. However, it is of considerable interest that streptomycin, which resembles the other 3 drugs structurally, differs in its bacterial resistance pattern and also fails to lower serum cholesterol.

No evidence is available to explain the mechanism by which paromomycin and related antibiotics reduce serum cholesterol concentrations. It is, however, reasonable to assume that this mechanism is similar in paromomycin, neomycin and kanamycin, and it is suggested that it depends on the effect of the drugs upon the intestinal bacterial flora.

Summary. Oral administration of paromomycin for 5 to 16 weeks, in daily doses of 2 g, resulted in significant ($p<0.01$) reduction of average total serum cholesterol concentrations by 12 to 24% (average: 18%) in 7 of 10 patients studied. There was no significant change in serum cholesterol levels of the remaining 3 patients. Serum cholesterol concentrations remained low during paromomycin administration and returned to control levels after the drug was discontinued. There were no major side-effects. The possible role of the intestinal bacterial flora in the cholesterol lowering effect of paromomycin and

other related antibiotics was discussed.

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Density-Gradient Sedimentation of Skin-Sensitizing Antibody and β_2A-Globulin in Serum of Allergic Individuals.* (29018)

A. I. TERR AND J. D. BENTZ (Introduced by W. D. Block)
Veterans Administration Hospital, and Montgomery Allergy Research Laboratory, University of Michigan Medical Center, Ann Arbor

Two classes of antibodies, whose sedimentation coefficients are 7S and 19S respectively, have been recognized in many species including the human. The skin-sensitizing antibody (SSA) of human atopic hypersensitivity has not yet been clearly identified with either of these classes of antibody. Sehon has reported that ragweed SSA sediments with the 19S globulins(1). Stanworth(2) and Augustin(3) have observed that SSA to horse dander and grass pollen, respectively, appeared to be associated with the 7S globulins. Heimlich *et al* found equal activity in serum fractions enriched with either 7S or 19S globulins (4). Rockey and Kunkel localized the SSA in a glucagon-sensitive patient in a sedimentation zone intermediate between 7S and 19S (5).

Recently attention has been focused on the possibility that human SSA may be a β_2A-globulin(6,7). The sedimentation coefficient of β_2A-globulin has not been firmly established, but present evidence suggests that it is in the 7S class of globulins but with a tendency to form polymers resulting in complexes of the order of 9S to 13S(8). In this study we have investigated the sedimentation properties of both skin-sensitizing antibody and β_2A-globulin in the serum of patients allergic to ragweed pollen by sucrose density-gradient ultracentrifugation.

Materials and methods. For reference purposes purified and concentrated 7S and 19S globulins were sedimented separately in sucrose density gradients. The 7S fraction used for this purpose was immunoelectrophoretically pure gamma globulin. It was prepared from normal serum by Na_2SO_4 precipitation followed by starch-block electrophoresis. The starch-block eluates were further purified by ion-exchange chromatography on a DEAE-cellulose column. The 19S fraction was obtained by gel filtration of serum on a Sephadex G-200 column. 0.2 ml samples of each purified fraction were layered over 5.0 ml sucrose gradients and centrifuged for 18 hours at 35,000 rpm in a Spinco model L ultracentrifuge using the SW-39 swinging bucket rotor. Thirty successive fractions were collected from a hole punctured in the bottom of the tube and assayed for protein spectrophotometrically at 280 mμ.

0.2 ml samples of serum from 4 untreated ragweed-sensitive patients were sedimented under conditions identical to the reference samples. The resulting fractions were assayed for: 1) protein, 2) skin-sensitizing antibody by the Prausnitz-Küstner (P-K)

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