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A Quantitative Metabolic Defect in Lipid Metabolism Associated with Abnormal Serum Lipoproteins in Man

By Max W. Biggs, M.D., and David Colman, B.S.

Tritium-labeled cholesterol has been fed to a selected series of patients to demonstrate a quantitative metabolic defect in lipid metabolism in the presence of abnormal serum lipoprotein spectra. Patients with abnormal serum lipoprotein spectra carry a greater fraction of their newly absorbed cholesterol in the esterified form than do normals.

THE LIPOPROTEINS of human serum are conveniently defined and quantitated in the ultracentrifuge according to their flotation rates under carefully defined conditions.[1] Inasmuch as the concentration of certain serum lipoprotein molecules so defined (S_f 12–20; S_f 20–100*) show a positive correlation with the incidence of human atherosclerosis,[2] those factors which determine the lipoprotein spectrum of the serum in any individual become of potential importance in understanding the pathologic physiology of atherosclerosis.

A search for determining factors important in lipoprotein metabolism logically includes several varied aspects of cholesterol metabolism. The interrelationships between serum lipoprotein spectra and oral cholesterol metabolism are under investigation in this study. Labeled cholesterol has been administrated to a series of 10 patients, and it has been possible to demonstrate a quantitative metabolic defect in lipid metabolism in patients who have abnormal ultracentrifugal lipoprotein spectra.

Tritium-labeled cholesterol[3] has been fed to 10 selected patients: two with xanthoma tuberosum, two with xanthoma tendinosum, three with clinical atherosclerosis, and three normals. Patients with xanthomata have been used in four instances because they afford a unique opportunity to study extremes in lipoprotein spectra.[4] Patients with xanthoma tuberosum have elevated serum cholesterol values associated with an extremely abnormal ultracentrifuge pattern; the lipoprotein spectrum approaches that seen in cholesterol-fed rabbits. In xanthoma tendinosum, on the other hand, there is also a hypercholesterolemia but here the ultracentrifuge lipoprotein spectrum is of particular interest in that the hyperlipoproteinemia remains almost entirely within the S_f 0–12 class of lipoprotein molecules. The 10 patients selected then afford a sampling over a wide range of lipoprotein spectra. Besides providing a wide range of serum lipoprotein spectra the patients also provide wide variations in serum cholesterol values as well. Within the 10 patients of the group, however, there is no correlation between the level of serum cholesterol and the type of centrifuge pattern found. As a result it has been possible to evaluate independently the quantitative metabolic differences in lipid metabolism observed in the various individuals with respect to the absolute serum cholesterol level and also with respect to the concentrations of various lipoprotein molecules.

Experimental Procedure

A single dose of tritium-labeled cholesterol, between 0.55 and 0.77 mc., was administered to each

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* Units are Svedbergs of flotation (S_f). One S_f unit equals a migration rate of 10^{-13} cm. sec. dyne Gm. at 26 C. in a medium of sodium chloride solution of density 1.063.

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patient at the beginning of the experiment. The cholesterol, average dose = 0.63 Gm., was dissolved in 15 cc. of warm Wesson oil and emulsified into 200 cc. of whole milk together with 60 Gm. of ice cream. After the ingestion of this labeled fatty meal, periodic blood samples were obtained, and the serum free and total cholesterol specific activities were determined. The cholesterol in each serum sample was precipitated as the digitonide which in turn was combusted for tritium activity determinations as previously described.[5] The experiment was done on an outpatient basis and the patients ate their regular diets at home.

Just prior to administering the tritium cholesterol a blood sample was taken for ultracentrifugal analysis of the serum lipoprotein spectrum. Three serum cholesterol determinations were made on each patient according to the method of Schoenheimer-Sperry[6] as modified by Colman.[7] These determinations were done at approximately weekly intervals usually on the serum of days 1, 7 and 14 following the start of the experiment.

Results

For the sake of clarity the experimental results are presented in graphic form in figures 1 through 10. An ultracentrifugal analysis of the lipoprotein spectrum of the serum of each patient at the beginning of the experiment tops each figure. The concentration of lipoprotein molecules, S_f 0-12, S_f 12-20, S_f 20-100 and S_f 100-400, read from each plate, is included in the legend. It should be noted that the ultracentrifuge plates were not made at the same serum concentration in each case; the fold concentration is included for each. The shaded area in frame 5 of each plate is proportional to the concentration of S_f 12-20 molecules. The shaded area in frame 2 is the area read for S_f 20-100 molecules. The concentration of S_f 0-12 molecules has been taken from frame 5; the concentration of S_f 100-400 molecules from frame 1.*

Beneath each ultracentrifuge plate is the corresponding cholesterol specific activity absorption curve for that patient. Here the free cholesterol specific activities and the total cholesterol specific activities have been plotted as a function of time in days. The abscissa is broken at the right to include specific activity determinations over a several weeks period.

Identification of the patient together with certain pertinent information such as the tritium-cholesterol dosage is included in the legend.

The serum cholesterol values are included in table 1.

TABLE 1.—*Serum Cholesterol Values on the 10 Patients Studied*

Patient No.	Sample No. 1		Sample No. 2		Sample No. 3		Average		Average Ratio Total Chol / Free Chol.
	Free	Total	Free	Total	Free	Total	Free	Total	
	mg. %	mg. %	mg. %	mg. %	mg. %	mg. %	mg. %	mg. %	
1	141	496	151	566	138	496	143	519	3.6
2	162	560	140	546	144	588	149	565	3.8
3	51	223	50	232	48	224	50	226	4.5
4	84	358	88	367	74	331	82	352	4.3
5	37	178	49	208	40	194	42	193	4.6
6	73	273	78	268	75	258	75	266	3.5
7	72	275	69	283	58	239	66	266	4.0
8	154	500	142	538	143	550	146	529	3.6
9	63	268	58	243	71	358	64	290	4.5
10	76	259	72	258	72	259	73	259	3.5

Discussion

Examination of the 10 cholesterol specific-activity absorption curves shows a quantitative difference in the way various individuals handle oral cholesterol with respect to its partition after absorption into the free and esterified pools of serum cholesterol. Patient 1, after 24 hours, shows a free serum cholesterol specific activity 2.19 times as great as the total serum

* The method of plate reading employed in this laboratory has been developed by Dr. John Gofman and will be reported in detail elsewhere.

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cholesterol specific activity; while patient 10, after 24 hours, shows a free serum cholesterol specific activity only 0.52 times as great as the total serum cholesterol specific activity. The remaining eight patients lie distributed between these two extremes.

Ultracentrifugal analyses of the lipoprotein spectra of several thousands of "normal" young men and women show that the normal lipoprotein spectrum consists of a moderate or high concentration of S_f 0–12 molecules, with only low concentrations of molecules with greater flotation rates than this (S_f 12–20; S_f 20–100; S_f 100–400). In the following discussion S_f 0–12 molecules are treated as normal; S_f 12–400 molecules as abnormal.

A qualitative comparison of the cholesterol specific activity absorption curves with the ultracentrifuge plates in each case shows that those patients with a "normal or nearly normal" lipoprotein spectrum, with the bulk of their lipoprotein molecules in the S_f 0–12 class, have a cholesterol specific activity absorption curve wherein the free cholesterol specific activity is greater than the esterified cholesterol specific activity during active absorption of the tritium-cholesterol dosage. On the contrary those patients with a "moderately or grossly abnormal" lipoprotein spectrum with high concentrations of S_f 12–400 molecules do not show this relationship, but rather the abnormal centrifuge plates accompany cholesterol specific activity absorption curves wherein the free cholesterol is lower than or equal to the esterified cholesterol specific activity.

To correlate the cholesterol specific activity absorption curves against the total serum cholesterol and against the concentrations of various lipoprotein molecules it has been necessary to transpose the cholesterol specific activity absorption curves into some numeric evaluation. For this purpose the ratio of the free cholesterol specific activity over the total cholesterol specific activity at 24 hours has been used. From the qualitative characteristics of the centrifuge plates and the cholesterol specific activity absorption curves (figs. 1 to 10) it is seen that when normal molecules (S_f 0–12) predominate the free cholesterol specific activity at 24 hours is greater than the total cholesterol specific activity. When abnormal molecules predominate (S_f 12–400) the esterified cholesterol has the greater specific activity.

In table 2 the ratio of free cholesterol specific activity over total cholesterol specific activity, the ratio of normal S_f 0–12 molecules over abnormal S_f 12–400 molecules, and the total serum cholesterol values are listed for each patient. Calculation of Pearson's product-moment coefficient of correlation between the ratio of free cholesterol specific activity over total cholesterol specific activity and the ratio of normal molecules (S_f 0–12) over abnormal molecules (S_f 12–400) gives a value of −0.93 (0.765 is significant at 1 per cent level). Calculation of the same correlation coefficient for the ratio of free cholesterol specific activity over total cholesterol specific activity and the total serum cholesterol values in milligrams per 100 cc. gives a value of +0.39 which cannot be proven significant from these data.

Thus the cholesterol specific activity absorption curves during the period of active tracer-cholesterol absorption show a positive correlation with the lipoprotein spectrum; however, from the data they cannot be correlated in significant fashion with the total serum cholesterol values in the same individuals. This positive correlation of the cholesterol specific activity absorption curves with the lipoprotein spectra and the failure of a significant correlation with the total serum cholesterol is interpreted as indicating that an ultracentrifugal analysis of the serum lipoprotein spectrum evaluates a metabolic defect in lipid metabolism which may be completely independent of the total serum cholesterol values.

Warner[1] reported in his observations on the metabolism of tracer cholesterol following oral ingestion that in dogs and terminal patients the free cholesterol specific activity is greater than the esterified cholesterol specific activity during the period of active absorption. We have previously observed that rabbits do not handle oral cholesterol in similar fashion but rather show a higher cholesterol ester specific activity than free cholesterol specific activity.[9] These observations are entirely consistent inasmuch as dogs and many terminal patients

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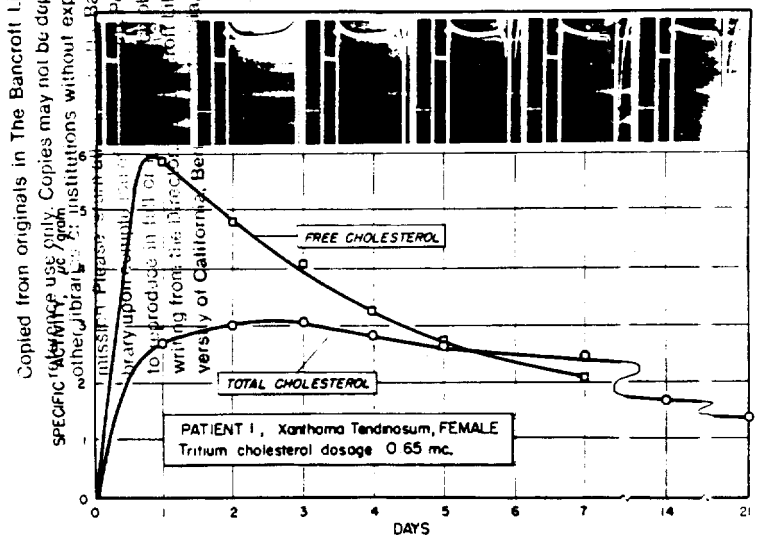

FIG. 1. Patient 1, a 52 year old female with xanthoma tendinosum of something more than 10 years duration received 0.60 Gm. of tritium cholesterol (S.A. = 1.07 mc./Gm.). The rise in serum cholesterol specific activity, free and total, has been plotted against time in days. The ultracentrifuge plate shows the following concentrations of lipoprotein molecules in the serum: S_f 0–12 = 974 mg. per 100 cc.; S_f 12–20 = 102 mg. per 100 cc.; S_f 20–100 = 59 mg. per 100 cc.; and S_f 100–400 = 14 mg. per 100 cc. The ultracentrifuge plate was made at a two-fold concentration.

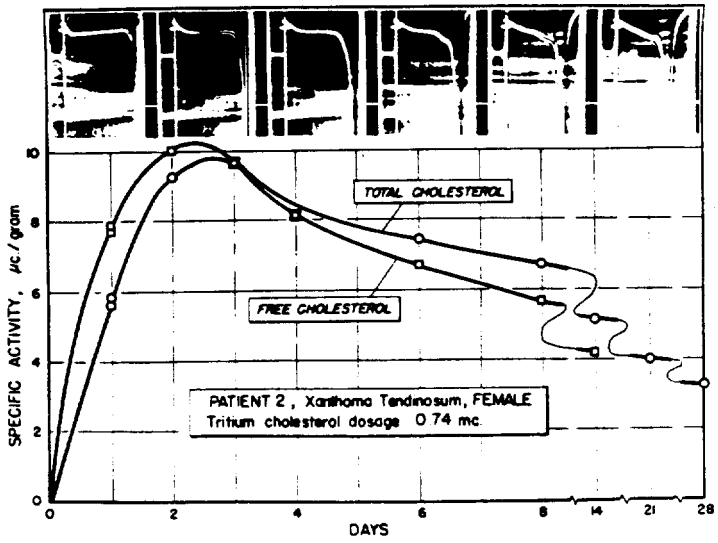

FIG. 2. Patient 2, a 51 year old female with xanthoma tendinosum of approximately 30 years duration, received 0.76 Gm. of tritium cholesterol (S.A. = 1.07 mc./Gm.). The rise in serum cholesterol specific activity, free and total, is plotted against time in days. The ultracentrifuge plate shows the following concentrations of lipoprotein molecules in the serum: S_f 0–12 = 966 mg. per 100 cc.; S_f 12–20 = 252 mg. per 100 cc.; S_f 20–100 = 166 mg. per 100 cc.; and S_f 100–400 = 28 mg. per 100 cc. The ultracentrifuge plate was made at a one-fold concentration.

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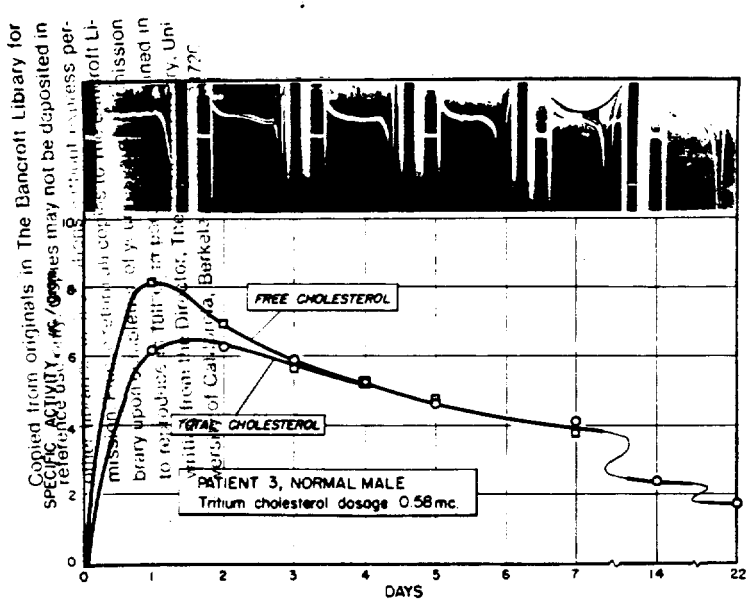

FIG. 3. Patient 3, a normal male, age 31, received 0.54 Gm. of tritium-cholesterol (S.A. = 1.07 mc. Gm.). The rise in serum cholesterol specific activity, free and total, is plotted against time in days. The ultracentrifuge plate shows the following concentrations of lipoprotein molecules in the serum: S_f 0–12 = 274 mg. per 100 cc.; S_f 12–20 = 53 mg. per 100 cc.; S_f 20–100 = 77 mg. per 100 cc.; and S_f 100–400 = 10 mg. per 100 cc. The ultracentrifuge plate was made at a five-fold concentration.

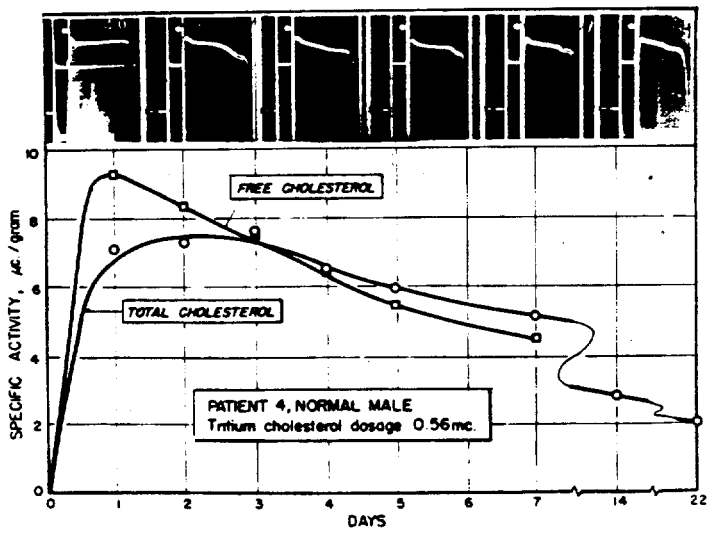

FIG. 4. Patient 4, a normal male, age 31, received 0.53 Gm. of tritium-cholesterol (S.A. = 1.07 mc. Gm.). The rise in serum cholesterol specific activity, free and total, is plotted against time in days. The ultracentrifuge plate shows the following concentrations of lipoprotein molecules in the serum: S_f 0–12 = 446 mg. per 100 cc.; S_f 12–20 = 80 mg. per 100 cc.; S_f 20–100 = 130 mg. per 100 cc.; and S_f 100–400 = 27 mg. per 100 cc. The ultracentrifuge plate was made at a five-fold concentration.

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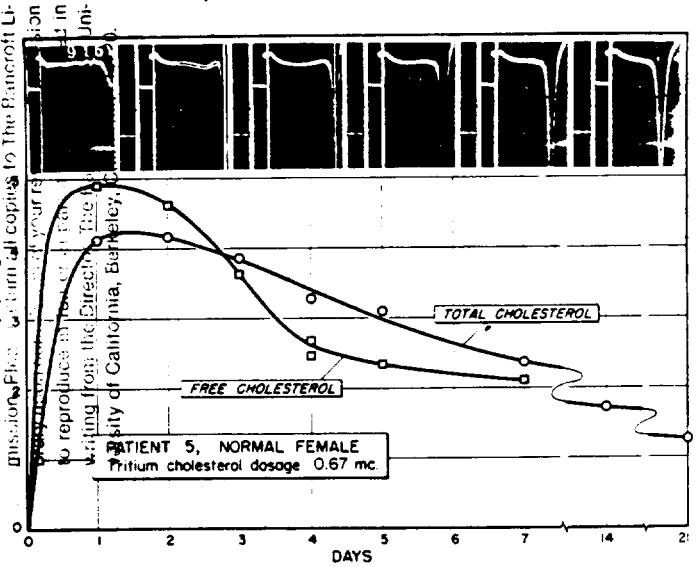

FIG. 5. Patient 5, a normal female, age 26, received 0.63 Gm. of tritium-cholesterol (S.A. = 1.07 mc. Gm.). The rise in serum cholesterol specific activity, free and total, is plotted against time in days. The ultracentrifuge plate shows the following concentrations of lipoprotein molecules in the serum: S_f 0–12 = 259 mg. per 100 cc.; S_f 12–20 = 15 mg. per 100 cc.; S_f 20–100 = 49 mg. per 100 cc.; and S_f 100–400 = 10 mg. per 100 cc. The ultracentrifuge plate was made at a five-fold concentration.

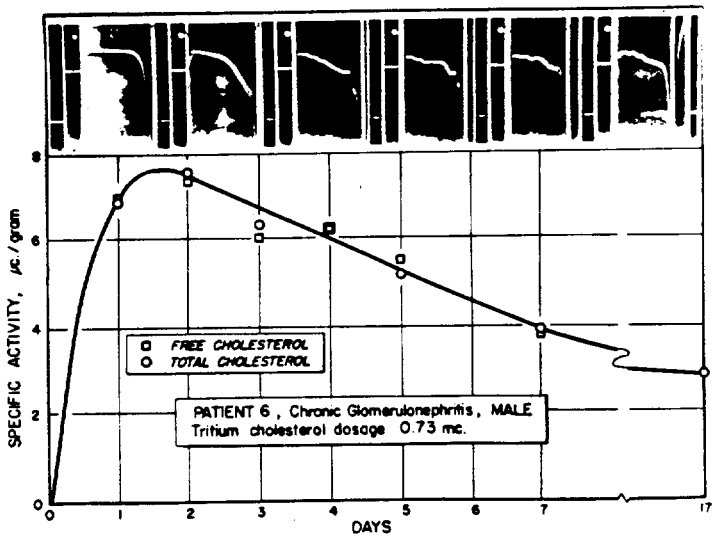

FIG. 6. Patient 6, a 41 year old male with a clinical diagnosis of atherosclerosis, hypertension and nephritis, received 0.86 Gm. of cholesterol (S.A. = 0.85 mc. Gm.). The rise in serum cholesterol specific activity, free and total, is plotted against time in days. The ultracentrifuge plate shows the following concentrations of lipoprotein molecules in the serum: S_f 0–12 = 441 mg. per 100 cc.; S_f 12–20 = 79 mg. per 100 cc.; S_f 20–100 = 191 mg. per 100 cc.; and S_f 100–400 = 95 mg. per 100 cc. The ultracentrifuge plate was made at a five-fold concentration.

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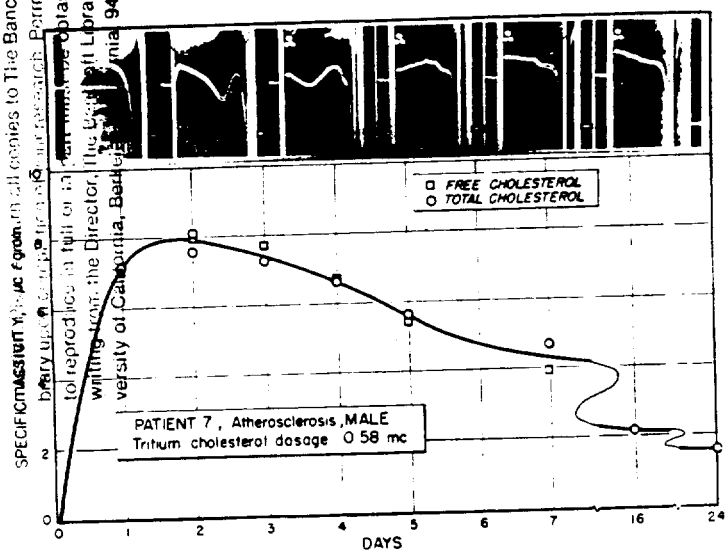

FIG. 7. Patient 7, a 42 year old male who had experienced a previous myocardial infarction received 0.54 Gm. of tritium-cholesterol (S.A. = 1.07 mc./Gm.). The rise in serum cholesterol specific activity, free and total, is plotted against time in days. The ultracentrifuge plate shows the following concentrations of lipoprotein molecules in the serum: S_f 0–12 = 432 mg. per 100 cc.; S_f 12–20 = 61 mg. per 100 cc.; S_f 20–100 = 146 mg. per 100 cc.; and S_f 100–400 = 222 mg. per 100 cc. The ultracentrifuge plate was made at a five-fold concentration.

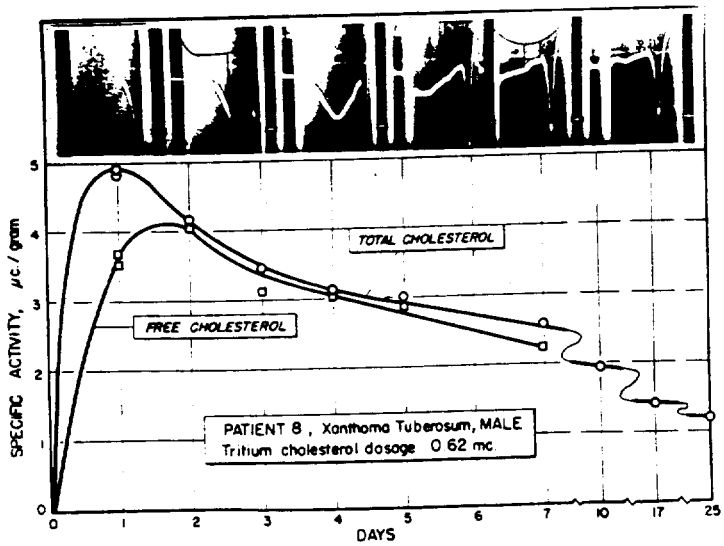

FIG. 8. Patient 8, a 42 year old male with xanthoma tuberosum of three years duration, received 0.58 Gm. of tritium-cholesterol (S.A. = 1.07 mc./Gm.). The rise in serum cholesterol specific activity, free and total, is plotted against time in days. The ultracentrifuge plate shows the following concentrations of lipoprotein molecules in the serum: S_f 0–12 = 211 mg. per 100 cc.; S_f 12–20 = 80 mg. per 100 cc.; S_f 20–100 = 493 mg. per 100 cc.; and S_f 100–400 = 254 mg. per 100 cc. The ultracentrifuge plate was made at a four-fold concentration.

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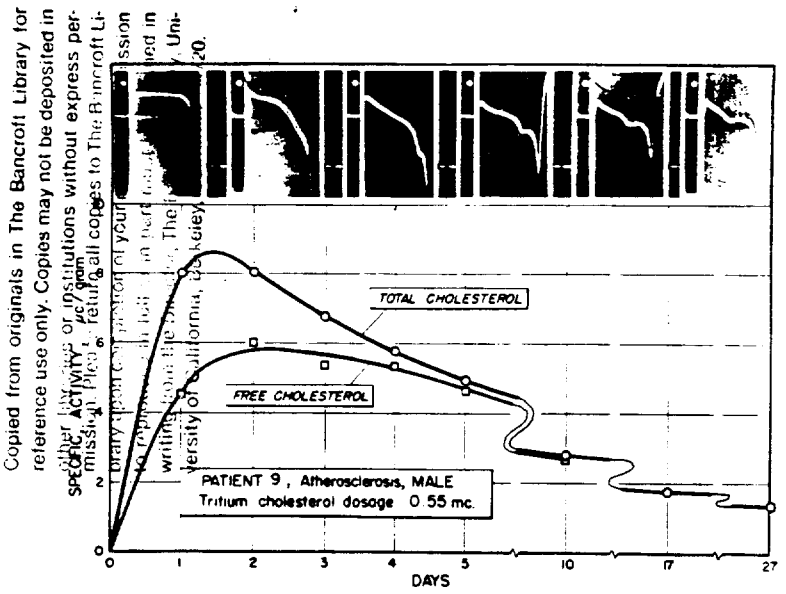

FIG. 9. Patient 9, a 42 year old male, showed a grossly abnormal ultracentrifugal lipoprotein spectrum but no demonstrable disease at this time. He received 0.51 Gm. of tritium-cholesterol (S.A. = 1.07 mc. Gm.). The rise in serum cholesterol specific activity, free and total, is plotted against time in days. The ultracentrifuge plate shows the following concentrations of lipoprotein molecules in the serum: S_f 0–12 = 178 mg. per 100 cc.; S_f 12–20 = 104 mg. per 100 cc.; S_f 20–100 = 270 mg. per 100 cc.; and S_f 100–400 = 81 mg. per 100 cc. The ultracentrifuge plate was made at a five-fold concentration.

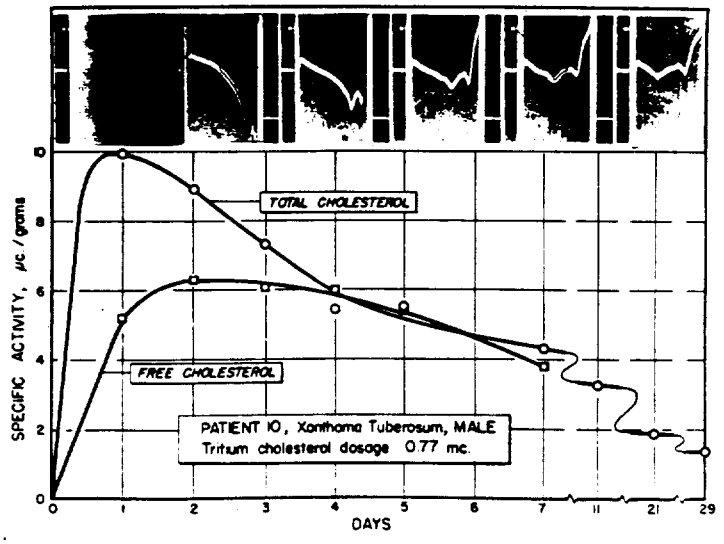

FIG. 10. Patient 10, a 34 year old male with xanthoma tuberosum of approximately three years duration, received 0.72 Gm. of tritium-cholesterol (S.A. = 1.07 mc. Gm.). The rise in serum cholesterol specific activity, free and total, is plotted against time in days. The ultracentrifuge plate shows the following concentrations of lipoprotein molecules in the serum: S_f 0–12 = 124 mg. per 100 cc.; S_f 12–20 = 99 mg. per 100 cc.; S_f 20–100 = 282 mg. per 100 cc.; and S_f 100–400 = 156 mg. per 100 cc. The ultracentrifuge plate was made at a five-fold concentration.

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shows that would be classified as a normal or nearly normal lipoprotein spectrum. Rabbits on the other hand show an abnormal lipoprotein picture after cholesterol feedings. Dogs do not get atherosclerosis from cholesterol feedings alone; rabbits do.

Less how applicable observations made in rabbit atherosclerosis are to the human disease is still under debate; however, as time passes, more and more observations on lipid metabolism in the rabbit are proving to have a parallelism in the "atherogenic" man. It has been demonstrated in both rabbits and man that exogenous cholesterol is only partially absorbed; however, once absorbed, that it

TABLE 2.—*Correlation Study of Cholesterol Specific Activity Absorption Curves, Lipoprotein Molecular Spectrum, and the Total Serum Cholesterol*

Patient No.	Cholesterol specific activity absorption curves: Free Chol. S.A. μc/Gm. / Total Chol. S.A. μc/Gm.	Lipoprotein molecular spectrum: S0-12 molecules/mg. % / S12-400 molecules/mg. %	Total serum cholesterol mg. %
1	2.19	5.57	519
2	1.34	2.17	565
3	1.32	1.97	226
4	1.30	1.89	352
5	1.20	3.50	193
6	1.00	1.21	266
7	1.00	1.01	266
8	0.77	0.26	529
9	0.56	0.39	290
10	0.52	0.23	259

mixes with the metabolic cholesterol pools of the serum and tissues including aorta.[9, 10] It has been demonstrated that the cholesterol fed makes up the bulk of the atheromatous cholesterol deposits in the aorta in experimental atherosclerosis.[10] Ultracentrifugal lipoprotein spectra of varying degrees of abnormality are to be found in humans and many patterns closely simulate those seen in the atherosclerotic rabbit (patients 8, 9 and 10). It has now been demonstrated that those patients with abnormal lipoprotein spectra handle oral cholesterol with respect to its partition after absorption into the serum free and esterified cholesterol pools, in an abnormal fashion; in a fashion identical with that seen in the rabbit.

At this point it must be emphasized that the fundamental abnormality producing the variations in the cholesterol specific activity absorption curves observed in the patients in this study remains obscure. The problem assuredly concerns cholesterol ester metabolism, but whether the defect is in the metabolism of esterified cholesterol as a unit (that is, altered cholesterol esterase activity), or in the metabolism of one of its component parts, cholesterol and/or fatty acid, is not known. That the defect in metabolism involves cholesterol plus fatty acid in an esterified form is of additional interest in view of the fact that dietary alteration of the serum lipoprotein spectrum is most effective upon co-reduction of fat and cholesterol in the diet.

Until the various fundamental aspects of lipid metabolism are clarified and a more direct attack on the problem can be made, the bulk of evidence at hand supports the belief that judicious control of dietary fat and cholesterol as a prophylactic measure in patients with abnormal lipoprotein spectra is worth while. Such treatment would appear particularly indicated in patients such as 8, 9 and 10.

Finally it may be added that the data adds further evidence to that of McGinley and Gofman[4] that the diseases classified as xanthoma tuberosum and xanthoma tendinosum, although they have a hyperlipoproteinemia in common, probably are caused by entirely different fundamental metabolic defects.

SUMMARY

Tritium-labeled cholesterol has been used in a selected series of patients to demonstrate a quantitative metabolic defect in lipid metabolism in the presence of abnormal serum lipoprotein spectra. This metabolic defect involves the partition of oral cholesterol into the free and esterified cholesterol pools of the serum. Patients with abnormal serum lipoprotein spectra carry a greater proportion of their newly absorbed cholesterol in the esterified form than do normals.

The different cholesterol specific activity absorption curves found correlate with the

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