Hald, P. M., Heinsen, A. J. & Peters, J. P. (1947). *J. clin. Invest.* **26**, 983.
Hamilton, L. D., Gubler, C. J., Cartwright, G. E. & Wintrobe, M. M. (1950). *Proc. Soc. exp. Biol., N.Y.*, **75**, 65.
Henry, R. J. (1952). *Clin. Chem.* **4**, 4.
Howland, W. S., Zucker, M. B. & Clifton, E. E. (1957). *Surg. Gynec. Obstet.* **105**, 529.
Josephson, B. & Dahlberg, G. (1952). *Scand. J. clin. Lab. Invest.* **4**, 216.
Karvonen, M. J., Pekkarinen, M., Metsala, P. & Rantanen, Y. (1961). *Brit. J. Nutr.* **15**, 157.
Keys, A. (1956). *J. chron. Dis.* **4**, 364.
Keys, A., Anderson, J. T. & Grande, F. (1957). *Lancet*, **273**, 959.
Keys, A., Karvonen, M. J. & Fidanza, F. (1958). *Lancet*, ii, 175.
Keys, A., Kimura, N., Kusukawa, A., Bronte-Stewart, B., Larsen, N. & Keys, M. H. (1958). *Ann. intern. Med.* **48**, 83.
Keys, A., Mickelsen, O., Miller, E. v. O., Hayes, E. R. & Todd, R. L. (1950). *J. clin. Invest.* **29**, 1347.
King, E. J. & Wootton, I. D. P. (1956). *Micro-analysis in Medical Biochemistry*, 3rd ed. London: Churchill.
Kornerup, V. (1950). *Arch. intern. Med.* **85**, 398.
Lippincott, L. S. (1927). *J. Lab. clin. Med.* **12**, 679.
Paterson, J. C. S., Marrack, D. & Wiggins, H. S. (1953). *J. clin. Path.* **6**, 105.
Pryce, J. D. (1960). *Lancet*, ii, 333.
Scott, E. M. (1960). *J. clin. Invest.* **39**, 1176.
Shuey, H. E. & Cebel, J. (1949). *Bull. U.S. Army med. Dep.* **9**, 799.
Thomas, C. B., Holljes, H. W. D. & Eisenberg, F. F. (1961). *Ann. intern. Med.* **54**, 413.
Vahlquist, B. C. (1941). *Acta Paediat., Uppsala*, **28**, suppl. 5.
Winters, R. W., Graham, J. B., Williams, T. F., McFalls, V. W. & Burnett, C. H. (1958). *Medicine*, **37**, 97.
Wootton, I. D. P. (1956). *Clin. Chem.* **2**, 296.
Wootton, I. D. P. & King, E. J. (1953). *Lancet*, **264**, 470.
Wootton, I. D. P., King, E. J. & Smith, J. M. (1951). *Brit. med. Bull.* **7**, 307.

Individual variation in the lipid transport system

By ROBERT E. OLSON, *Department of Biochemistry and Nutrition, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pa*

The systems responsible for the transport of lipids in the animal body show great variation between and within different species of the animal kingdom. Even in the normal human subject the individual variations are impressive, the range of variation in concentration of serum lipids being considerably larger than that for glucose, amino acids, creatine, or serum albumin. As in all biological variation, the variation in the lipid transport system is a product of both genetic and environmental factors. The multi-enzyme systems concerned with the transformations of lipids and lipoproteins in animal tissues are, like all enzymes, under genetic control. Their rates of formation and breakdown, under normal conditions, are sufficiently variable to produce variation in their concentration, and hence in the steady-state concentration of intermediates and products, many of which appear in the plasma. Under pathological conditions the absence of one or more of these enzymes may produce a gross abnormality of lipid transport. In addition to these endogenous variables it has now been clearly established that the lipid transport system responds dramatically to nutritional factors, not only in the sense of transient changes in lipid level as a function of alimentation but also in the sense of long-term adaptation of fasting levels of serum lipids and lipoproteins to habitual nutritional intakes.

Here I should like first to present a schema of normal fat transport based upon our current knowledge of fat metabolism in various tissues. Some aspects of it are still controversial although its main elements are solidly grounded in the experimental evidence. It will serve as a working hypothesis for discussion and further research. I should then like to comment upon the variations noted in several species of mammal and finally to discuss the variations noted in man under normal and some pathological conditions.

Schema of normal lipid transport

Transport of lipid from one organ is a vital activity because of the primary role of fats as an energy source and as an energy store. A brief presentation of a schema of normal fat transport will be made in terms of (1) the physiological units participating in fatty acid transport, i.e. the plasma lipoproteins, and (2) the rate and direction of movement of fatty acids by these lipoproteins under various conditions (Frederickson & Gordon, 1958; Olson & Vester, 1960).

The plasma lipoproteins may be looked upon as vehicles for fatty acid transport in an aqueous medium. It now seems certain that no 'free lipid' exists in plasma and the transportable lipid is usually combined with protein and mostly with other lipids to provide a variety of lipoprotein complexes. There appear to be four main lipoprotein vehicles for lipid transport. They are (1) the chylomicrons, (2) the low-density β-lipoproteins, (3) the high-density α-lipoproteins and (4) albumin for the transport of non-esterified fatty acids. Variation in the concentrations of these four main lipoprotein classes in different species including man extends over a considerable range.

Chylomicrons. These chylous globules are the least soluble of the plasma lipoproteins. They are particles which range from 0·3 to 1·5 μ in diameter, can be seen in a dark-field microscope, have molecular weights in a range of 10^{10}–10^{12} and are composed mainly of triglyceride. Their rising concentration in the plasma after a fatty meal produces a visible milkiness. The mean composition of chylomicrons in the mammal appears to be 1% protein, 87% triglyceride, 8% phospholipid, 3% cholesterol ester and 1% cholesterol. They flotate easily in the ordinary laboratory centrifuge at 1500 *g* for 10 min.

Chylomicrons originate in the intestine after ingestion and digestion of dietary fat. The fatty acids and mono- and di-glycerides produced in lipolysis are absorbed by the mucosa and resynthesized into triglycerides in the intestinal cell. The chylomicrons are produced by wrapping these triglycerides in a thin envelope of phospholipid, cholesterol ester and protein. Other lipids present in the diet, such as sterols and the fat-soluble vitamins, are also incorporated into the chylomicron. Dietary cholesterol merges with the intracellular pool of cholesterol in the intestinal cell, is esterified, and incorporated into the chylomicron at levels as high as 10% of the total lipid. Desai & Glover (1961) have shown that, in addition to chylomicrons, a complex of dietary sterols, bile acids, mucopolysaccharides and protein appears in the plasma after administration of 7-dehydrocholesterol. Since similar complexes

have been noted in bile, it is probable that this, unlike the chylomicron, is an 'overflow' product of increased biliary secretion. Chylomicrons are cleared from the blood with a half-time of 20–30 min. Tissues which participate in this clearing have not all been identified but Bragdon (1959) found in the rat that, 10 min after administration of [^{14}C]palmitate-labelled chylomicron, the radioactivity appeared principally in liver, muscle, particularly heart muscle, and adipose tissue. The role of the chylomicrons in bearing lipids from the intestine through the thoracic duct to the liver, adipose tissue (which together clear about 75% of the alimentary load) and other tissues is shown in Fig. 1.

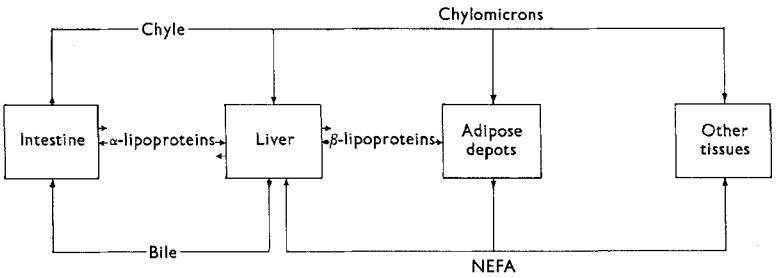


Fig. 1. Schema of fat transport in the mammal. NEFA, non-esterified fatty acids.

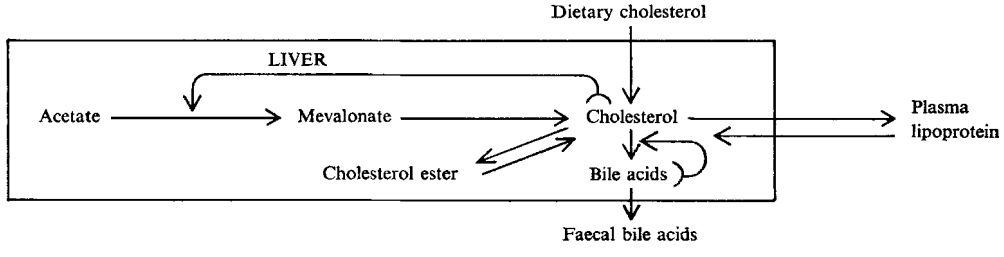
Low-density β-lipoproteins. The low-density β-lipoproteins are a heterogeneous group of lipoglobulins which range in density from 1·06 to 0·96. They are ordinarily revealed by flotation in the ultracentrifuge at a density of 1·063 and flotate in the range of $S_{f_{2-400}}$ at 26° (S_f = Svedberg flotation unit ($-S \times 10^{-13}$ sec) at a density 1·063 and temperature 26°). The molecular weights of this group of more soluble lipoproteins range from 10^6 for S_{f_6} to 10^8 for $S_{f_{400}}$. The peptide portion of these lipoproteins appears to be immunochemically indistinguishable, and although the lowest-density family $S_{f_{100-400}}$ has a mobility of α_2-globulin on starch, the family appears to move in free electrophoresis as β-globulins.

β-Lipoproteins vary considerably in their lipid composition; the lowest-density members of the group contain considerably more triglyceride and less cholesterol than the highest-density member. The β-lipoprotein that is most plentiful in human serum has a density of 1·03 and a flotation rate of S_{f_6}. It has a molecular weight of 2×10^6 and a composition of 21% protein, 8% cholesterol, 40% cholesterol ester, 22% phospholipid and 9% triglyceride. The band of $S_{f_{100-400}}$ averages 7% protein, 8% cholesterol, 14% cholesterol ester, 18% phospholipid and 15% triglyceride. Isotopic studies of both the protein and lipid moieties of the β-lipoproteins would suggest that the lowest-density fraction, i.e. the $S_{f_{100-400}}$ fraction, rich in triglyceride, is secreted by the liver, delivered to the periphery by the plasma, and undergoes lipolysis principally by a lipoprotein lipase present in adipose tissue. The triglyceride of this lipoprotein is split into fatty acids and resynthesized into neutral fat in the adipose tissue. The lipoprotein molecule now reduced in tryglyceride concentration appears in the plasma as a higher-density β-lipoprotein of the $S_{f_{0-12}}$ category.

These data would support the view that the higher-density $S_{f_{0-12}}$ fraction represents the bare vehicle for the transport of triglyceride from liver to adipose tissue and the range of lipoproteins noted in the β-group reflects the extent to which the vehicle is loaded with cargo, i.e. triglyceride. It seems probable that the phospholipid, cholesterol and cholesterol ester of the β-lipoprotein molecule serve as part of the vehicle for lipid transport from liver to periphery without actively contributing to it. Isotope studies have shown that the fatty acids of the cholesterol ester and phospholipid turn over at relatively slow rates compared to triglyceride and are probably not part of the main flow of traffic from liver to adipose tissue.

Although cholesterol is part of the lipoprotein vehicle and hence 'passive' in transport, changes in the cholesterol balance of the organism often result in an elevation of the level of the β-lipoproteins in the plasma. Since peripheral cells can synthesize enough cholesterol for their respective needs, there is no apparent physiological reason for transporting extra cholesterol. It may, in fact, be looked upon as a form of storage of excess sterol, the liver simply synthesizing extra $S_{f_{0-12}}$ lipoprotein when the rate of influx plus synthesis of sterol exceeds the rate of katabolism plus excretion. This function of the liver accounts for part of the large variation in the concentration of $S_{f_{0-12}}$ lipoproteins in mammals and man.

The extent to which the liver can control the rate of synthesis and katabolism of cholesterol thus is a critical factor in controlling the level of β-lipoprotein in the plasma. Furthermore, it bears little or no relationship to the primary transport function of these lipoproteins, since it appears that their function is to move triglyceride, not cholesterol. Metabolic feed-back plays a part at two steps in the sequence as shown below:



The concentration of free cholesterol in the liver appears to control the rate of incorporation of acetate carbon into mevalonate, an irreversible process. Secondly, the concentration of bile acids in the liver affects the rate of oxidation of cholesterol. These two feed-back processes attempt to achieve a balance in cholesterol metabolism. A rise in serum cholesterol concentration or in liver cholesterol ester or in both is a sign of failure of control.

High-density α-lipoproteins. The high-density α-lipoproteins have been separated into two main categories with hydrated densities of 1·075 and 1·145. They are generally revealed by flotation in saline at density 1·21 in the ultracentrifuge and their flotation rates are in the range of $-S_{0-20}$ ($-S$=Svedberg flotation unit ($-S \times 10^{-13}$ sec) at density 1·21 and temperature 26°). The molecular weights of these proteins are considerably lower than those of the β-lipoproteins and are in the range

https://doi.org/10.1079/PNS19620025 Published online by Cambridge University Press

of (2 to 4) $\times$ 10^5. The α-lipoproteins contain a larger amount of protein and a smaller amount of lipid, featuring a much higher phospholipid : cholesterol ratio. The peptide portion of the two high-density lipoproteins is the same, but different from the peptide of the β-lipoproteins. The precise role in fat transport of the α-lipoproteins is somewhat more nebulous than that of the β-lipoproteins although they may play a part in transporting sterols and phospholipids from the chylomicron to the liver. The high-density lipoproteins also serve as vehicles for the transport of α-tocopherol and 17-ketosteroids, and under some conditions may transport free fatty acids. The concentration of the α-lipoproteins in man is relatively constant and does not fluctuate with nutrition or endocrine change to the same degree as that of the β-lipoproteins.

Non-esterified fatty acids. A small but metabolically active fraction of non-esterified or 'free' fatty acids (NEFA, FFA) is attached to albumin under normal conditions. The physiological range of concentration of NEFA is 0·3–3·0 moles fatty acid/mole albumin or 0·2–2·0 m-moles/l. In metabolic studies in which [^{14}C]-palmitate complexed with serum albumin has been used as a tracer, the half-time of this lipid fraction has been found to be 2–3 min in a variety of mammals. This fractional turnover rate of about 30%/min corresponds to the utilization of 2000 kcal/day in man and this value may become even higher during fasting. As shown in Fig. 1, the principal function of NEFA is to provide readily oxidizable substrate from the adipose depots when carbohydrate deprivation occurs.

In adipose tissue, it is carbohydrate deprivation that triggers the release of NEFA, elevates the concentration of the protein in the blood, promotes uptake by the other tissue, including the liver, and results in the oxidation of fatty acids as their coenzyme A derivatives. The catecholamine hormones, adrenalin and noradrenalin, also stimulate the release of NEFA. Certain hormones such as thyroxine appear to act permissively on NEFA release; insulin and glucose antagonize the release of NEFA and favour fat synthesis in adipose tissue.

To summarize, the movement of lipid in the body is, as shown in Fig. 1, primarily from intestine to liver after absorption of fat and from liver to adipose depots by way of β-lipoproteins in the postprandial period. In fasting, the adipose tissues release NEFA for oxidation. The enterohepatic cycle involves the recirculation of sterols and bile acids through chylomicrons and portal flow with ultimate excretion of sterols in the stool.

Species variations

The serum cholesterol concentration of different species varies widely despite roughly similar rates of lipid transport among the various compartments of the body. The partition of the cholesterol between the α- and β-lipoproteins also varies widely among various common species. Table 1 shows data on serum cholesterol, α-lipoprotein and β-lipoprotein concentration for several species. It may be seen that the correlation between total serum cholesterol and the α- and β-lipoprotein concentrations is very poor. The dog has a relatively high cholesterol level, a high α-lipoprotein, and a low β-lipoprotein concentration. The monkey is intermediate for all

values and man has a high total cholesterol, a medium α-lipoprotein and a high β-lipoprotein concentration. It is of some interest that the species proneness to atherosclerosis correlates better with the mean β-lipoprotein concentration than with total serum cholesterol.

Table 1. *Distribution of serum cholesterol among plasma lipoproteins in seven species*

Species	Serum cholesterol (mg/100 ml)	α-lipoprotein (mg/100 ml)	β-lipoprotein (mg/100 ml)
Rabbit	50	100	100
Rat	80	150	80
Cat	100	300	50
Chicken	100	100	160
Monkey	120	300	300
Dog	140	700	60
Man	225	300	500

Table 2 shows a further breakdown of the lipoprotein concentrations among the α- and β-families in rat, dog and man. Dog and man have most of the α-lipoprotein in the $-S_{0-4}$ fraction, whereas the rat has more of the $-S_{4-20}$ proteins. Dog and rat have similar β-lipoprotein spectrums and a low total concentration, whereas man has the very high concentration of $S_{f_{0-12}}$ vehicle. It is of interest that the concentrations of the low-density $S_{f_{20-400}}$ fraction which actively transports triglyceride are more nearly similar in all three species.

Table 2. *Concentration of serum lipoproteins in rat, dog and man*

	α-lipoproteins (mg/100 ml)			β-lipoproteins (mg/100 ml)			
Species	$-S_{0-4}$	$-S_{4-20}$	Total	$S_{f_{0-12}}$	$S_{f_{12-20}}$	$S_{f_{20-400}}$	Total
Rat	70	80	150	35	0	45	80
Dog	550	150	700	30	0	30	60
Man	250	50	300	350	20	130	500

For explanation of symbols see, pp. 137, 138.

In choline deficiency in the rat, in which liver fat accumulates, it has been shown (Olson, Jablonski & Taylor, 1958) that the concentration of β-lipoprotein is reduced essentially to zero. Choline appears to be essential in the rat for the secretion of β-lipoproteins, and in its absence triglyceride is secreted into the liver cell cytoplasm instead of into the plasma.

In experimental hypercholesterolaemia in animals, the secretion of β-lipoproteins by the liver is greatly increased and concentrations rise to very high levels. This state is best induced by giving cholesterol to species such as the rabbit, in which the rate of hepatic cholesterol oxidation is genetically low, or to the rat given bile acids plus antithyroid drugs to suppress a genetically adequate pathway.

Normal variations in man

Both the postabsorptive steady-state concentration of lipoproteins in the plasma and the rate of clearing absorbed or newly synthesized triglyceride vary considerably

https://doi.org/10.1079/PNS19620025 Published online by Cambridge University Press

in healthy men and women. At birth the serum cholesterol (80 mg/100 ml) and β-lipoprotein (100 mg/100 ml) concentrations are low but they rise to values of 140 mg/100 ml for cholesterol and 250 mg/100 ml for β-lipoprotein in infancy and remain at that point until adolescence. At puberty the serum cholesterol level of the male rises further to about 190 mg/100 ml at 20 years and then steadily upward in well-nourished societies until it reaches about 250 mg/100 ml at age 50, where it remains until senescence. This increase is due solely to elaboration of more β-lipoprotein. In females the serum cholesterol concentration increases very slightly at puberty, owing to an increase in α-lipoprotein, and tends to remain lower than in the male until the menopause, at which time it rises rapidly to the level in the male and may even overtake it. This rise is due to a great increase in β-lipoprotein accompanied by a fall in α-lipoprotein. The effect of oestrogens in increasing the α : β-lipoprotein ratio is well validated in both normal and castrated men and women. At any point on the serum-cholesterol–age regression curve the value of the standard deviation is approximately 20% of the mean.

It is of some interest that this rather wide range of variation and the slope of the serum-cholesterol–age regression curve are considerably reduced in those countries in which malnutrition is prevalent, particularly in countries in which the population subsists on diets low in saturated fat. Under these conditions, the range of serum cholesterol for the whole population may be from 120 to 200 mg/100 ml with correspondingly lower β-lipoprotein concentrations.

Such findings have led epidemiologists to conclude that the intake of saturated dietary fat is an important cause of relative hypercholesterolaemia and hyper-β-lipoprotinaemia in man (Keys, 1957; Bronte-Stewart, 1958). Similar conclusions have been forthcoming from the metabolic wards in which patients have been given carefully measured diets whose fat content varied in kind and amount. It has been found that a reduction from 40 to 10% in the proportion of calories obtained from fat results in a fall in serum cholesterol, a fall in $S_{f_{0-12}}$ β-lipoprotein, but a rise in the $S_{f_{20-400}}$ fraction. This latter effect is due to increased synthesis of triglycerides by the liver. There is very little change in total β-lipoprotein under these conditions. If polyunsaturated fat (from vegetable or fish oils) is given at a level to provide 20% of the total fat calories (in ordinary western European and American diets the value is above 4%) the serum content of cholesterol and of all the β-lipoproteins falls. These effects are upon the fasting levels of serum lipoproteins and persist as long as the diet is maintained. The mechanism of this effect is not entirely elucidated but appears to be the result of an increased katabolism of cholesterol in the liver. Other dietary constituents, such as carbohydrate and protein, exercise lesser effects upon the fasting levels. As far as is known, very little effect upon net fat transport is caused by these changes in β-lipoproteins. NEFA concentrations tend to be lower on high-carbohydrate diets and higher on high-fat diets.

Pathological variations in man

Several specific hereditary disorders have been identified in man in which fat transport is markedly altered. The first is familial hypercholesterolaemia which is

https://doi.org/10.1079/PNS19620025 Published online by Cambridge University Press

characterized by an elevated level of serum cholesterol and β-lipoproteins, a clear fasting serum, tendon nodules, xanthlasma and, less frequently, skin xanthoma of the tuberous type. Coronary disease is prevalent. The β-lipoprotein spectrum in these patients is increased mainly in the $S_{f_{0-12}}$ range with significant but somewhat lesser increases in the $S_{f_{12-400}}$ range. The increase in serum β-lipoprotein in this disorder appears to be due to hepatic overproduction of cholesterol and possibly other constituents of the β-lipoproteins (Olson, 1958). A favourable response of hypercholesterolaemia to an increase in the proportion of partly unsaturated fat in the diet is noted in many but not all patients. The transport of lipid from liver to adipose tissue and the mobilization of fat from the depots appears to be unchanged. On the other hand, the high concentration of $S_{f_{0-12}}$ lipoproteins present in the plasma results in transport of unwanted and unneeded sterols and other lipids of the β-lipoprotein to artery, tendon and skin. This disorder represents an extension of the normal trend towards high fasting $S_{f_{0-12}}$ lipoproteins in some normal individuals. The genetic analysis of this disorder is not entirely clear but it appears to be characterized by single gene with incomplete dominance resulting in homozygotes with high, and heterozygotes with moderately elevated, serum β-lipoproteins.

The second, genetic hyperlipidaemia, is familial hyperlipaemia. This disease is characterized by marked elevation of plasma triglyceride levels and lesser increases in cholesterol and phospholipids. The β-lipoprotein spectrum is distinctive in that the $S_{f_{0-12}}$ fraction is reduced by as much as 50% with a several-fold increase in the lower-density $S_{f_{12-400}}$ group. Chylomicrons are poorly cleared after a fatty meal as are all the low-density lipoproteins in the $S_{f_{12-400}}$ range. This is essentially a disorder of clearing fat from the blood and a lack of lipoprotein lipase has been suggested (Havel & Gordon, 1955). A genetic picture similar to that for essential hypercholesterolaemia appears to characterize this disorder. The homozygotes are seriously crippled. In addition to an inability to ingest and clear dietary fat from their plasma, these children develop hepatosplenomegaly, abdominal crises, childhood atherosclerosis, xanthomatosis, and usually die before reaching puberty. The heterozygotes survive childhood to develop early atherosclerosis and coronary artery disease as adults. Low-fat diets often improve the hyperlipaemia in these cases.

A third hereditary disorder of lipid transport is acanthocytosis, a syndrome consisting of anaemia with abnormal 'thorny' red cells, retinopathy, cerebellar ataxia, a complete absence of β-lipoproteins and inability to form chylomicrons (Salt, Wolff, Lloyd, Fosbrooke, Cameron & Hubble, 1960). The disease usually presents as 'coeliac disease' in infancy with steatorrhoea, malnutrition, anaemia and hypocholesterolaemia. No chylomicrons are formed after a fatty meal and a deficiency of essential fatty acids and the fat-soluble vitamins has also been noted in these patients. The red-cell lipids are also abnormal (Ways, Reed & Hanahan, 1961). Biopsy of jejunum shows a histological picture consistent with fatty engorgement. Only α-lipoproteins are detectable in the serum in homozygotes and hence the serum cholesterol level ranges from 40 to 60 mg/100 ml. In heterozygotes, who are otherwise healthy, concentration of the β-lipoproteins is reduced approximately by half. The patients improve on a low-fat diet.

In this condition, it would appear that the enzymic lesion is the inability to form certain lipoproteins, particularly the β-lipoproteins and the chylomicrons. This results in reduction in absorption of fat and fat-soluble vitamins, and a reduction in delivery of fatty acids to the adipose depots via β-lipoproteins. The NEFA appear to be present in normal concentrations. The adipose lipids are probably synthesized from glucose in the fat cell and are undoubtedly low in essential fatty acids. A gas chromatographic study of these depot lipids would be of great interest.

Acquired disorders of lipid transport occur in diseases such as uncontrolled diabetes mellitus, nephrosis, biliary cirrhosis, myxoedema and hepatic failure. The changes in lipoprotein concentrations that occur in these diseases are summarized in Table 3. In diabetes mellitus and nephrosis the defect appears to be a failure to clear low-density lipoprotein from the serum. In the first instance the reason is

Table 3. *Variations of serum lipoprotein concentration in man in hereditary and acquired disorders*

Disease	α-lipoproteins (mg/100 ml)	β-lipoproteins (mg/100 ml) $S_{f_{0-12}}$	$S_{f_{12-20}}$	$S_{f_{20-400}}$	Total
Genetic disorders:					
Essential hypercholesterolaemia	250	850	80	150	1080
Essential hyperlipaemia	280	160	80	1500	1740
Acanthocytosis	200	0	0	0	0
Acquired disorders:					
Diabetes mellitus (no Rx)	300	390	170	1200	1760
Nephrosis	250	250	50	1000	1300
Biliary cirrhosis	0	2500*	800	300	3600
Myxoedema	400	450	60	150	660
Hepatic failure	200	200	10	40	250
Normal subjects	300	350	20	130	500

For explanation of symbols see pp. 137, 138.

*An abnormal low density β-lipoprotein with a high phospholipid : cholesterol ratio and a flotation rate of $S_{f_{11}}$ is present in these patients.

probably carbohydrate deprivation in the adipose tissue cells which are secreting NEFA at an accelerated rate; in the second the lack of serum albumin appears to block the clearing process. The hyperlipaemia of biliary cirrhosis is one of over-production of an abnormal low-density lipoprotein (Myers, Olson, Lewis & Moran, 1957). In myxoedema the levels of all lipoproteins are moderately elevated owing to a preferential reduction in cholesterol oxidation in the liver. In severe hepatic failure the plasma lipoprotein concentration falls because of the terminal inability of the liver to synthesize them.

Conclusions

Individual variation in the lipid transport system is prominent in both experimental animals and human subjects. This variation is a function of both genetic and environmental factors. A schema for fat transport has been outlined and changes in the rate of transfer of fat from one compartment of the body to another have been illustrated by conditions of abnormal fat metabolism.

REFERENCES

Bragdon, J. H. (1959). *Ann. N. Y. Acad. Sci.* **72**, 845.
Bronte-Stewart, B. (1958). *Brit. med. Bull.* **14**, 243.
Desai, J. C. & Glover, J. (1961). *Biochem. J.* **79**, 31P.
Frederickson, D. S. & Gordon, R. S. (1958). *Physiol. Rev.* **38**, 585.
Havel, R. J. & Gordon, R. S. (1955). *Circulation*, **12**, 485.
Keys, A. (1957). *J. Amer. med. Ass.* **164**, 1912.
Myers, J. D., Olson, R. E., Lewis, J. H. & Moran, T. J. (1957). *Trans. Ass. Amer. Phycns*, **70**, 243.
Olson, R. E. (1958). *Perspectives Biol. Med.* **2**, 84.
Olson, R. E., Jablonski, J. R. & Taylor, E. (1958). *Amer. J. clin. Nutr.* **6**, 111.
Olson, R. E. & Vester, J. W. (1960). *Physiol. Rev.* **40**, 677.
Salt, H. B., Wolff, O. H., Lloyd, J. K., Fosbrooke, A. S., Cameron, A. H. & Hubble, D. V. (1960). *Lancet*, ii, 325.
Ways, P., Reed, C. F. & Hanahan, D. J. (1961). *J. clin. Invest.* **40**, 1088.

Some aspects of physical and physiological individual variation

By ROBERT W. MCCAMMON, *Director, The Child Research Council, 4200 East Ninth Avenue, Denver 20, Colorado, USA*

Introduction

I would like first to thank the members of the Society for this opportunity to participate in the symposium on individual variation. The title of this paper was chosen deliberately to permit freedom of selection from a wide range of data, and then hedged with the first three words lest it give the impression that I would presume to attempt an exhaustive discussion of physical and physiological variation between individuals. In considering the assignment I decided that I should limit myself to those variations that are more clearly established and that I should confine my material to data from the Child Research Council. I hope this will not be interpreted as parochial disinterest in events outside my own small world. It is intended as a means of sharing some of the results of over 30 years of study of individual variation in the same group of subjects. We are indebted to many outside our study for information, for ideas and for stimulation, and this indebtedness grows greater with each succeeding year.

Physical and physiological variation between individuals cannot be separated realistically. Great muscle strength and endurance come with bulging biceps, gargantuan caloric intake produces the large waist line, and poor resistance to disease is rarely a companion of vigorous physical proportions. However, I shall discuss them as if they were separate, not so much for the sake of convenience as in an attempt to conceal my lack of knowledge about how physical variation produces differences in function and vice versa. The examples chosen are only some representatives of hundreds of variations that exist between individuals, some of them obvious and some more subtle. They are also related to findings in basically healthy, well-fed children of similar ethnic extraction and do not reflect variation due to disease or want.

Before undertaking any discussion of individual variation, it is important to understand the difference between variation and abnormality. Custom has established the pattern of much medical thinking in this respect. It is customary to obtain