crease of cohesion within the collagen. Should the reticular and elastic fibres be involved in epidermal-dermal adherence[2] the great swelling pressure of collagen would be sufficient to rupture these. It is concluded that swelling of collagen in the upper corium may lead to blister formation.

Summary. The ease of separation of the epidermis from the corium by acids, bases, and salt solutions parallels the swelling of collagen in these agents. Separation due to swelling agents can be reversed by shrinking agents. The adherence of normal epidermis to the corium is increased by shrinkage of the collagen.

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Distribution of Cholesterol, Cholesterol Esters and Phospholipid Phosphorus in Normal Blood.

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Many observations indicate that not only the absolute amounts of the different lipids, but also the ratios of these lipids to each other in the cells and the surrounding medium are important in physiological and pathological conditions. The most easily accessible system for the study of these ratios is blood. Much work has been done on changes in the individual lipid components in different diseases, but only a few papers deal with their interrelationships. Recently Peters and Man[1] studied the interrelations of serum lipids in normal persons and in patients with different diseases. The study of cell lipids, however, has been comparatively neglected so far, perhaps because the changes that occur there are relatively small when compared to the changes that take place in plasma lipids. In animal experiments (unpublished) we observed that under the influence of different factors the changes in the cell lipids were frequently opposite in direction to those in the plasma lipids. It occurred to us that these changes, although small, might still be significant, and it seemed advisable to investigate under different conditions the cholesterol, cholesterol ester, and phospholipid phosphorus content of both blood cells and plasma, simultaneously. To obtain a baseline for further observations we first determined the various lipid values on a group of normal individuals.

Material and Methods of Analysis. The observations here presented were made on 2 groups of patients. The first group consisted of 10 healthy males and 10 healthy females whose ages ranged from 19 to 35. The second group was made up of 20 surgical patients with no diseases known to affect lipid metabolism. This number was equally divided between the 2 sexes, and their ages were between 70 and 90 years. Two patients whose plasma cholesterol values, (334 mg % and 86 mg % respectively), differed from the mean by more than twice the standard deviation* were excluded and replaced by 2 others.

[1] Peters, J. P., and Man, E. B., *J. Clin. Invest.*, 1943, **22**, 707, 715.

* The standard deviation was calculated by the help of the formula $SD = \sqrt{\frac{\Sigma d^2}{n-1}}$

The standard error can be calculated from this formula as follows: $SE = \frac{SD}{\sqrt{n}}$

Results were considered as probably significant where $m_1 - m_2 > 2\sqrt{SE_1^2 - SE_2^2}$.

TABLE I.
Mean Values and Standard Deviations of the Different Lipid Factors in the Young, Old, and Combined Age Groups.

Group	No.	Total cholesterol mg %		Cholesterol esters mg %		Phospholipid P mg %	
		Cells	Plasma	Cells	Plasma	Cells	Plasma
Young group, 20-35 yrs	20	171.0 ± 30.7	186.2 ± 25.9	18.4 ± 24.3	128.7 ± 16.3	13.6 ± 1.3	9.1 ± 1.1
Old group, 70-90 yrs	20	175.0 ± 25.0	199.1 ± 43.0	11.7 ± 15.0	129.8 ± 31.6	14.7 ± 1.1	9.0 ± 1.3
Combined groups	40	173.0 ± 27.6	192.7 ± 35.5	15.3 ± 20.3	129.3 ± 25.0	14.1 ± 1.4	9.0 ± 1.2

Blood was withdrawn from one of the cubital veins in the postabsorptive state (12 to 14 hours after the last meal) and was mixed with heparin. Within 15 minutes after the blood sample was taken the hematocrit value was determined, 5 cc of blood was prepared for extraction,[2] and the remainder of the blood was centrifuged to separate plasma and cells. Five cc of the separated plasma was also extracted. Aliquot amounts of the extracts were used for the determination of the different lipid fractions. Cholesterol was determined according to Bloor,[3] cholesterol esters according to Bloor and Knudson,[4] and phospholipid phosphorus according to Bloor[5] with the modification of Fiske and Subbarow.[6] The lipid fractions were determined in whole blood and plasma and the cell values were calculated from these and the hematocrit values. The calculated cell values were more consistent in our hands than the direct determinations on the centrifuged cells. The parallel values obtained by calculation checked well, whereas the direct determinations gave consistently lower figures, with poorly checking parallels. This was undoubtedly due to the fact that the addition of cells to the alcohol ether mixture always resulted in a coarse precipitate which had a tendency to clump further on heating. This experience is in contradistinction to the results of Boyd[7] who found that the experimental error was greater in indirect than in direct determinations. On the other hand, Man and Gildea[2] found that the Bloor's method of extraction, used by us, gave higher values, and checked better with their own results than Boyd's method.

Results. Our findings are summarized in Table I. All values are given in mg %. In order to obtain insight into the interrelationships of the various lipids different ratios

[2] Man, E. B., and Gildea, E. F., *J. Biol. Chem.*, 1937, **122**, 77.

[3] Bloor, W. R., *J. Biol. Chem.*, 1916, **24**, 227.

[4] Bloor, W. R., and Knudson, A., *J. Biol. Chem.*, 1916, **27**, 107.

[5] Bloor, W. R., *J. Biol. Chem.*, 1918, **36**, 33.

[6] Fiske, C. H., and Subbarow, Y., *J. Biol. Chem.*, 1925, **66**, 375.

[7] Boyd, E. M., *J. Lab. Clin. Med.*, 1936, **22**, 237.

TABLE II.
Mean Values and Standard Deviations of the Different Lipid Ratios.

	Cholesterol esters	Cell cholesterol	Cell phospholipid P	Plasma cholesterol	Cell cholesterol
No. of subjects	Total cholesterol in plasma	Plasma cholesterol	Plasma phospholipid P	Plasma phospholipid P	Cell phospholipid P
40	0.68 ± 0.06	0.94 ± 0.26	1.60 ± 0.29	21.30 ± 2.60	12.32 ± 2.24

were calculated. These are presented in Table II. Due to the amount of chemical work involved in these determinations, relatively small groups were employed. Notwithstanding this, our values, and not only the means, but also the standard deviations, are in close agreement with the data of Peters and Man,[1] obtained on a rather large group of patients. Contrary to expectations, the differences found between corresponding values of the 2 age groups were very slight. The cholesterol ester/total cholesterol ratio was found to be somewhat lower and the coefficient of variation of the individual ratios somewhat greater than by other workers.[8,9] This slight difference can be explained by the different methods used.

As indicated by the coefficient of variation, the phospholipid values were more constant than the cholesterol values. Of the various ratios calculated, the ratio of the plasma cholesterol/plasma phospholipid phosphorus was found to be the most constant.

Comment. Partos and Hertzog[10] were perhaps the first to point out the importance of the simultaneous determination of the different lipids in red cells and plasma. Unfortunately their lipid values differ greatly from the generally accepted figures. Consequently little importance can be attached to the deductions made on the basis of their findings. On the other hand, enough experimental evidence was adduced by other workers with regard to the antagonistic effect of different lipids on the various physicochemical and biological mechanisms to warrant further investigation along the lines suggested. Differences exist in the influence exerted on the various processes not only between phospholipids and cholesterol, but also between the different members of the phospholipid group and between cholesterol esters and cholesterol. At this time we only want to mention a few of these antagonisms to point out the importance of further investigations in this direction.

Lecithin promotes,[11] free cholesterol inhibits cobra venom hemolysis.[12] Cholesterol esters, however, have no protective effect on hemolysis.[13] Cholesterol protects mammals against convulsions caused by tetanus toxin; lecithin increases sensitivity towards it.[13] Cholesterol and lecithin have an opposite effect on experimental epilepsy.[14] The intraperitoneal administration of cholesterol increases the depth and length of anesthesia in rabbits and mice.[15] Lecithin has no such effect. Similarly cholesterol decreases phagocytosis both *in vivo* and *in vitro*. Whereas lecithin has little or no effect on phagocytosis, it can neutralize the influence of cholesterol on it.

The choice of some of the ratios presented in Table II might seem to require explanation. The importance of at least 2 of these ratios is well known, however. The diagnostic significance of the cholesterol ester/total cholesterol ratio in plasma needs no further explanation. The constancy of the plasma cholesterol/plasma phospholipid phosphorus ratio has been recently pointed out.[1] In a subsequent paper the interpretation of some other ratios will be discussed.

[8] Sperry, W. M., *J. Biol. Chem.*, 1936, **114**, 125.

[9] Brun, G., H. K. Lewis Co., London, 1940.

[10] Partos, A., and Hertzog, A., *Z. f. d. ges. exp. Med.*, 1932, **84**, 374.

[11] Kyes, P., *Berliner Klin. Wchnschrft.*, 1902, **39**, 886 and 918.

[12] Ransom, F., *Dtsch. med Wchnschrft.*, 1901, **27**, 194.

[13] Degkwitz, R., *Ergebnisse der Physiol.*, 1932, **32**, 821.

[14] Aird, R. B., and Gurchot, C. L., *Arch. Neur. and Psych.*, 1939, **42**, 491.

[15] Foldes, F. F., and Beecher, H. K., *J. Pharm. Exp. Therap.*, 1943, **78**, 276.

The fact that there is practically no difference in the lipid values and their ratios in the young and old age group seems to be significant. This finding is in contradiction to some earlier views and speculations.[16] It compares favorably, however, with the finding that the plasma cholesterol and cholesterol ester values of infants are practically the same as those of adults.[17]

This constancy of the lipid values in different age groups indicates that even small changes, if uniformly encountered under pathological conditions, might prove to be significant.

Summary. 1. Total cholesterol, cholesterol esters, and phospholipid phosphorus were determined simultaneously in blood cells and plasma on 20 young healthy adults and 20 old patients with no known disorder of lipid metabolism. 2. Practically no difference was found in the lipid values of the 2 age groups. 3. Various ratios have been calculated from the lipid values determined. 4. The possible importance of similar studies under pathological conditions is pointed out.

16 Parhon, C. J., and Parhon, M., *Compt. Rend. soc. biol.*, 1923, **88**, 231.

17 Hodges, R. G., Sperry, W. M., and Andersen, O. H., *Am. J. Dis. Child.*, 1943, **65**, 858.

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Distribution of Cholesterol, Cholesterol Esters and Phospholipid Phosphorus in Blood in Thyroid Disease.

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That changes of the plasma cholesterol level accompany thyroid diseases has been reported repeatedly.[1,2] The variations of the phospholipid phosphorus values have been investigated less frequently.[3,4] The most extensive recent study on this subject is that of Peters *et al.*[2] With the exception of a brief comment by Boyd,[5] no data have been published on the changes of the blood cell lipids in thyroid disease.

In a previous paper the distribution of some lipid values in blood cells and plasma of normal persons was presented.[6] In the following, the results of similar studies made on hypo- and hyperthyroid patients before and after adequate clinical treatment are reported, and an effort is made to correlate our findings with a new concept of the pathological chemistry of thyroid disease.

Material and Methods of Analysis. The studies were carried out on unselected patients of the Thyroid Clinic of the Massachusetts General Hospital. The only discrimination made was that mild cases of hyperthyroidism (basal metabolic rate below +30%) were excluded.

The hypothyroid group consisted of 7 patients, 6 of them female, one male. The ages of the patients ranged from 41 to 69 years. The basal metabolic rate was between +3% and —40% before, and between +11% and —13% after treatment. None of the patients received any form of thyroid medication within 6 months of the study.

1 Hurxthal, L. M., *Arch. Int. Med.*, 1933, **51**, 22; 1933, **52**, 86; 1934, **53**, 762.

2 Peters, J. P., and Man, E. B., *J. Clin. Invest.*, 1943, **22**, 715.

3 Gildea, E. F., Man, E. B., and Peters, J. P., *J. Clin. Invest.*, 1939, **18**, 739; Man, E. B., Gildea, E. F., and Peters, J. P., *J. Clin. Invest.*, 1940, **19**, 43.

4 Boyd, E. M., and Connell, W. F., *Quart. J. Med.*, 1939, **8**, 41.

5 Boyd, E. M., and Connell, W. F., *Quart. J. Med.*, 1936, **5**, 455.

6 Foldes, F. F., and Murphy, A. J., PROC. SOC. EXP. BIOL. AND MED., 1946, **62**, 215.