EGG YOLK AND SERUM-CHOLESTEROL LEVELS: IMPORTANCE OF DIETARY CHOLESTEROL INTAKE

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Dietary fats and oils apparently fall into two classes with respect to their effects on the serum-cholesterol levels in man. On the one hand, animal fats and hydrogenated and tropical vegetable fats elevate the serum-cholesterol levels whereas vegetable oils and marine oils do not have this effect. Generally it is felt that it is the composition of the fatty acids of the particular fat or oil that determines these effects, because there is no cholesterol in hydrogenated or tropical vegetable fats yet cholesterol is present in marine oils. Kinsell and Sinclair (1957) have suggested that the serum-cholesterol-lowering activity of an oil depends on its content of essential fatty acids. Ahrens *et al.* (1957) have proposed that the ability of a certain fat or oil to raise or lower the serum-cholesterol level can be predicted roughly by its iodine value. Keys *et al.* (1957) have provided a regression equation taking account of both the saturated and the polyunsaturated fatty-acid content of the fat or oil.

Egg-yolk lipid has been of interest to us because gramme for gramme we have found that on feeding it there occurs a higher and more rapid elevation of the serum-cholesterol level than with any other dietary fat. Despite this, it has a relatively high iodine value (72) and it has approximately 14 to 19% of linoleic acid, thought to be of the natural *cis cis* variety. Therefore it was felt that it would be of interest to determine the factors responsible for this very rapid rise in serum-cholesterol level which follows the feeding of egg.

Material and Methods

Most of the experiments illustrated here were carried out over a four-year period under the usual metabolism ward control on one volunteer to exclude individual variations. This man aged 46 was receiving daily physiotherapy and occupational therapy for contractures resulting from a traumatic hemiplegia sustained eleven years previously. No other known disorders were detected. Two other healthy male volunteeers were used later for confirmation of the observed trends.

Venous blood was drawn every other day in the fasting state. All the cholesterol estimations were performed in duplicate by the method of Abell *et al.* (1952) as modified by Anderson and Keys (1956). The faecal fat excretion was estimated (van de Kamer *et al.*, 1949) on pooled three-day collections. Iodine values were determined by the method of Wijs (1898), phospholipids by the method of Marinetti *et al.* (1959), and the fatty acids of the esterified fraction on a Barber–Colman gas chromatogram after preliminary methylation (Stoffels *et al.*, 1959).

The plan of the experiment was similar to that employed previously (Bronte-Stewart *et al.*, 1956). The basal diet consisted of maize-meal products and white bread. This diet was supplemented by sugar and casein (" casilan ") in order to maintain, by suitable adjustment, an isocaloric and isonitrogenous state whenever other supplements were introduced. The caloric content was sufficient to maintain constant body weight, and the vitamin and mineral requirements were met by suitable pharmaceutical preparations. This basal diet has a very low cholesterol content (approximately 17 mg./day) and is nearly fat-free (7 g./day). The cholesterol content of the basal diet could be reduced to zero by substituting egg-white for the 50-g. casein supplement. As no significant differences in serum-cholesterol levels resulted from this manœuvre, the more readily available casein was retained as the daily protein supplement.

The dietary fat supplements under test were fed in each instance for 10 days. After 10 days the supplement was withdrawn from the basal diet and no further supplement was tested until the serum-cholesterol levels had reached a steady state. The effect of the various supplements was ascertained by comparison with the response of the serum-cholesterol levels to the feeding of 53 g. of egg-yolk lipid daily (10 egg yolks) from the domestic fowl (*Gallus domesticus*). For this reason this amount of egg yolk was fed repeatedly, approximately once every four months, and the excellent reproducibility in this individual is illustrated by the almost identical responses over a prolonged period (see Fig. 1).

Preparation of Egg-yolk Fractions

The fractions were prepared in batches sufficient to cover a full 10-day feeding period. Yolks were separated from whites of the eggs, and the lipid was extracted from the yolks by the method of Lea and Rhodes (1954). The acetone-insoluble fraction was extracted with chloroform and methanol to separate egg-yolk protein from egg-yolk phospholipid. The acetone-soluble fraction was fractionated into the unsaponifiable and saponfiable fractions by the addition of potassium hydroxide and absolute alcohol and continuously extracting the unsaponifiable matter with ether for 48 hours. The saponifiable fraction after the addition of sulphuric acid was re-esterified at the outset with ethyl alcohol but later with glycerol (see Fig. 5). The effectiveness of the technique was ensured by the failure to detect cholesterol

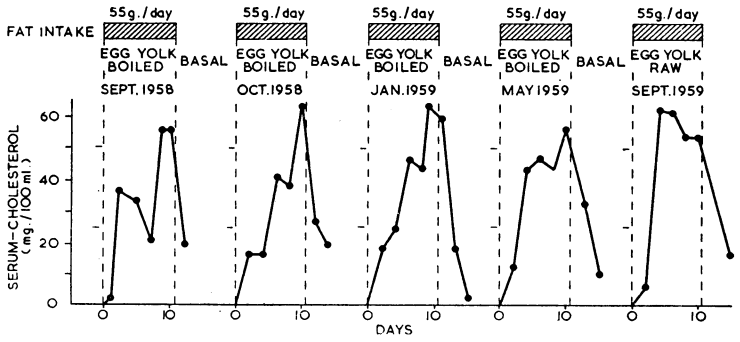

FIG. 1.—Egg yolk fed to the same individual (repeatedly) on several different occasions gives reproducible effects on the serum-cholesterol levels. No differences were noted whether egg yolk was fed raw or boiled.

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in the acetone-insoluble and phospholipid in the acetone-soluble fractions.

With the exception of the ostrich, where only one egg was analysed, all analyses were performed on the combined yolks of five eggs chosen at random. The lipid content of ostrich (*Struthio australis*), duck (*Anas domesticus*), penguin (*Spheniscus demersus*), and domestic fowl (*Gallus domesticus*) eggs was estimated gravimetrically after preliminary extraction and the cholesterol content, phospholipid content, and iodine value were determined. The nature of the fatty acids in the esters was determined by gas chromatography.

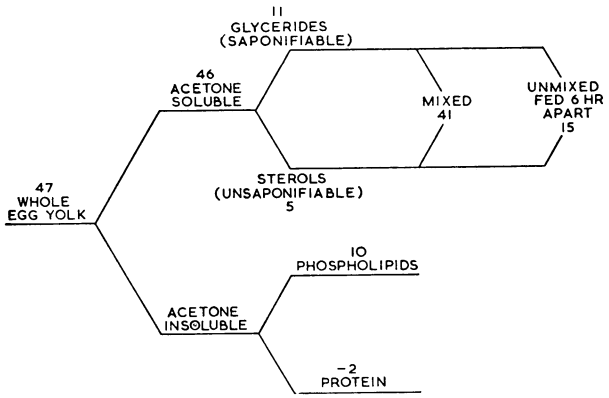

FIG. 5.—Summary of the egg fractionation procedure. The figures depict the mean change in serum-cholesterol levels over a 10-day feeding period.

Results

Egg Yolks from Different Species

The composition of the egg yolk from the different species is shown in Tables I and II. The feeding of amounts of egg yolk that would be similar in fat content (as, for example, 170 g. ostrich egg yolk daily instead of 10 egg yolks from the domestic fowl) led to no significant differences in response between the domestic fowl, ostrich, and duck, but significantly lower serum-cholesterol levels were seen on each of the two occasions when penguin egg yolk was fed (see Fig. 2).

TABLE I.—*Composition of Egg Yolks of Different Species. All Figures are Based on Wet Weight of Egg Yolk*

	Hen	Ostrich	Penguin	Duck
Average weight of yolk ..	17·5 g.	371 g.	22·5 g.	28·5 g.
Fat content ..	5·3 g.	119 g.	6·2 g.	8·4 g.
Acetone soluble fraction ..	19·4%	32·7%	19·8%	18·4%
Phospholipid	9·0%	5·6%	7·7%	11·1%
Protein	22·1%	15·0%	22·5%	21·9%

TABLE II.—*Fatty-acid Composition of Both the Acetone-soluble (Glycerides and Sterols) and the Acetone-insoluble Fraction (Phospholipids) of Different Species are Shown*

	C14	C16	C16:1	C18	C18:1	C18:2	C18:3	C20:4
Acetone-soluble Fraction								
Hen ..	1·6	29·1	2·0	2·5	50·3	14·5		
Ostrich	0·4	26·4	4·5	3·2	49·2	16·3		
Duck	0·4	22·7	3·8	3·0	63·7	4·6	0·4	1·5
Penguin*	0·9	18·8	5·5	6·2	55·9	2·1		
Acetone-insoluble Fraction								
Hen ..	0·3	36·5	1·3	17·1	29·7	15·2		
Ostrich	0·3	28·0	1·1	27·7	23·8	13·5		
Duck	0·4	35·1	2·9	9·2	48·9	2·4		1·7
Penguin†	0·6	28·1	1·7	19·6	32·7	0·5		

* 10·6% were unidentified—mostly very long chain fatty acids.
† 16·6% were unidentified—mostly very long chain fatty acids.

Whole Egg versus Egg Yolk and the Effect of Cooking

There were no differences between the effects of feeding boiled egg yolks and raw egg yolks on the serum-cholesterol levels (see Fig. 1). Inconclusive findings were obtained on comparing whole egg with egg yolk. In one individual slightly higher serum-cholesterol levels were seen with whole egg than with egg yolk whether fed in the raw or cooked state. In another individual no differences were found.

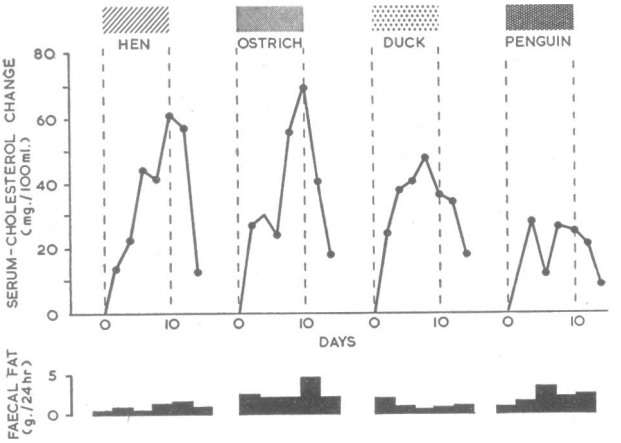

FIG. 2.—There are no significant differences in serum-cholesterol response to the feeding of hen, ostrich, and duck egg yolk. A significantly lower response occurs after the feeding of penguin egg yolk.

Effect of Egg-yolk Fractions

Acetone-insoluble Fractions.—Neither egg-yolk protein (29 g.) nor egg-yolk phospholipid (16 g.) fed in amounts equivalent to that in 10 egg yolks produced any significant rise in serum-cholesterol levels (see Fig. 3).

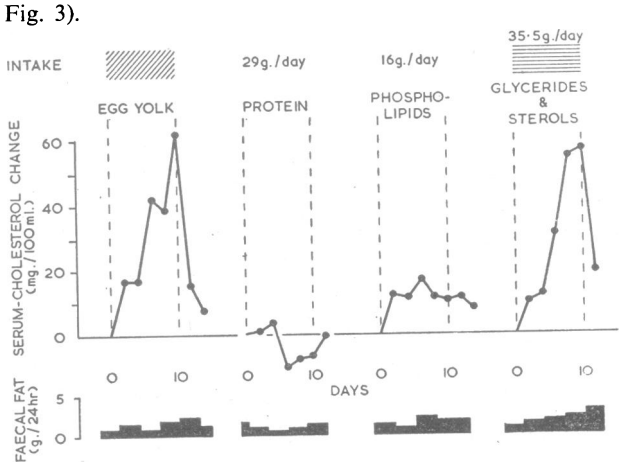

FIG. 3.—Serum-cholesterol response to egg yolk can be reproduced by the feeding of the acetone-soluble fraction (glycerides and sterols) but not by the acetone-insoluble fraction (protein and phospholipids).

Acetone-soluble Fraction.—An immediate and sustained rise in serum levels followed the feeding of the acetone-soluble fraction (35.5 g.), equivalent to that seen on feeding egg yolk (See Fig. 3).

Saponifiable and Unsaponifiable Fractions.—If fed separately, neither the unsaponifiable matter of the acetone-soluble fraction (3 g.) nor the saponifiable matter (32.5 g.) led to any significant rise in serum-cholesterol levels (see Fig. 4). When these two fractions were fed together, however, an immediate rise in serum levels occurred, equivalent to that seen on feeding the acetone-soluble fraction before saponification (see Fig. 4). This effect was seen whether the saponifiable matter was fed as ethyl esters (which caused diarrhoea and a high faecal

fat excretion) or as glycerol esters, where the faecal fat excretion remained normal throughout. This effect was seen, too, whether these two fractions were mixed (dissolved) or unmixed prior to feeding, provided that both

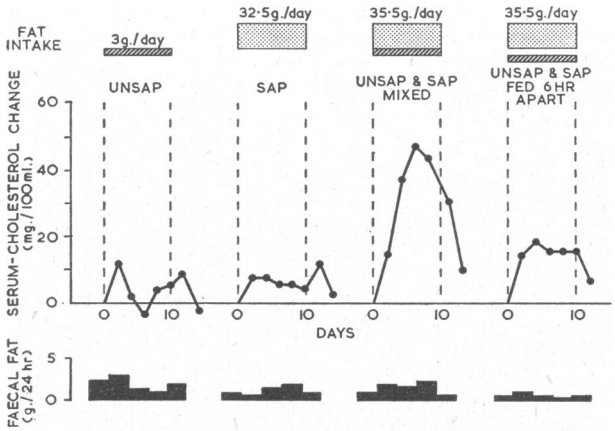

FIG. 4.—Following saponification of the acetone-soluble fraction the serum-cholesterol response on feeding either the saponifiable (sap) or the unsaponifiable (unsap) fraction, is negligible unless they are fed together. Even a delay of only six hours between the feeding of the one and the feeding of the other considerably diminishes the serum-cholesterol response.

were fed at the same time. The experiment was repeated in that both fractions were fed on the same day but the unsaponifiable matter was fed at 6 a.m. and the saponifiable matter was fed with the midday meal. This delay of only six hours between the feeding of the one and the feeding of the other was sufficient to nullify largely the response seen on feeding both concurrently (see Fig. 4). With the exception of the occasions when the saponifiable fraction was fed after esterification with ethyl alcohol, all changes seen occurred in the presence of normal fat absorption.

Sterol and Fatty-acid Substitutions

The above experiments were repeated except that crystalline laboratory reagent cholesterol (3 g.) was substituted for the egg unsaponifiable matter and a hydrogenated sunflower-seed oil (32.5 g.) of similar iodine value (74) for the egg saponifiable matter. Cholesterol fed with egg saponifiable matter, egg unsaponifiable matter with hydrogenated sunflower-seed oil, or cholesterol with

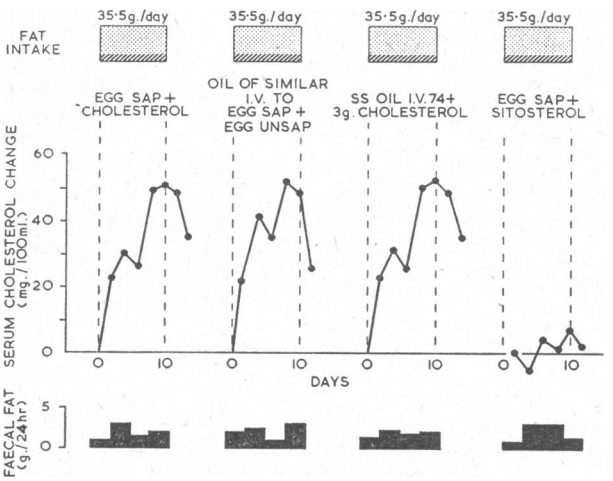

FIG. 6.—Serum-cholesterol responses are the same if crystalline cholesterol is substituted for the egg unsaponifiable fraction or if an oil is fed of similar iodine value (hydrogenated sunflower-seed oil) to the egg saponifiable fraction. On the other hand, this effect is not seen if sitosterol is fed with the egg saponifiable fraction.

hydrogenated sunflower-seed oil, all gave serum cholesterol responses equivalent to that seen on feeding the acetone-soluble fraction or egg yolk (see Fig. 6).

Role of the Sterol Fraction

When another sterol, beta-sitosterol (3 g.) or the unsaponifiable matter of a vegetable oil such as coconut oil, was fed with the egg saponifiable matter or the hydrogenated vegetable fat, no rise in serum cholesterol levels occurred (see Fig. 6 and Table III). Intermediate effects were seen if mixtures of beta-sitosterol and cholesterol replaced the unsaponifiable matter in the proportions of 1½ g. to 1½ g. and 2 g. to 1 g. respectively.

TABLE III.—*Mean Serum-cholesterol Change is Determined by the Nature of the Unsaponifiable and the Saponifiable Fractions When Fed in Combination*

Unsaponifiable Fraction	Saponifiable Fraction	Serum-cholesterol Change (mg./100 ml.)
Egg unsaponifiable ..	Hydrogenated sunflower-seed oil, I.V. 74	+42
Cholesterol, 3 g. ..	" "	+48
Sitosterol, 3 g.	" "	+3
Cholesterol, 1·5 g.; sitosterol, 1·5 g.	" "	+27
Cholesterol, 1 g.; sitosterol, 2 g.	" "	+18
Coconut oil, 3 g. ..	" "	+10
Cholesterol	Natural sunflower-seed oil I.V. 132	+4
"	Cod-liver oil	+7
"	Coconut oil	+48
"	Egg sap	+46

Stepwise reductions of the amount of cholesterol fed with the hydrogenated sunflower-seed fat supplement (32.5 g.) was not associated with any change in serum-cholesterol response until the amount of cholesterol added fell below 0.5 g. daily. It was only below this level that different effects were noted (see Fig. 7). It appeared that incremental daily supplements from 25 up to 500 mg. of cholesterol were associated with increasing concentrations of cholesterol in the serum, but above 500 mg. no further increase was seen. These supplements were added to a basal diet which contained 17 mg. of cholesterol.

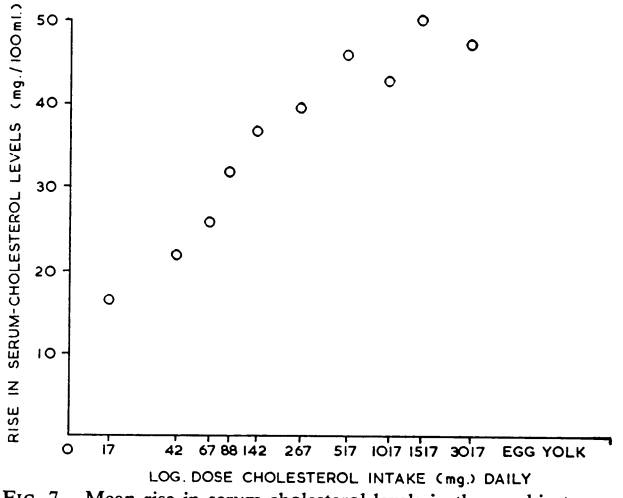

FIG. 7.—Mean rise in serum-cholesterol levels in three subjects on adding incremental supplements of dietary cholesterol to basal diet which contains 17 mg. of cholesterol. Basal diet was supplemented throughout with 32.5 g. of hydrogenated sunflower-seed fat. Figures shown are means of levels attained at end of 10-day feeding periods.

Role of Accompanying Fatty Acids

If the egg unsaponifiable fraction or 3 g. of cholesterol was fed daily in the company of the glycerol esters of natural unhydrogenated sunflower-seed oil (I.V. 132)

or cod-liver oil (I.V. 160), there was no significant rise above the levels seen on the basal diet. On the other hand, if fed with the glycerol esters of coconut oil (I.V. 7) the mean rise in serum-cholesterol levels resembled that expected after the feeding of egg yolk (see Table III).

Discussion

Despite its high iodine value and high content of essential fatty acids, egg-yolk lipid when it is fed gives rise to a prompt and marked increase in serum-cholesterol levels. Egg-yolk lipid differs from most other fat-containing foodstuffs in that it contains not only triglycerides but also phospholipids and large quantities of cholesterol. Most of the fat is in the form of lipoprotein. Biotin is also present—a substance claimed to enhance cholesterol deposition in animals (Okey, 1946). From our present experiments it would appear that the serum-cholesterol-raising properties of egg yolk are confined to the acetone-soluble fraction. This fraction contains triglycerides and cholesterol, a small proportion of which is esterified. In the acetone-soluble fraction there is no phospholipid or protein, the lipoprotein complex is disrupted, and presumably biotin, a water-soluble substance (Mellville, 1944), would have been removed.

Separation of the triglycerides from the cholesterol components by column chromatography was impracticable for the large amounts necessary for the 10-day feeding periods. We had to be content with saponification as the next stage.

The feeding of the unsaponifiable and saponifiable fractions separately without any pronounced effects on the serum cholesterol initially led to concern lest the process of saponification had destroyed the active principle. On redissolving these two fractions before feeding, or on feeding them together, the activity returned. This effect was largely abolished if a delay of only as little as six hours separated the feeding of the one from the feeding of the other. It appeared that both fractions had to be in the upper gastro-intestinal tract at the same time.

Our findings are not quite in agreement with those of Pollak (1958), who fed raw and cooked eggs to rabbits, in that we were unable to show any difference between uncooked and cooked eggs, nor could we find any consistent difference between whole eggs and egg yolks. Nevertheless, like Pollak, we cannot ascribe these effects to avidin-biotin relationships.

The combined role of the unsaponifiable and saponifiable fractions drew our attention to both the sterol and the fatty acids ; a view held from our earlier experiments (Bronte-Stewart *et al.*, 1956). In these earlier experiments we were unimpressed with the effect of crystalline cholesterol when fed alone but observed a sharp rise in serum-cholesterol levels when this was fed in the company of the saturated fatty acid fraction of a vegetable oil. We concurred with the views of Messinger *et al.* (1950), Mayer *et al.* (1954), and Keys *et al.* (1956) that the changes in serum-cholesterol level were due to some factor in addition to the cholesterol content of the dietary fat. Our findings agreed with the feeding experiments of Swell *et al.* (1955), who found greater rises of the serum-cholesterol level of rats when cholesterol was given with saturated fatty acids, compared with unsaturated fatty acids. Connor *et al.* (1961) have noted, in man, marked changes in serum-cholesterol levels on withdrawing and introducing egg yolk into the diet. They believed these changes were due to the dietary cholesterol intake, as they could not be accounted for by differences in the protein content or fatty acid composition of the diet. They could not, however, exclude the possibility that the effects may have been due either to the egg phosphatides or to the physico-chemical state of cholesterol in egg yolk, which is in the form of lipoprotein complexes.

In the present study our substitution experiments have led us to the conclusion that the serum-cholesterol-raising properties of egg yolk could be adequately explained by its content of cholesterol and the nature of the accompanying fatty acids. The importance of both these factors was shown by the fact that, firstly, plant sterols did not have the same effect as cholesterol, whereas if an oil of high-iodine-value was fed with cholesterol or the egg unsaponifiable matter no significant rise in serum-cholesterol levels was seen.

The role of the accompanying fatty acids might explain why cholesterol-containing marine oils and penguin eggs did not raise the serum-cholesterol levels greatly. Unfortunately, breeding regulations prevented the acquisition of further supplies of penguin eggs, so that these studies on eggs from different species had to be abandoned. Throughout the experimental period we obtained our domestic-fowl eggs from the same source because Reiser (1951) has shown that the nature of the diet of laying hens affects the fatty-acid composition of the egg yolk. Despite the differences in feeding habits of ostriches, ducks, and domestic fowls, the fatty acids of their egg yolks are not greatly different. Horlick and O'Niel (1958) showed different effects on the serum-cholesterol levels on feeding eggs where the fatty acids were altered deliberately by changes in the hen's diet. Gordon *et al.* (1958) could not achieve this effect.

Dietary cholesterol was thought to play little part in the regulation of serum-cholesterol levels in man (Keys *et al.*, 1956). The reasons now seem clear: firstly, little effect will be seen unless fed with a suitable fat ; secondly, a delay of as little as six hours between the feeding of cholesterol and the feeding of the fat will be associated with little effect ; and thirdly, as Beveridge *et al.* (1960) have shown, the cholesterol dose-response curve rises to a plateau at about 500 to 600 mg. daily. These authors have pointed out that 600 mg. daily approximates the dietary cholesterol intake of most people ingesting the usual variety of non-vegetarian foodstuffs. Previous studies, which have failed to reveal any dramatic effects of cholesterol added to the diet, have added cholesterol supplements to a non-vegetarian diet.

The reason why such small doses of cholesterol have this effect is not clear. It would appear that the mechanism responsible operates within the gut, possibly in its upper regions, as a delay of only six hours betwen the feeding of the sterol and the fat considerably nullified the effect of both fed together. As a result of these experiments, together with others on rats, Wilkens (1959) suggested that these effects could be explained on a simple physico-chemical basis—namely, the degree of solubility of cholesterol in the various oils and fats (Bronte-Stewart, 1961). Recently emphasis has been placed on the role of the bile acids, the breakdown products of cholesterol (Chaikoff *et al.*, 1952). For example, Howe *et al.* (1960) have shown how the proportion of tri- to di- and monohydroxy cholanic acids in the gut influenced the rate of cholesterol absorption. Knowledge of mechanisms controlling cholesterol

absorption is too inadequate at present for further speculation in this regard.

Summary

Egg-yolk lipid has a relatively high iodine value and a relatively high content of polyunsaturated fatty acids, but when fed to a man a rapid rise in serum-cholesterol levels follows.

The feeding of fractionated egg yolk reveals that this activity resides in the acetone-soluble fraction, but on saponification of this fraction neither the unsaponifiable nor the saponifiable fractions give a rise in serum-cholesterol levels when fed separately. For a rise to be seen they have to be fed together, because a delay of only six hours between the feeding of the one and the other considerably nullifies this effect.

It was shown by substitution that the effects of the unsaponifiable and saponifiable fractions could be reproduced by cholesterol on the one hand and a fat of a similar iodine value on the other. Cholesterol fed with oils of high-iodine value was without effect.

Further experiments revealed that the range of intake of cholesterol where an effect on the serum levels was observed was between 40 to 500 mg. daily, which is below the usual daily intake expected in non-vegetarian diets.

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CARPAL-TUNNEL SYNDROME

WITH PARTICULAR REFERENCE TO SURGICAL TREATMENT

BY

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The history of this common disorder was briefly summarized in a previous publication (Garland, Bradshaw, and Clark, 1957). In 1963 every British neurologist will have seen large numbers of victims, but from personal observation we know that the syndrome is not recognized in many countries in Eastern Europe and Asia. There is still, however, no unanimity in Great Britain as to the optimum method of treatment. Although our main purpose is to show the excellent results of surgical treatment, the diagnosis is still sometimes incorrectly made, or, more frequently, the symptoms are attributed to something else, so that diagnostic criteria must be discussed.

The diagnosis is usually very easy to the trained neurologist but perhaps to few others, and we think this is easily explained. In our experience the commonest, the most important, and sometimes the only physical sign is weakness of the abductor pollicis brevis, the sole action of which is to abduct the thumb at right angles to the palm (Figs. 1 and 2), though this was not the experience of Kendall (1960). This can be difficult of assessment in an uncooperative patient, and in minimal degree can only be assessed against a control, which might be the unaffected hand of the patient; obvious wasting of the abductor pollicis brevis is very much less common. Another pitfall is the testing of objective sensory change in the usual median nerve distribution, and, since pain is frequently the only modality to be affected, it is often difficult or impossible, even in the most experienced hands, to make an accurate assessment; this is made still more complex because pain sensation may be diminished or accentuated. Another common and misleading feature of the syndrome, for which no adequate explanation has yet been given, is the complaint of pain proximal to the wrist and which is sometimes claimed to reach as high as the shoulder.

We have not infrequently seen patients who have failed to improve after surgical treatment (not advised by ourselves) because they were suffering from a cervical root pain, and in fact this is the only common differential diagnosis; further, because of the age-group usually involved, a large number of these patients have radiological evidence of cervical disk damage, and indeed some may be suffering from ipsilateral root pain as well as the carpal-tunnel syndrome. Ipsilateral cervical rib never produces the syndrome under discussion.

The main cause of failure, of which we have had little experience, arises through the surgeon's failure to make a complete division of the anterior carpal ligament (Goodman and Gilliatt, 1961). In 1963 we are surprised to find that there are those who feel that surgical treatment is either unnecessary or frequently