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THE RELATIONSHIP BETWEEN DIETARY FAT AND THE PREVENTION OF ATHEROSCLEROSIS

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Atherosclerosis is the underlying pathological process of almost all cases of clinical coronary heart disease and often also of cerebrovascular disease. The incidence and mortality of coronary heart disease in the higher developed countries are extremely high and have reached epidemic proportions. For instance in the U.S.A. one third of all deaths (or 600,000 persons a year) is due to coronary heart disease. About 30% of these deaths occur in middle age, hence premature. International epidemiological studies established a relationship between the incidence of atherosclerotic cardiovascular disease, the level of cholesterol and phospholipids in the blood, and dietary habits. Population groups with a low serum cholesterol content show a lower incidence of coronary heart disease than groups with higher contents. The incidence is also related to dietary habits, i.e. population groups with a high coronary death rate invariably consume diets containing a high amount of saturated fats and cholesterol. In the United States e.g. in Framingham and Albany, prospective studies were carried out within one population group. Large groups of initially healthy men were periodically examined over prolonged periods. These studies distinctly demonstrated that the chance of developing coronary heart disease is particularly related to the blood cholesterol level. This means that if the other factors mentioned hereafter are the same, the risk of disease increases as the blood cholesterol level is higher; in persons with a high content of e.g. 260 mg cholesterol per 100 ml serum the risk is 3 to 4 times greater than in persons with levels of less than 220 mg per 100 ml. These studies also demonstrated a number of other risk factors as: hypertension, diabetes, excessive cigarette smoking, physical inactivity, emotional stress and a positive family history of premature vascular disease.[1]

However, I want to demonstrate that on account of the results of animal experimental, clinical and pathological investigations it must be assumed that the type of dietary fat can influence the degree of atherosclerosis and the frequency of its complications.

In 1957 experiments were started at the Unilever Research Laboratory in Vlaardingen which were aimed at obtaining more direct evidence. In these experiments the degree of atherosclerosis was determined by direct observation of the arterial blood vessels. Rabbits were fed normal, cholesterol-free diets, containing optimal amounts of protein, vitamins and salts. The fat content of the diet was 40 cal%.

Comparisons were made between maize oil which is rich in poly-unsaturated fatty acids, and coconut fat which contains a high percentage of saturated fatty acids. Both are vegetable oils containing no cholesterol.

The experiments with the rabbits lasted one year after which the animals were autopsied. The degree of the aorta atherosclerosis was assessed

using an arbitrary scale, ranging from 0 for no, to 4 for very serious lesions. In the group fed a maize oil containing diet hardly any atherosclerosis had developed (mean degree: 0.1), but the animals fed coconut fat showed distinct atherosclerotic changes (degree: 1.1) (see Fig. 1). In Addition, a third group of rabbits was investigated which received a diet in which the fat had largely been replaced by carbohydrates. This low-fat group has an atherosclerosis degree of 0.5 which lies between that of the groups fed maize oil and coconut fat. Consequently, the fat-rich maize oil diet had more favourable effect than the low-fat diet.

The result of the histological investigation confirmed the macroscopic observations, namely that the nature of the dietary fat influences the degree of atherosclerosis in rabbits.

A following investigation was carried out with rabbits which already had a certain degree of atherosclerosis, namely degree 2.3. The object was to establish whether types of fats of different nature also exert a different influence on an existing atherosclerosis. This was indeed the case. After about one year the animals which had received the diet with coconut oil displayed very severe lesions (degree 3.7), then followed the rabbits which had received the carbohydrate-rich low-fat diet (degree 3.1), whereas the animals of the soybean oil group had a distinctly lower degree of atherosclerosis, namely 2.7 (the soybean oil used, just as the maize oil, contains a high percentage of poly-unsaturated fatty acids). Again it appears that the fat-rich soybean oil diet has a more favourable effect than the low-fat diet. From the fact that the final degree 2.7 and the initial degree 2.3 are about the same, it follows that the process is stopped but not that the atherosclerotic lesions decrease. Low-fat or coconut fat-containing diets caused a pronounced increase in the existing degree of atherosclerosis. Consequently, the nature of the dietary fat also influences an existing atherosclerotic process.

The microscopic picture of the atherosclerosis in the rabbits bore a striking resemblance to that of the atherosclerosis in men (see Fig. 2). Actually the correspondence between animal and human atherosclerosis becomes clearer in prolonged animal experiments.

Similar prolonged experiments with rabbits have also been carried out by others; they obtained the same results, also regarding the histological similarity between man and rabbit. These results have been criticized with the remark that the rabbit is not a suitable experimental animal, because it would be too sensitive to atherosclerosis. This argument (apart from the fact whether it is sound) has lost much of its value, because meanwhile investigations have been carried out with other animal species (monkeys, pigs, chickens and pigeons). In all cases the degree of atherosclerosis appeared to be dependent on the type of dietary fat and the histological picture showed a good correspondence with that of the human atherosclerosis.[2] On the basis of these facts the extrapolation from animal to man seems justified, in other words, the type of dietary fat may also influence human atherosclerosis.

The correctness of this extrapolation from animal to man can only be proved by experiments with men, in which, however, because of the difficulties on making the diagnosis, not the degree of atherosclerosis should serve as criterion, but the frequency at which complications of atherosclerosis occur, such as angina pectoris and myocardial infarction. A number of these

experiments which are difficult to carry out and rather time-consuming are still in progress and some have already been concluded with encouraging favourable results. The experiments are usually performed with groups of middleaged men, who receive diets, which are generally based on a decrease in the amount of fat with a high percentage of saturated fatty acids, decrease of the amount of cholesterol and increase of the amount of fat rich in poly-unsaturated fatty acids. All these changes are relative to the habitual diets or, in other words, saturated fatty acids are partially replaced by poly-unsaturated fatty acids. In these experiments a distinction must be made between investigations directed towards the primary prevention in healthy persons, i.e. persons free from clinical coronary heart disease, or towards secondary prevention in subjects which have already experienced an attack of coronary heart disease.

One of the best, most accurate and recent investigations is the study of Leren[3] in Norway. Over a period of 5 years he studied 412 men aged 30 and 67 years who 1 - 2 years previous to the beginning of the experiment had suffered a heart attack. Half of this group continued to consume the conventional diet which for 40 cal% consisted of mainly fats rich in saturated fatty acids; the others likewise received 40 cal% fat containing diets, which fat consisted mainly of soybean oil. Consequently, the latter diet was rich in poly-unsaturated fatty acids, especially linoleic acid, the most common representative of these fatty acids. After 5 years the linoleic acid-rich diet appeared to have had a distinctly favourable effect. The incidence of myocardial re-infarction and new cases of angina pectoris was distinctly lower than in the control group. Also important is the observation by Leren that the differences do not become significant until after 2 years. This again emphasizes the necessity of a long period of observation in the study of atherosclerosis.

Also in the United States and England experiments have been or are being carried out, which are directed towards secondary prevention. However, it should be borne in mind that in many cases the design of the experiments (e.g. number of participants, experimental period, distribution of the subjects over experimental and control groups, statistic analysis, type of diet and adherence to the diet) will not fully bear criticism. With a few exceptions, during which no differences between experimental and control groups could be established, the results obtained so far correspond satisfactorily with those of the investigation by Leren, viz. a decreased incidence of cardiovascular events in the diet group.

I would like to emphasize the following very important point: in not a single case was it found that the experimental diet caused an increased incidence. If the type of dietary fat should not have any influence at all it is to be expected statistically that the experimental diet would cause a negative result as often as it would a positive one. However, the experimental diets induced either an unchanged or a decreased incidence of coronary events but never an increased one.

Bearing in mind that "prevention is better (and probably also easier) than cure", more distinct results are to be expected from the experiments which are directed towards primary prevention of atherosclerosis.

Indeed, the first results of such investigations, which are still going on, like the Chicago Coronary Prevention Evaluation Programme[1], the Finnish study of Turpeinen[4], and the New York Anti-Coronary Club[5], are promising to

be highly positive. Especially in the latter two investigations involving 200 - 800 persons and which have been going on for 6 to 10 years, already distinct, significant differences occurred in the frequency of coronary heart disease in favour of the experimental groups which were fed diets containing less saturated and more poly-unsaturated fatty acids and less cholesterol. The latest publication in this series is that by Dayton et al.[6] Their study started in 1959 with 846 middle-aged and elderly men of the Los Angeles Veterans Administration Center, who participated in the study regardless of possible pre-existing atherosclerotic complications. Again a significatnly lower incidence of atherosclerotic events appeared in the group fed a diet of which the 39 cal% fat has a low content of saturated fatty acids and cholesterol and a high content of linoleic acid.

Summarizing, it can be concluded from the results of the discussed investigations that in man as well as in aminals the atherosclerotic process can indeed be influenced favourable, by changing the type of the dietary fat.

It goes without saying that in a coronary heart disease prevention programme attention should also be paid to correction or control of the other factors which increase the risk of developing coronary heart disease, such as hypertension, diabetes mellitus, obesity, excessive cigarette smoking, etc.

In these experiments the decrease in clinical coronary heart disease frequency was always accompanied by a decrease in blood cholesterol concentration. This observation justifies the generally accepted conclusion that a reduction of blood cholesterol level will result in a reduction of the incidence of atherosclerotic diseases.

So far the most effective way to influence blood cholesterol content in man is changing the nature of the dietary fats. Even more than 15 years ago, the influence of a number of oils and fats which differ in fatty acid composition was ascertained by Kinsell et al.[7], Ahrens et al.[8], Keys et al.[9], Hegsted et al.[10] and many others. At the moment there is general agreement that dietary fats rich in poly-unsaturated and low in saturated fatty acids (such as sunflower seed oil) induce lower serum cholesterol and phospholipid levels than fats with a high content of saturated fatty acids (such as butter and coconut oil).

To obtain more detailed information on the normal influence of the type and amount of fat on human blood lipid composition, Thomasson et al.[11] performed a series of experiments with liquid formula diets using volunteers, namely Trappist monks. These diets were given for 6 weeks as the sole energy source adequate to maintain a constant body weight. Their composition differed only with respect to the type (Expt. 1) or amount (Expt. 2) of fat.

Experiment 1

Under these strictly uniform experimental conditions first the influence of 50 cal% of 10 dietary fat mixtures of widely divergent fatty acid composition was studied. These fatty acid compositions are represented graphically by means of the triangular phase diagram used among others by Ahrens (Fig. 3). Each angle represents 100% of a type of fatty acid, namely saturated, mono- or di-unsaturated. In fact olive oil (68% oleic acid), safflower oil (72% linoleic acid) and glyceryl trilaurate (in which

5% safflower oil) were used as well as mixtures of these basic components in the ratios 1 : 2, 2 : 1 and 1 : 1.

The change from the normal 25 cal% fat-containing Trappist diet to the 50 cal% fat-containing liquid formula diets took place abrubtly. The average plasma cholesterol level on consumption of the usual Trappist diet was 145 mg per 100 ml. The influence of the 10 dietary fat mixtures on the plasma cholesterol level is shown in Fig. 4, which represents stereographically the relationship between the dietary fat composition and the change of the cholesterol level. The basal triangle shows again the fatty acid composition of the dietary fats (the corners representing 100% saturated, 100% mono-unsaturated and 100% di-unsaturated fatty acids). The tilted plane represents the average plasma cholesterol level induced by the liquid formula diets. The mean cholesterol content of 145 mg/100 ml on the normal Trappist diet is replaced by 100% and the change in cholesterol level induced by the dietary fats (indicated by 10 rods) is expressed in % with respect to this normal (100%) value. This is done because statistical analysis of numerous other experiments in man and in animals have indicated that the change in % of the cholesterol content (Δ %) is independent of the initial (or the control) value.

Fig. 4 shows that the cholesterol level is strongly dependent of the type of dietary fats. Some types of fat cause a decrease, other types an increase, whereas a third group of fats does not influence the plasma cholesterol content at all. The saturated glyceryl trilaurate caused the highest levels, the di-unsaturated safflower oil the lowest whereas the monounsaturated olive oil occupies an intermediate position.

In this investigation the relationship between fatty acid composition, and Δ % is represented by a flat plane. In other words the dietary fat mixtures influenced the plasma cholesterol level to a degree which could be expected on account of their respective fatty acid composition.

It has to be emphasized that the normal Trappist diet contained ca. 25 cal% fat and the liquid formula diets 50 cal%. Consequently, an increase in fat content of the diet (a doubling of the amount of fat calories) does not necessarily implicate an increase of cholesterol level. Both an increase as well as a decrease may occur, dependent of the type of fat consumed. The phospholipid levels were changed to the same extent as the cholesterol contents; the ratio of the cholesterol/phospholipid contents remained constant under these various dietary fat conditions.

Experiment 2

In a second experiment[12] the influence of different amounts of fat in the diet was studied. The diets contained 20, 35 or 50 cal% of one of the following fats:

a. 90% glyceryl trilaurate and 10% safflower oil

b. olive oil

c. safflower oil

The figures in Table 1 clearly show that the differences in final plasma cholesterol and in phospholipid levels between the groups fed the

Table 1

Influence of the dietary fat content and the dietary fatty acid composition on the total cholesterol and lipoid-phosphorus values. Changes in these values are the individual final values expressed as the % of the individual initial values

Dietary fat			90% glycerol trilaurate + 10% safflower oil			Olive oil			Safflower oil		
Cal%			20	35	50	20	35	50	20	35	50
Dietary fatty acids (cal%)		Sat.	18.2	31.8	45.3	3.4	5.9	8.5	1.8	3.2	4.5
		18.1	0.2	0.4	0.6	14.1	24.7	35.2	2.3	4.0	5.7
		18.2	1.6	2.8	4.0	2.5	4.4	6.3	15.9	27.8	39.8
n			8	7	6	8	8	9	8	9	8
Serum total cholesterol	initial	(mg/100 ml)	202	203	195	198	194	195	198	204	205
	final	(mg/100 ml)	202	201	205	175	172	186	164	160	164
	change	(mg/100 ml)	0	-2	+10	-23	-22	-9	-34	-44	-41
		(%)	+1	-1	+7	-12	-12	-3	-16	-22	-20
Serum lipoid phosphorus	initial	(mg/100 ml)	8.5	8.5	8.7	8.9	7.8	8.2	8.2	8.8	8.8
	final	(mg/100 ml)	8.8	9.3	10.0	8.4	7.4	8.0	7.5	7.0	7.0
	change	(mg/100 ml)	+0.3	+0.8	+1.3	-0.5	-0.4	-0.2	-0.7	-1.8	-1.8
		(%)	+4	+12	+16	-6	-4	-2	-7	-20	-21
Ratio TC/LP			23.0	21.6	20.5	20.8	23.2	23.2	21.9	22.9	23.4

20 cal% fat containing diets were definitely smaller than those between the groups consuming the higher amounts of fat containing diets. The lowest blood lipid levels were induced by the diets containing the higher amounts of safflower oil. These results justify the conclusion that a reduction in the fat content of the diet - as is often recommended - will not in all cases induce a decrease in blood lipid levels. In order to obtain low blood lipid levels it is therefore more recommendable to change the nature of the dietary fat than to decrease the fat content of the diet.*

The results of all these epidemiological, animal experimental, clinical and pathological investigations led us therefore to the conception that by changing correctly the type of dietary fat it must be possible to decrease the serum cholesterol content and thus retard or prevent the incidence of atherosclerosis.

Remarks

Finally some remarks. Another possibility to control atherosclerotic cardiovascular diseases is the pharmacological approach of the problem. With the help of various drugs, such as estrogens, thyroid derivatives, nicotinic acid, atromid-S and cholestyramine, it appeared to be possible to lower the blood lipid (cholesterol) levels.

Unfortunately at the moment no favourable results are yet available of clinical investigations into the influence of these drugs on the incidence of atherosclerotic coronary heart disease. Furthermore, to most of the drugs known so far troublesome side effects have been ascribed, and it does not seem very attractive to prescribe drugs to a large part of the population during their whole life. The change in the type of dietary fat on the other hand causes no unfavourable side effects.

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References

1. J. Stamler: Lectures on Preventative Cardiology, Grune & Stratton Inc., New York, 1967.
2. H. Malmros: Lancet I, 94 (1970).
3. P. Leren: Acta. Med. Scand. Suppl 466 (1966).
4. O. Turpeinen et al: Amer. J. Clin. Nutr. 16, 255 (1968).
5. G. Christakis et al: Amer. J. Public Health 56, 299 (1966).
6. S. Dayton et al: Lancet II, 1060 (1968).
7. L. W. Kinsell et al: J. Clin. Nutr. 1, 224 (1953).
8. E. H. Ahrens, Jr. et al: Lancet II, 943 (1957).
9. A. Keys et al: Metabol. 14, 747 (1965).
10. D. M. Hegsted et al: Amer J. Clin Nutr. 17, 281 (1965).
11. H. J. Thomasson et al: Pathol. Microbiol. 30, 629 (1967).
12. A. J. Vergroesen et al: Proc. 2nd Intern. Congr. Artherosclerosis, Chicago, 1969. Edit. R. J. Jones, in press.

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*From this and other experiments (to be published) the conclusion might be drawn that the normal human adult diet should contain 30 - 40 grams of linoleic acid per day to reduce the generally increased blood lipid concentrations.

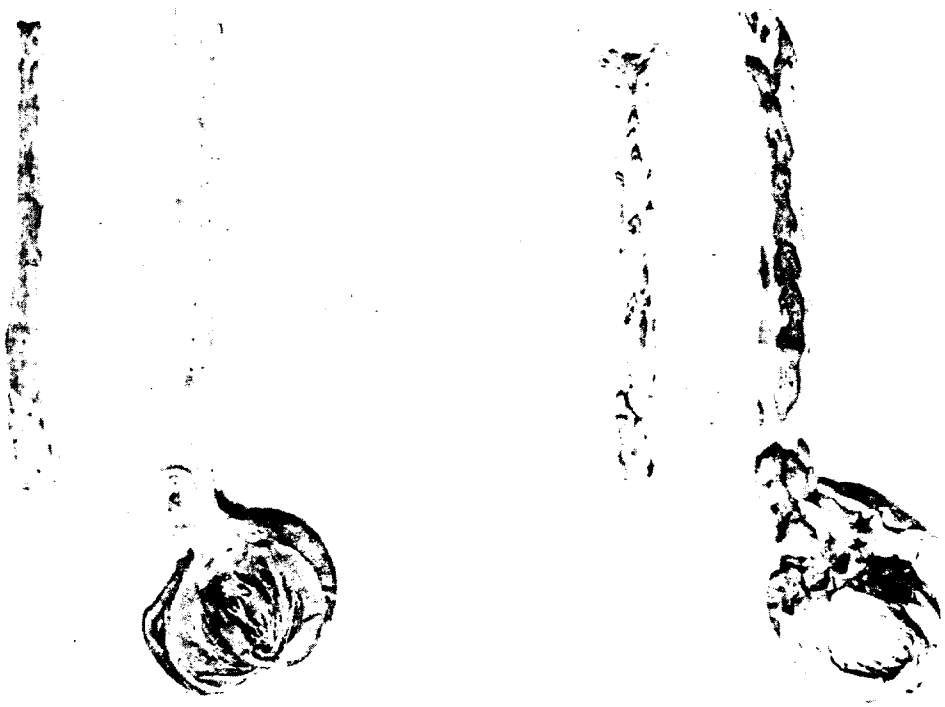

Figure 1 - Macroscopic aspect of rabbit heart and aorta: (at left) normal, maize oil, 40 cal%; (at right) atherosclerotic coconut oil, 40% cal%.

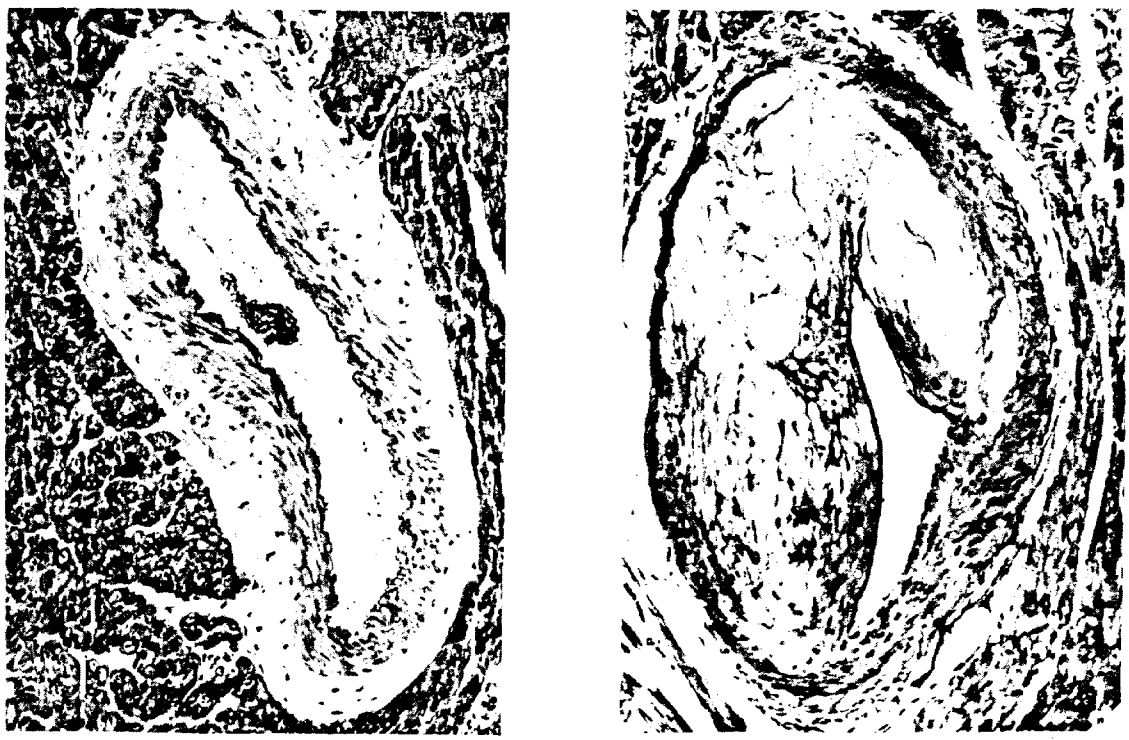

Figure 2 - Microscopic aspect of plaque of coronary artery and surrounding myocardial tissue: (at left) normal, intima is only one cell-layer thick; (at right) atherosclerotic, intima has swollen strongly.

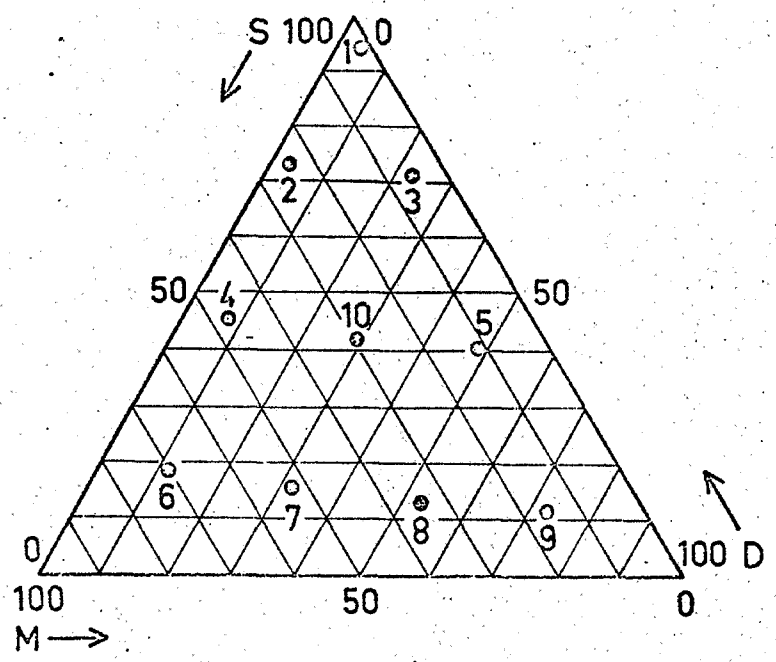

Figure 3 -

Diagram of the fatty acid composition of the ten "liquid formula diets" used in the first LFD experiment: (S) saturated, (M) monounsaturated, (D) diunsaturated fatty acids.

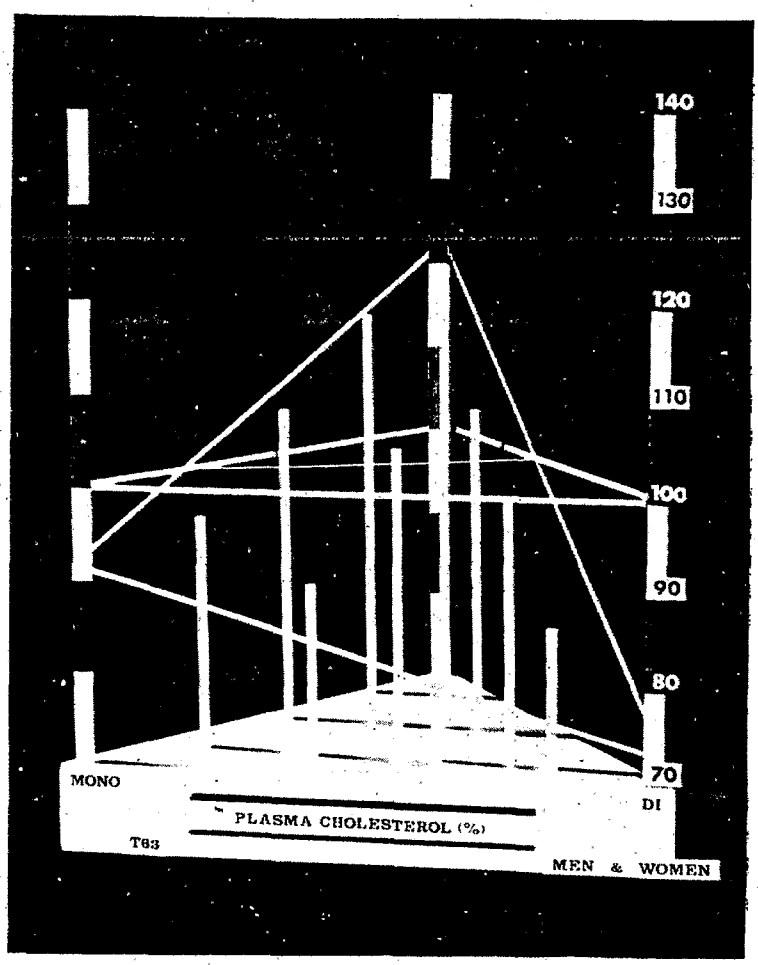

Figure 4 -

Three-dimensional diagram of the plasmacholesterol concentrations (in % of the initial values) caused by a 6-week diet of the ten "liquid formula diets", the fatty acid composition of which is given in the basal triangle.