no advantage in giving tetanus antitoxin and toxoid together. All the disadvantages that apply to antitoxin given by itself apply equally when it is given with any other drug.

Summary and Conclusions

The limitations of prophylactic tetanus antitoxin in the prevention of tetanus are demonstrated. In a survey of 33 cases of tetanus, 80% of patients did not receive prophylactic serum because of the trivial nature of their wounds. Anaphylaxis followed therapeutic use of serum in four of the five patients who developed tetanus in spite of prophylactic antitoxin given at the time of injury. One of these reactions was fatal.

In a controlled clinical trial the incidence of reactions after tetanus antitoxin and that after tetanus toxoid are compared. Reactions after tetanus antitoxin are more common than those after tetanus toxoid. Active follow-up of patients reveals that the total incidence of reactions after serum, excluding subjects known or likely to be sensitive to it, is about 25% and is higher than is generally appreciated.

One-third of casualty patients give a history of having had serum previously. This is associated with accelerated elimination of a subsequent dose of serum and increased risk of sensitivity reactions.

In view of the doubt concerning the value of tetanus antitoxin in prophylaxis, the high incidence of reactions, and the adverse effect on the therapeutic use of serum if tetanus should develop subsequently, a trial has been made in a large casualty department of progressive abandonment of the use of tetanus antitoxin. There is no evidence that the incidence of tetanus has increased since policy with regard to tetanus antitoxin was first modified four years ago. It is recommended that adequate wound treatment

and antibiotics be substituted for tetanus antitoxin as the modern prophylaxis against tetanus, together with active immunization by toxoid against future injury.

We are pleased to have the opportunity to acknowledge the assistance and advice received during this work from Professor G. M. Wilson, Dr. J. Colquhoun, and Dr. I. B. Sneddon. We also wish to thank consultants in Sheffield and in the Sheffield Region for permission to include their cases of tetanus in the study. We are grateful to the casualty registrars, casualty officers, and nursing staff of the casualty department of Sheffield Royal Infirmary who have worked in the department since 1959 for their help in running the clinical trial and for being prepared, sometimes at risk to their professional reputation, to follow the course of action described in this paper.

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LONG-TERM ADMINISTRATION OF CORN OIL IN MANAGEMENT OF PATIENTS AFTER MYOCARDIAL INFARCTION: A FOUR-YEAR STUDY

BY

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There is still no proof that hypercholesterolaemia is a direct cause of atherosclerosis or myocardial infarction. It is generally agreed, however, that the reduction of high serum cholesterol levels is desirable in the overall management of atherosclerosis and its complications. Pharmacological approaches to the problem have generally proved disappointing, but the demonstration by Beveridge *et al.* (1955) that the addition of corn oil to a diet low in animal fat would significantly reduce the serum cholesterol encouraged the idea that a physiological approach was feasible, and the corroboration of his findings (Ahrens *et al.*, 1957; Keys *et al.*, 1957) supported the hope that this might be a practical procedure.

This hospital was already involved in the M.R.C. anti-coagulant trial, and the large number of patients which would have been necessary for significant comparisons of mortality and morbidity between treated and control groups were not available. The outcome, therefore, was a less ambitious trial which it was hoped would answer the following questions. Firstly, was some kind of dietary programme feasible, and if so what? Secondly, did it have a sustained or merely transient effect on the serum lipids? Thirdly, were its clinical results encouraging?

At the time of writing all patients have been on this regime for at least two and a half years, and some for more than four years.

Methods and Subjects

Corn oil—maize oil (B.P.), linoleic acid content 56%—was chosen as the supplementary dietary oil. Messrs. Boots Ltd. undertook to supply and distribute it to all patients included in the trial and to guarantee its fatty-acid composition. Two diets were prepared—one of 1,630 calories (155 g. carbohydrate, 65 g. protein, and 80 g. fat), and the other of 2,080 calories (245 g. carbohydrate, 75 g. protein, and 85 g. fat). When 57 g. of corn oil is added to these diets the daily intakes become 2,045 and 2,595 calories respectively, and the oil comprises 41.5% of the total fat in the former and 40.0% of the total fat in the latter. This small percentage difference is of no practical significance. A diet was allocated according to the height, build, and occupation of the patient, and in this way some degree of metabolic parity was achieved. The 1,630-calorie diet is reproduced in Table I.

Each patient was given a 2-oz. (57-ml.) medicine glass and told to take the oil as it suited him. Each patient under-

stood that he could withdraw from the study at any time but that while still participating he was expected to adhere to the treatment schedule. The patients as a group were co-operative and conscientious. Some dietary relaxation was permitted at Christmas and the New Year and during summer holidays.

TABLE I.—*Low-animal-fat Diet Sheet Issued to Patients Taking 2 oz. (57 ml.) of Corn Oil Per Day*

*Low-Animal-Fat Diet. 1,630 Calories
(155 C., 65 P., 80 F.)*

Foods to avoid.—Animal fats, including butter, dripping, lard, cream, fat meat egg yolk, whole-milk cheese. Foods which may contain animal fat, such as ice-cream, cakes made with eggs, pastry.

Use daily.—Skimmed milk, $\frac{1}{2}$ pint (425 ml.); vegetarian margarine, $\frac{1}{2}$ oz. (20 g.); "marmite" (1 teaspoonful), as drink or sandwich; wholemeal bread, rolls, biscuits—as indicated.

Sample Menu

Breakfast.—1 cup cereal, e.g., porridge, cornflakes; bread, 1½ thin slices or/2 oatcakes or/3 ryvitas or/1 wheaten roll; milk, margarine from allowance; tea, no sugar.

Mid-morning.—Tea with milk; 1 plain biscuit, e.g., digestive.

Dinner.—1 cup fat-free soup; good helping lean meat, fish, chicken, tripe; 2 small potatoes; vegetable—good helping fruit or jelly or/milk-pudding, using milk from allowance.

Tea.—Lean meat with salad or fish or tripe or chicken or/skim-milk (cottage) cheese; fruit if liked; vegetables if liked; 1 thin slice wholemeal bread or 2 ryvitas or/2 vitawats; milk and margarine from allowance; tea with milk.

Supper.—Remainder of milk allowance; 1 plain biscuit.

All subjects were men between the ages of 43 and 65 (average 54.5) admitted with and surviving a first attack of acute myocardial infarction. Men with diabetes or renal disease, or whose blood-pressure exceeded 160/100 after four weeks in hospital, were not included. The severity of the acute illness did not exclude a patient.

Serum cholesterol was estimated by Henly's (1957) modification of the method of Zlatkis *et al.* (1953). As a result of preliminary work (Watson *et al.*, 1963) which defined the pattern of the fall and subsequent rise in serum cholesterol following an acute myocardial infarction, the control cholesterol levels were taken as the readings on the 22nd and 29th days after infarction for most of the patients, but on the 29th day and 8th week after infarction for those with severe attacks. These dates allow return of the serum cholesterol to pre-infarction levels. This was shown to be so whether the patients received anticoagulants or not.

Before discharge each patient's height and weight were recorded and anticoagulants discontinued in those who had been receiving them. Standard weights were calculated from height and age according to British tables (Levine, 1923). The patients were seen at monthly intervals for the first three months and thereafter every three months. They attended at the same time of the morning and on the same day of the week.

In the course of the major trial a simple experiment was interpolated which it was hoped might show whether corn oil was necessary for the continuing control of the lowered cholesterol, or whether, now that control had been achieved, a diet low in animal fat would by itself maintain the control. Seven patients who had completed at least two years on the major trial, and who represented typical responses to the treatment, had the corn oil withdrawn for a period of five months. During this time they continued with a diet low in animal fat and attended at monthly intervals for serum cholesterol estimations. At the end of this period the corn oil was reintroduced and since then each of the seven has been followed for a minimum period of four months.

Results

The clinical and biochemical results are summarized in Tables II and III. During the first two years of the trial there were four deaths (Cases 1–4), giving a mortality rate of 14.3%, no withdrawals, and no reinfarctions. The patients who died died at home and necropsies were not

obtained, but it is assumed from the description of the final illness that these patients died from a reinfarction. After the initial two-year period two men withdrew from the trial. One of these (Case 8) died 16 months later, and the other (Case 11), who was restarted on anticoagulants, died 18 months later. One of the patients (Case 7) who continued with the dietary regime died after 26 months' survival. Two patients (Cases 17 and 28) were readmitted to hospital on one occasion each, because of severe chest pain, but in neither case was reinfarction proved. At the time of writing 21 patients were still participating in the trial, having a mean survival of 39.4 months. This figure includes the seven from whom corn oil was withdrawn for the five-months period. Five patients have completed four continuous years of the regime.

TABLE II.—*Summary of Clinical Data for 28 Patients Started on Treatment Between 4 and 8 Weeks After Their First Myocardial Infarction. There Were No Reinfarctions Apart from Those Which Were Presumed to be the Cause of the 5 Deaths*

Period on Treatment (Months)	Man-months of Exposure	Deaths		Withdrawals	
		No.	Rate/100 m.m.e.*	No.	Rate/100 m.m.e.*
1–3	82	1	1.22		
–6	81				
–9	81				
–12	81	2	2.47		
–15	75				
–18	73	1	1.37		
–21	72				
–24	72				
–27	53	1	1.89	2	3.78
–30	48				
–33	42				
–36	27				
–39	24				
–42	24				
–45	18				
Total	853	5	0.59	2	0.23

*m.m.e. = man-months of exposure.

The patients have found this a relatively easy regime. At intervals one or two have developed a temporary distaste for the oil and have stopped taking it for a few days, but they have always resumed full dosage. One or two have become lax in their adherence to the diet and this has particularly affected their intake of eggs, but all seem to be completely avoiding butter, fried food, and cream, and to be trimming excess fat from their meat.

No fully objective analysis of the incidence and severity of angina has been made. At present 13 make no complaint of angina although their activity is, of course, sensibly limited. Eight experience varying degrees of effort angina, and six of these use glyceryl trinitrate as required, but none is incapacitated.

Two-year Cholesterol Control

The mean serum cholesterol levels and weights for 24 patients studied for two years are summarized in Table III. The serum cholesterol begins to fall after the administration of the dietary regime. The mean fall of 42 mg./100 ml. by the third month is significant ($P < 0.001$). The fall continues, reaching its mean maximum reduction of 72 mg. by the 12th month of the trial, thereafter rising slightly to a mean value of 241 mg./100 ml. at the end of two years. This average fall of 58 mg./100 ml. below the mean pretreatment level is still significant ($P < 0.001$). A study of Table III shows that there is no predictable relation between cholesterol levels and weight trend.

The maximum percentage fall in serum cholesterol and the mean percentage fall for each patient from the 3rd to the 24th month are shown in Table IV. Seventeen of the patients had a maximum fall greater than 25% of their pretreatment cholesterol level, and 17 had a mean reduction

of more than 15%. While there tends to be a greater percentage fall the higher the initial cholesterol level, this is not absolute. The maximum and mean percentage falls are charted in Fig. 1. There is a high degree of correlation between these two values ($r=0.94$, $P<0.001$). The relation is of a straight line form having the formula $y=9.60+1.08x$. Although this relation might be anticipated, the figures prove that those who achieve the largest absolute falls in their cholesterol levels are those most likely to achieve the largest sustained falls.

The maximum and average percentage falls in serum cholesterol for the eight patients receiving the 2,000-calorie basic diet are shown in Table V. These results are only slightly poorer than those for the rest of the group and justify the simple assessment of calorie requirement which was based on work, weight, and body-build.

Three-and-a-half-year Cholesterol Control

The average cholesterol levels for eight patients followed for three-and-a-half years are shown in column B of Table III. The average cholesterol levels for this group

TABLE III.—Average Serum Cholesterol Levels (mg./100 ml. $\pm$ 1 S.D.) and Weights of 24 Patients Treated for 24 Months and of 8 of the Same Group Treated for 42 Months. The Pretreatment Cholesterol Level is the Average of Control I and II

	A. Cases 5-28			B. Cases 21-28		
	Cholesterol	Weight		Cholesterol	Weight	
		lb.	kg.		lb.	kg.
Pretreatment	299 $\pm$ 37	157	71.2	313 $\pm$ 32	156	70.8
Month 1	285 $\pm$ 51	155	70.3	312 $\pm$ 56	156	70.8
" 2	279 $\pm$ 52	154	69.9	311 $\pm$ 37	157	71.2
" 3	257 $\pm$ 45	153	69.4	286 $\pm$ 48	155	70.3
" 6	243 $\pm$ 34	151	68.5	253 $\pm$ 41	155	70.3
" 9	232 $\pm$ 35	153	69.4	245 $\pm$ 38	158	71.7
" 12	227 $\pm$ 39	152	68.9	224 $\pm$ 46	155	70.3
" 15	233 $\pm$ 39	154	69.9	232 $\pm$ 44	155	70.3
" 18	245 $\pm$ 40	153	69.4	244 $\pm$ 37	154	69.9
" 21	244 $\pm$ 40	153	69.4	240 $\pm$ 48	154	69.9
" 24	241 $\pm$ 36	152	68.9	247 $\pm$ 41	153	69.4
" 27				241 $\pm$ 43	152	68.9
" 30				249 $\pm$ 48	152	68.9
" 33				262 $\pm$ 47	152	68.9
" 36				272 $\pm$ 55	150	68.0
" 39				284 $\pm$ 64	151	68.5
" 42				286 $\pm$ 75	150	68.0

This table shows that the fall and rise of cholesterol is unrelated to weight.

TABLE IV.—Results from Table III Treated to Show (A) Maximum Percentage Fall in Serum Cholesterol of 24 Patients Treated for 24 Months, (B) The Average Percentage Reduction from the 3rd to the 24th Month of Treatment, and (C) the Average Percentage Reduction for 8 of the Same Group from the 3rd to the 42nd Month of Treatment

Case No.	Average Pre-treatment Cholesterol (mg./100 ml.)	A		B		C	
		Lowest Cholesterol (mg./100 ml.)	Maximum % Fall	Mean Cholesterol during 3-24 Months	Mean % Fall	Mean Cholesterol during 3-42 Months	Mean % Fall
5	249	194	22.0	228	8.4		
6	252	185	26.6	208	17.5		
7	274	172	37.2	194	29.2		
8	297	251	15.5	285	4.0		
9	288	205	28.8	223	22.6		
10	264	236	10.6	251	4.9		
11	261	235	10.0	258	1.1		
12	308	224	27.2	254	17.5		
13	262	180	31.3	215	18.0		
14	326	252	22.7	295	9.5		
15	318	235	26.1	276	13.2		
16	287	195	32.0	232	19.2		
17	251	166	33.8	202	19.5		
18	359	193	46.3	226	37.1		
19	325	240	26.1	263	19.1		
20	238	176	26.1	202	15.1		
21	272	224	17.7	242	11.0	257	5.5
22	369	280	24.1	302	18.2	324	12.2
23	323	226	30.0	277	17.3	297	8.1
24	289	140	51.5	185	36.1	198	31.5
25	341	218	36.1	265	22.3	277	18.8
26	289	192	33.5	228	21.1	222	23.2
27	318	180	43.4	221	30.5	216	32.1
28	310	182	41.3	238	23.2	240	22.6
Means	299	210	29.1	245	18.2	254	19.3

of eight follow closely those of the larger group of 24 during the first two years and a good degree of control is maintained for a further six months. From this point, however, the trend of the average cholesterol level is upwards, but even by the end of the third year the mean difference of 41 mg./100 ml. between the third-year level and the pretreatment level is still significant ($P<0.02$). After this point the mean levels are not significantly below those of the pretreatment level. While this is true for the group, Fig. 2 shows that in Cases 26 and 27 there is continuing reduction in the cholesterol level.

Response to Withdrawal of Corn Oil

The cholesterol levels for the seven patients from whom corn oil was withdrawn for a period of five months and

FIG. 1.—Graph showing the relation between the maximum and mean percentage reductions in serum cholesterol levels for 24 patients during the first two years of the dietary regime.

TABLE V.—Degree of Lowering of Serum Cholesterol Over 2 Years of the 8 Patients Given the Bigger Diet (2,000 cal.)

Case No.	Maximum % Fall	Average % Fall
7	37.2	29.2
8	15.5	4.0
10	10.6	4.9
15	26.1	13.2
19	26.1	19.1
21	17.7	11.0
23	30.0	17.3
24	51.5	36.1
Means	26.8	16.9

FIG. 2.—Serum cholesterol levels for two subjects observed for 45 months.

subsequently restarted are shown in Table VI. The results of section A of this table show the upward trend apparent in the group reported above. Nevertheless, the mean value of 259 mg./100 ml. immediately before the corn oil was

TABLE VI.—Cholesterol Levels (mg./100 ml.) of 7 Patients (a) on Corn Oil and Diet Low in Animal Fat for the Previous Year, (b) When the Oil was Withdrawn for 5 Months, and (c) When Restarted

Case No.	Control Mean	(a) Diet and Corn Oil				(b) Diet Alone					(c) Diet and Corn Oil	
		12 Months				5 Months					4 Months	
		3	6	9	12	1	2	3	4	5	2	4
9	288	211	228	230	238	326	348	331	301	374	270	283
10	264	240	262	252	272	265	275	267	274	274	260	245
15	318	235	262	278	302	368	342	329	368	345	346	348
17	251	230	220	230	239	258	255	259	267	273	241	268
18	359	206	214	215	233	269	268	305	295	309	293	240
19	325	240	241	254	296	350	334	335	360	310	293	355
20	238	194	230	242	238	231	238	220	265	274	260	239
	292	222	237	243	259	295	294	292	304	308	280	283

withdrawn is still significantly below the control mean level of 292 mg./100 ml. ($P < 0.01$), and the rise after one month off corn oil to a level of 295 mg. is also significant ($P < 0.05$). It is difficult to claim that this rise is due to the withdrawal of corn oil, but the fall in cholesterol level which occurred after restarting the corn oil seems to show that during the period off oil the cholesterol levels were less well controlled or not controlled at all. It is probably correct to infer from these results that though this group of seven patients was beginning to show a poor response to the regime it still had some degree of cholesterol lowering due to corn oil, and that this was not maintained by a diet low in animal fat alone.

Discussion

This study shows that a diet of about 1,600 to 2,000 calories, low in animal fat and supplemented by 57 g. of corn oil a day, can produce and maintain a significant reduction in the serum cholesterol level for at least three years. In individual patients it is probable that the degree of control has extended beyond four years. In a group of 24 men followed for at least two years the average maximum reduction in serum cholesterol levels was 29.1% and the average mean fall during this period was 18.2%. In a group of eight patients followed for 42 months the mean reduction achieved during this time was 19.3% of the pretreatment cholesterol level. Not all patients responded to the same extent. In some the response may be regarded as insignificant, and a way of selecting patients who might be suitable for this regime would be of value. There is no early clue to the individual response which can be expected, for some of the patients achieved their maximum percentage reduction in cholesterol level two years or more after starting the regime. Nor is there any clue to why some patients responded better than others. All seemed to be frank in reporting their degree of participation, and all attended regularly at out-patient sessions. The trial was conducted under ideal conditions in that each patient had regular free delivery of a standardized corn oil. It is felt, therefore, that the results achieved by this trial are as good as can be expected in practice.

There seems to be a general falling off in the degree of control of serum cholesterol level after the third year. This study does not prove the reasons for this and the observation does not apply to all subjects. The likely causes are that dietary adherence becomes less strict or some kind of tolerance to the action of corn oil develops.

The results given in Table VI show that a diet low in animal fat alone cannot be expected to maintain a low serum cholesterol level.

The essential condition for inclusion in this trial was not hypercholesterolaemia but myocardial infarction. It is interesting nevertheless that the average cholesterol level before treatment was 299 mg./100 ml., a finding which compares closely with the observations of Oliver and Boyd (1953). The question of optimum control cholesterol levels was studied in detail (Watson *et al.*, 1963), and the control levels accepted for this study do not exaggerate the degree of response achieved by the dietary regime. While in a general way patients with higher cholesterol levels achieved greater falls in serum cholesterol, subjects with lower cholesterol levels also achieved satisfactory reductions.

The recommendation to patients with heart disease that they reduce weight is one which can be justified on a number of grounds. There is no evidence from this trial that it makes a direct contribution to the lowering of serum cholesterol or to the maintenance of lowered levels once they have been achieved.

From a clinical point of view the results are encouraging. A mortality rate of 14.3% for 28 patients over two years is only slightly greater than the two-year mortality for a comparable group of male patients on anticoagulants (M.R.C., 1959). This slightly greater mortality has to be set against the more lenient conditions for inclusion, and one of the advantages of this regime is its availability to all.

Summary

The results of the long-term administration of a diet low in animal fat and supplemented with corn oil to a group of 28 male patients after their first myocardial infarction are reported.

The results show that in 70% of patients the regime will produce a maximum fall in cholesterol levels greater than 25% of the starting value and will maintain a mean reduction of 15% over a period of two years in almost the same 70% of patients.

Considering the subjects as a group, a significant lowering of the serum cholesterol can be maintained for a period of three years, after which time escape from control seems to begin. In individual patients there is evidence of cholesterol control continuing after four years of therapy.

It is concluded that corn oil, together with a diet low in animal fat, is feasible as a long-term measure for the lowering of serum cholesterol, being safe, acceptable to the great majority of patients, and having virtually no clinical contraindications.

I am grateful to Professor L. J. Davis, now retired, and Professor E. M. McGirr for allowing me to study patients under their care; Miss Christine Dickson for many of the cholesterol estimations; and Boots Pure Drug Co. Ltd. for the supply and delivery of corn oil.

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