The amount of phenobarbitone which has been given before the eruption and illness appear may vary greatly, and in Chavany and Vannier's (1929) first case 1½ gr. (0.1 g.) daily for nine days proved fatal. In our cases the highest daily dosage was 2 gr. (0.13 g.). Our diagnosis was based on the characteristics of the skin eruptions, the history of exposure to phenobarbitone, and the clinical course, which conformed closely to other accounts of phenobarbitone eruptions. In view of the risk involved no attempt was made to establish the diagnosis by deliberate re-exposure to the drug. Tests of this type, according to Sulzberger and Baer (1945), may in any case be misleading, since a patient in a refractory phase will fail to react to the drug which caused the eruption. They also state that skin tests are of no value in drug eruptions of this kind.

In our fourth case the possibility that epanutin may have caused the eruption cannot be excluded, but the clinical condition and course of the illness was so similar to the other three cases that we are more inclined to incriminate phenobarbitone. The cause of death in these cases is far from obvious.

In the necropsy reports of other fatal cases no specific changes were found, and death was usually ascribed to terminal bronchopneumonia. In the cases described by Millard (1933) and Poole and Wehger (1934) chronic nephritis was also reported, but renal damage has not been a general finding. In our first case there was certainly chronic renal disease, but this was not found in our other fatal case. It is probable that where there is defective excretion phenobarbitone hypersensitivity is more likely to be fatal. Cerebral irritation was a feature of three of our cases, but there was no rise in cerebrospinal-fluid pressure as was found by Jenkins (1949) in a remarkable case of phenobarbitone idiosyncrasy in which the patient twice became unconscious a few hours after a small dose of the drug. Cerebral oedema, however, was found at necropsy in both of our fatal cases. No evidence of disseminated lupus erythematosus or periarteritis nodosa was found in any of the cases, though it is interesting that Rennie *et al.* (1951) describe periarteritis nodosa as a sequela of an exfoliative dermatitis due to phenobarbitone. It can surely only be coincidence that in two of our cases a clinical but unsubstantiated diagnosis of coronary thrombosis had earlier been made, though Winton (1946) has described severe phenobarbitone eruption in a proved case of myocardial infarction.

On the basis of this small experience it would not be fruitful to speculate too far on the nature of this illness. Nevertheless, the absence of specific pathological changes, the fulminant course, and the appearance of these patients in the terminal stages suggest that they died from a biochemical cause. It may be that this conception, nebulous though it be, receives some support from the recovery of our fourth patient, after treatment with A.C.T.H. when in an apparently moribund condition. The response in this case was so remarkable that we have no doubt that this drug must be given further trial in similar cases.

It is not necessarily surprising that cortisone, on the other hand, proved ineffective, for experience with these two drugs in the treatment of disseminated lupus erythematosus and other collagen diseases (Irons *et al.*, 1951) has shown that A.C.T.H. has much the more rapid action; also it must not be forgotten that when given by the intravenous route, as in our case, the potency of A.C.T.H. is greatly enhanced.

Summary

Four cases of severe allergic reactions to phenobarbitone given in therapeutic dosage are described.

It is suggested that the potential dangers of phenobarbitone skin eruptions may not be sufficiently appreciated.

Post-mortem examination in these cases, as in those previously published, has shown no specific pathological changes.

The life-saving effect of intravenous A.C.T.H. in one case and the failure of cortisone to influence another is reported.

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CHOLESTEROL TOLERANCE IN CORONARY THROMBOSIS

BY

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This investigation was planned to determine whether the dietary cholesterol content bore any relation to coronary thrombosis, and, in particular, to learn if patients suffering from coronary thrombosis showed intolerance to cholesterol.

The subject of cholesterol and atheroma has received much attention of late, especially in America, and recently has been reviewed by Firstbrook (1951), who pointed out the importance of coronary artery disease as a cause of death and disability, defined the terminology and pathology, and gave seven main lines of evidence suggestive of plasma cholesterol being implicated in the development of atherosclerosis.

It may be stressed here that cholesterol feeding has proved to be the most consistent method of producing atheroma in experimental animals. Dauber and Katz (1942, 1943), using chicks, showed that atheromatous lesions could be produced consistently, even in omnivora, through a high cholesterol diet alone. Dauber (1944) proved that chicks were suitable experimental animals, when used before six months. The failure of high cholesterol feeding to produce atheroma, or even to raise the blood cholesterol, in some omnivora (Duff, 1935), in contrast to the constant success among herbivora, is possibly explained by the difference in cholesterol storage shown by Mienschick and Page (1933), who found that in rabbits the distribution of cholesterol was diffuse, while in cats the distribution was confined mainly to the liver. This difference may account for the difficulty in producing hypercholesterolaemia in omnivora. Nevertheless, no other method in the experimental field is as successful as cholesterol feeding in producing lesions morphologically identical to human atherosclerosis.

Among humans, atherosclerosis often occurs in diseases associated with hypercholesterolaemia—for example, in diabetes (Bowen *et al.*, 1939), myxoedema (Bruger and Rosenkrantz, 1942), nephritis (Weinhouse, 1943), and hereditary xanthomatosis (Boas and Aldersberg, 1945). It would therefore appear that even in humans the presence of hypercholesterolaemia predisposes to the production of atherosclerosis, although,

in view of the common sites for atheroma, the additional factor of local stress and strain on the vessel wall must be considered. That coronary artery disease is associated with hypercholesterolaemia has often been confirmed, the most recent careful investigation being by Basu and Stewart (1951).

Present Investigation

Many authorities have advocated a low cholesterol diet in the management of coronary thrombosis (Dock, 1947; Burns, 1948; Plotz, 1949). The present investigation was carried out to show the immediate post-absorptive changes after a test dose of cholesterol, and the effect of a prolonged low cholesterol diet on the incidence of coronary thrombosis.

Immediate Post-absorptive Changes

Two observations led one to expect there might be a significant post-absorptive rise in blood cholesterol concentration. First, Steiner and Domanski (1943) reported fluctuation from month to month in the cholesterol levels of 15 cases of atherosclerosis, in contrast to the constant level reported by Bloor (1943) in normal subjects. Morrison, Hall, and Gonzales (1949) confirmed this instability in cases of coronary artery disease. Secondly, Morrison, Berlin, and

Gonzales (1949) found a high rise in all blood lipid constituents after a fatty meal in 25 cases of atherosclerosis. Unfortunately, they did not quote the figures of this rise, nor were the quantities in their diet specified, but the high rise reported was contrary to the findings of Bruger and Somach (1932) and Chaikoff *et al.* (1934), who had shown that ingestion of food had no appreciable effect, early or late, on the blood cholesterol in the normal subject.

In the present investigation into the immediate post-absorptive changes in the blood-cholesterol levels, it was decided to employ a test analogous to the "glucose-tolerance test" used in the diagnosis of diabetes mellitus. Brun (1939) described such a test using 80 g. of olive oil with 4 g. of cholesterol added. This test dose, employed in the investigation of the lipid changes in patients with manic-depressive psychosis, showed increases in the serum cholesterol of 5 to 31 mg. per 100 ml. within two to six hours. Turner and Steiner (1939) gave a breakfast of eggs, buttered toast, and milk, with 20 g. of cholesterol added. They too reported little change in the blood cholesterol over 24 hours. Blotner (1935) described a fat-tolerance test, using as a test dose 500 ml. of 20% cream. His investigation showed that the obese had a greater rise in blood cholesterol than the malnourished. As substances such as cream and eggs are difficult to obtain, and as olive oil is not easy to take, a fresh means of giving cholesterol was devised.

TABLE I.—Results

Case No.	Age and Sex	Condition	B.P.	Fat in Diet*	Build	Cholesterol-tolerance Test. Serum Cholesterol in mg. per 100 ml.						
						Fast.	2 hrs.	4 hrs.	6 hrs.	8 hrs.	Maximum Variation	Occurring at
Group 1 patients:												
1	18 M	Pneumonia (convalescent)			Av.	259	258	278	275	292	+33	8 hours
2	29 M	Healthy subject			Under	250	245	256	259	268	+18	8 "
3	39 M	"			Over	214	206	228	243	242	+29	6 "
4	41 M	"			Under	254	282	282	270	269	+28	2 "
5	57 M	Anxiety state			"	246	256	261	266	266	+20	6 "
6	62 F	Obesity			"	374	372	396	402	400	+28	6 "
7	36 F	Rheumatoid arthritis			Av.	177	175	183	167	—	+6	4 "
8	55 F	"			Over	324	325	338	330	347	+23	8 "
9	56 F	"			Av.	268	252	261	277	286	+18	8 "
10	47 M	Chronic bronchitis			Over	280	326	324	268	304	+46	2 "
11	64 M	"			Under	173	220	212	198	200	+47	2 "
12	60 M	Bronchial carcinoma			"	182	187	166	174	161	-21	8 "
13	66 M	Congestive cardiac failure			Av.	184	184	191	212	204	+28	6 "
14	72 M	Cholangio-hepatitis (convalescent)			"	188	176	176	198	222	+34	8 "
15	18 F	Thyrototoxicosis			"	164	164	166	169	182	+18	8 "
16	51 F	"			Under	180	186	186	204	192	+24	6 "
17	49 F	"			"	196	222	—	192	181	+26	2 "
18	51 F	Malignant exophthalmos			Over	328	324	338	293	282	-46	8 "
19	47 F	Nephritis, type 1			Av.	204	218	228	214	213	+24	4 "
20	53 F	Pyelonephritis			Under	191	189	194	198	189	+7	6 "
				Mean values		232	238	245	240	247		
Group 2 patients:												
21	34 M	Nephritis, type 2			Av.	1,204	1,408	1,408	1,436	1,412	+232	6 hours
22	54 F	"			"	289	323	318	310	335	+46	8 "
23	61 F	"			"	512	552	563	587	—	+75	6 "
24	56 F	Diabetes mellitus			Over	238	276	249	252	298	+60	8 "
25	53 F	Myxoedema			"	295	348	417	408	408	+122	4 "
26	53 F	(receiving thyroid)			"	250	281	248	250	251	+31	2 "
27	62 F	"			"	405	504	529	529	457	+124	4 "
28	36 F	(receiving thyroid)			"	316	329	320	300	313	-16	6 "
29	59 F	"			Av.	261	255	255	252	258	-9	6 "
30	62 F	"			Over	319	321	319	283	303	-36	6 "
31	64 F	"			"	386	361	386	412	326	-60	8 "
32	51 M	Pulm. tuberc.; nephritis, type 2			Av.	424	446	432	438	378	-46	8 "
					Under	314	269	286	271	—	-45	2 "
					"	356	341	359	351	354	-15	2 "
Group 3 patients:												
33	41 M	Coronary thrombosis	134/76	Av.	Av.	245	246	246	252	248	+7	6 hours
34	42 M	"	175/105	"	Over	246	249	240	247	238	-8	8 "
35	45 M	"	150/90	++	"	235	233	231	237	273	+38	8 "
36	49 M	"	110/70	Av.	"	272	265	267	272	—	-7	2 "
37	53 M	"	175/110	"	"	330	341	336	329	338	+11	2 "
38	56 M	"	145/75	+	"	212	214	222	212	210	+10	4 "
39	56 M	"	130/90	Av.	"	325	342	332	334	334	+17	2 "
40	58 M	"	140/90	"	"	200	241	225	194	192	+41	2 "
41	59 F	"	100/75	"	Av.	381	365	391	380	376	-16	2 "
42	60 M	"	135/90	"	Over	324	340	328	337	324	+16	2 "
43	62 F	"	164/110	"	"	262	269	284	283	286	+24	8 "
44	62 M	"	146/106	"	Under	171	182	156	179	157	-15	4 "
45	65 M	"	125/80	"	Over	272	292	288	260	266	+20	2 "
46	66 M	"	185/105	++	Under	264	264	264	267	264	+3	6 "
47	67 M	"	150/80	Av.	Over	274	278	274	256	266	-18	6 "
48	59 M	Intermittent claudication	180/90	"	"	356	341	359	351	354	-15	2 "
49	63 M	"	160/100	"	"	285	296	296	284	295	+11	2 "
50	65 F	"	180/100	"	Av.	425	433	441	464	449	+39	6 "
				Mean values		282	288	288	285	286		

* In terms of standard British rations.

Cholesterol-tolerance Test

The test meal consisted of 5 g. of dry powdered cholesterol mixed into 25 g. of margarine: 5 g. of cholesterol was chosen as representing approximately 25 times the average daily intake in normal diet, and margarine was chosen as the vehicle as it is free from cholesterol and also because its fatty acid content is required for the absorption of cholesterol. It was found that this mixture could not be distinguished in taste from ordinary domestic margarine. The entire cholesterol-margarine mixture was spread on toast and flavoured with marmalade or jam, according to the patient's wishes. Tea, without milk but with or without sugar, was allowed. This comprised the test meal.

Cook (1942) reported that only a small quantity of the cholesterol ingested could be recovered from the faeces. Therefore absorption of most of the cholesterol was assumed. Furthermore, Group 2 in the present investigation (see results) showed that this meal could significantly raise the blood-cholesterol level in some patients.

The procedure of the test was that after the patient had fasted overnight for 12 hours the fasting specimen of blood was withdrawn. Thereafter, breakfast consisting of the test meal was given. Two, four, six, and eight hours later, further specimens of blood were taken. During the period of the test the patient's activities were restricted. Additional small quantities of carbohydrate foods were permitted as hunger demanded. Fluid, free from milk, was allowed as required. At the completion of the test all five specimens of blood were examined for cholesterol content by a modified Bloor method, this method having been found to be accurate to within 5 mg.

Material.—Cholesterol-tolerance tests were carried out on 50 patients, who were divided into three groups:

Group 1.—Healthy subjects and patients free from symptoms and signs of atherosclerosis who were not suffering from conditions associated with hypercholesterolaemia.

Group 2.—Patients suffering from conditions known to be associated with hypercholesterolaemia.

Group 3.—Patients suffering from atherosclerosis. The majority were patients with coronary thrombosis, but a small group with intermittent claudication (arteriosclerosis obliterans) was included. Coronary thrombosis was diagnosed only if there was both clinical and electrocardiographical evidence. In these subjects coincidental conditions associated with hypercholesterolaemia were excluded clinically.

Results (Table I)

Group 1.—Of the 20 subjects in this group, 16 showed a maximum variation by an increase within 5–35 mg. per 100 ml., a finding that is in keeping with the results obtained by Brun (1939); two had an increase over 35 mg. per 100 ml.—the figures being 46 and 47 mg. per 100 ml.; and two had a maximum variation shown by a fall in serum cholesterol, their figures being 21 and 46 mg. per 100 ml. below the fasting value. The mean values for this group showed a maximum increase of 15 mg.

Group 2.—Three patients with uncomplicated type 2 nephritis showed increases varying from 46 to 232 mg. per 100 ml. above the fasting level. The degree of hypercholesterolaemia in these patients could not be related to the plasma protein findings. One patient with diabetes mellitus showed an increase of 60 mg. per 100 ml. Two patients with untreated myxoedema showed increases of 122 and 124 mg. per 100 ml. The cholesterol-tolerance test, when repeated on these patients after beginning thyroid therapy, showed curves similar to those in Group 1. Five other cases of myxoedema receiving thyroid showed maximum variations by falls varying from 9 to 60 mg. per 100 ml. below fasting values. One patient with type 2 nephritis complicated by pulmonary tuberculosis showed a fall of 15 mg. per 100 ml.

Group 3.—Of the 18 patients in this group 15 showed maximum variations within ± 35 mg. of fasting levels. Only

three showed rises over 35 mg., the values being 38, 39, and 41 mg. per 100 ml. The mean values of the cholesterol-tolerance test in the group showed a maximum increase of 6 mg. The average fasting level was above normal, the normal average in this hospital's laboratory being 207 mg. per 100 ml. ± 34 . Only four of the individual fasting levels fell within this range. The degree of variation after cholesterol ingestion could not be correlated to age, sex, blood pressure, build, or duration of symptoms.

Effect of Prolonged Low Cholesterol Diet

In the atherosclerotic group notes were made of the patient's dietetic habits, particularly for the past 10 years, when their dietetic habits were compared against the standard British rations. Butter, cheese, eggs, milk, bacon, butcher's meat, and lard being rationed, and "offal" such as liver and kidney being very scarce, the only remaining rich source of cholesterol was fish. Margarine made from vegetable oils contains no cholesterol.

With allowance for supplementing the rations with fish, it was calculated that the average British diet for the past 10 years contained less than 200 mg. of cholesterol daily.

TABLE II

Food	mg. Cholesterol* per 100 g. Fresh Weight	Approx. Weekly British Ration in g.	Approx. Weekly Cholesterol Intake
Butter	240	120	290
Cheese	42	120	50
Eggs	313	70	200
Fish	56 (approx.)	Off ration: al- lowing 500	280
Flesh	68	250	170
Kidney	310	—	—
Lard	110	120	130
Liver	140	—	—
Milk	12	1,500	180
Total			1,300

* Average figures from Cook (1942).

The standard ration was taken as average. In the atherosclerotic group, only in two cases was this significantly exceeded (Table I). In the remaining 16 cases the patient's normal diet closely approximated the ration scale in the cholesterol-containing foods. Therefore for the past 10 years the cholesterol intake for these patients has been low. The blood cholesterol levels showed no relationship to the patient's diet.

Discussion

The results of the cholesterol-tolerance test showed no significant difference between Group 1 and the atherosclerotic group. Not only did both mean curves show no significant rise, but also in Group 1 and the atherosclerotic group the majority of the individual curves fell within the limits found in psychotics by Brun (1939). These results would therefore appear to show that in the atherosclerotic patients there is no abnormal post-absorptive increase in blood cholesterol and therefore atherosclerosis is not the cumulative result of temporary increase in blood cholesterol.

Although Schoenheimer and Breusch (1933) and Cook (1942) have shown that cholesterol can be synthesized in the body according to its needs, and that dietary restrictions did not reduce the blood cholesterol, the fact that atherosclerosis decreased in Germany during the fat-shortage years after the 1914–18 war (Aschoff, 1924) influenced many to treat coronary thrombosis by a low fat diet. However, the present restrictions on the diet of the British population has not reduced the number of deaths from coronary thrombosis. In fact, coronary thrombosis is rapidly increasing despite a low cholesterol content in the British rations for over 10 years, a period much longer than reported in the American therapeutic trials.

It would therefore appear from the results of the cholesterol-tolerance test, and also from the failure of prolonged low cholesterol feeding to reduce the incidence of coronary

thrombosis, that mere restriction of dietary cholesterol serves no purpose, immediate or late, in the prevention or treatment of coronary artery disease, and that the development of atheroma is not dependent on the cholesterol in the diet. This conclusion is in agreement with the findings of Keys *et al.* (1950), who showed that lowering of the blood cholesterol cannot be achieved by mere reduction of dietary cholesterol, but only by a diet entirely free from cholesterol, such as in a rice diet. Humans therefore resemble the majority of omnivora, in whom it has been shown that blood cholesterol concentration is not readily influenced by ingested cholesterol (Duff, 1935).

The present investigation finds no justification for the restriction of the cholesterol content in the diet of patients suffering from coronary thrombosis, as advocated by some authorities.

The results in Group 2 are of interest in confirming that the test dose of cholesterol was sufficient to raise the blood cholesterol significantly in patients suffering from some diseases, and therefore in the atheroma group the rise, which did not exceed the limits reported by Brun (1939), was not due to an inadequate dose of cholesterol. But of even greater interest was the effect of thyroid therapy on the cholesterol-tolerance tests of the myxoedematous patients. With one exception, which was in a myxoedematous patient not long on thyroid and later found to require a larger dose, the cholesterol-tolerance test showed, after the ingestion of cholesterol, a fall of the serum cholesterol below fasting levels. Turner (1933) showed that when thyroid was administered along with cholesterol feeds, atheroma failed to appear in rabbits. Herrmann (1946, 1947a, 1947b) also found thyroid effective in lowering the blood cholesterol in coronary thrombosis, but in view of the undesirable effect on the metabolic rate its use in coronary thrombosis cannot be advocated. He also showed that choline was even more effective, and Morrison and Gonzales (1949) reported worthwhile results in the treatment of coronary thrombosis with choline. This would appear to be a more hopeful measure in the correction of the hypercholesterolaemia of coronary thrombosis than dietetic restrictions.

Summary and Conclusions

The method of a cholesterol-tolerance test is described.

The results showed that there was no abnormal post-absorptive increase in blood cholesterol in coronary thrombosis. Reasons are given for considering that atheroma is not dependent on the cholesterol content of the diet, and that treatment of coronary thrombosis by a low cholesterol diet is unlikely to be of benefit.

The association of hypercholesterolaemia with atherosclerosis was once more confirmed.

The results of this cholesterol-tolerance test suggested that there might be intolerance of ingested cholesterol in a small group of patients—namely, those with nephritis (type 2), diabetes mellitus, and myxoedema.

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SOME OBSERVATIONS ON SUBTERTIAN MALARIA

BY

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As one becomes familiar with the features of subtertian malaria one is struck by the inconstant clinical picture which it presents. I therefore venture to record my impressions gained from several years' experience and several thousand cases of this disease.

Whereas in benign tertian and quartan malaria the clinical picture is more or less uniform, cases of subtertian malaria differ considerably. To confirm my previous impressions I have analysed 50 consecutive cases of acute subtertian malaria admitted to hospital. It is of course impossible to draw any rigid conclusions from such a small number of cases: this article merely attempts a general discussion of the clinical features of subtertian malaria, and the cases analysed do no more than lend support to my contentions. The series analysed consists of 12 adult males, 6 children, and 32 adult females. All these patients were Africans, except one child, who was a European.

Symptoms

Rigors.—One or more rigors are usually regarded as typical of malaria, taken in conjunction with other symptoms and signs. In subtertian malaria, however, they are by no means invariably present, and my impression is that they occur in only about two-thirds of cases. In malarial children convulsions do not as a rule replace rigors as they do in some other systemic infections. Rigors are unlikely to occur in the early or incubation period of subtertian malaria while the temperature is high and continuous (see below). In the present series 60% of patients had rigors, but this figure is probably low. The rigor itself, consisting of the cold stage, the hot stage, and the sweating stage, is in many cases typical, but a large proportion of patients complain only of feeling cold, and never show the hot and the sweating stages. A fair number complain of feeling cold, say, in the afternoon and, without feeling hot, sweat profusely during the night. It is worth while to keep in mind these different patterns of rigors.

Headache.—Severe headache is usual in malaria, and is seldom absent. Almost every febrile patient has some headache, but the malarial headache is characterized not so much by its severity as by its situation. It is in my experience both frontal and occipital, and extends down into the neck. In this series headache was present in 88% of patients.

Vomiting.—This is regarded as typical of the bilious remittent form of malaria, but, in fact, it occurs in most forms of this disease, and severe intractable vomiting should on occasion warn one of impending cerebral malaria.