After initial enthusiasm, two adverse reports on the efficacy of iproniazid in angina pectoris have appeared (Dewar *et al.*, 1959; Snow and Anderson, 1959). Both papers were based on controlled "double-blind" clinical trials. It seems unlikely that the drug will benefit many patients with angina pectoris.

Angina patients are particularly liable to develop cardiac infarction and to be admitted to hospital under the care of physicians not fully acquainted with their previous medical histories, and may be given pethidine for the relief of their pain. It is suggested, in the light of the two cases reported here and that reported by Papp and Benaim, that iproniazid be reserved for the most intractable cases of angina, and be given only where all other measures have failed. If a patient on iproniazid has to be admitted to hospital for any reason, his introductory letter should state, "No pethidine, please."

Summary

Two cases are described in which patients receiving iproniazid for angina pectoris were precipitated into rapid and deep coma by the injection of pethidine.

In each case intravenous prednisolone appeared to cause immediate and specific reversal of the reaction.

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EFFECT OF PHYSICAL EXERCISE ON ALIMENTARY LIPAEMIA

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The increase in turbidity of blood plasma after a fatty meal is a familiar observation. Its duration and intensity are of particular interest, because it has been shown that patients with coronary artery disease, taken as a group, exhibit delayed clearing of this visible lipaemia (Becker, Meyer, and Necheles, 1949; Schwartz, Woldow, and Dunsmore, 1952; Barritt, 1956). The mechanism by which this abnormality is related to coronary artery disease is unknown. As there is good evidence that the physical activity of work is a protection against coronary (ischaemic) heart disease (Morris and Crawford, 1958), we have studied the effect of exercise on the clearing of alimentary lipaemia, and the results of our observations are presented in this article.

Methods

Twenty-two healthy medical students, whose ages ranged from 20 to 25 years, volunteered for the tests. In the whole group there were 12 men and 10 women.

The subjects, having fasted overnight, were given one of the following standard breakfasts: 75-g. fat breakfast: $\frac{1}{2}$ oz. (14 g.) cornflakes, 1 oz. (28 g.) medium fat fried bacon, one fried egg, 2 oz. (57 ml.) cream, 3 oz. (85 ml.) milk, 1 oz. (28 g.) butter; 60-g. fat breakfast: $\frac{1}{2}$ oz. (14 g.) cornflakes, two boiled eggs, $\frac{1}{2}$ oz. (21 g.) butter; 2 oz. (57 ml.) cream, 4 oz. (114 ml.) milk. No restriction was placed on the amount of bread, tea or coffee, and marmalade which could be taken, but the students were asked to eat the same amount at each of the test meals.

The principle of the investigation was to measure plasma turbidity at a given time after the standard meal with the subject resting, then to repeat the test under similar conditions except that the subject did a standard amount of physical exercise; thus each individual acted as his own control.

The first six students who volunteered (group 1, see Table) were divided into two parties. After the first standard meal one party rested while the other exercised, and 10 days later, when the observations were repeated, the parties changed round, those who had previously rested taking exercise, and vice versa. This group took breakfast (75 g. fat) at 9 a.m., then either rested for the remainder of the test, spending most of their time sitting and reading, or took exercise. For exercise they walked 4 miles (6.4 km.) from 10.15 to 11.45 a.m. and 2 miles (3.2 km.) from 12.30 to 1.30 p.m., then rested for the final two and a half hours of the test. They were allowed a drink of clear fluid at 1.30 p.m. Care was taken to ensure that the conditions of each test were similar. The students smoked the same number of cigarettes on each occasion and drank the same type and amount of fluid.

Blood samples were taken into oxalate tubes before breakfast and at three, five, and seven hours after the start of the meal. The plasma was separated and the turbidity measured in a Unicam spectrophotometer at 6,700 Å.

Similar observations were made on another group of 14 students (group 2). These were given a 60-g. fat breakfast, after which they rested for three hours before taking exercise. They then walked 6 miles (9.6 km.) in two to three hours. During the test they were allowed only water to drink. One blood sample was taken, at six hours after the start of the meal; the plasma was separated and the turbidity measured.

The effect of short bursts of more strenuous exercise was tested. Two students (group 3) ate a 75-g. fat breakfast and then rested for three hours. In the subsequent four hours they cycled on a stationary machine for two periods of half an hour. In each period the cycling was equivalent to 5 miles (8 km.) up a slight incline.

Results

The results for group 1 taken as a whole are shown in Fig. 1. In four of the six students the plasma turbidity was lower throughout the test when exercise was taken after the meal than when they rested. The plasma of one student (Subject 1) was more turbid when she exercised than when she rested. In this case the plasma turbidity remained very low throughout the test on the occasion that she rested, and absorption of fat may have been affected by an alimentary disturbance. Nevertheless, these results have been included. Another student (Subject 3) had decreased plasma turbidity at three and five hours after exercise, but not at seven hours. In general the intensity of lipaemia after a fatty meal was

less when the students walked six miles (9.6 km.) than when they rested.

The results of the tests in groups two and three, together with those of the seven-hour blood samples taken from group 1, are presented in the Table. After exercise plasma turbidity fell in 15 cases, rose in four, and was unchanged in three. There were nine falls and two rises greater than 0.1 on the photometer scale. This decrease in lipaemia is statistically significant (see below).

The most interesting feature of the results is that the greatest change after exercise occurred in those subjects who, in the duplicated test, showed delayed clearing of lipaemia (Fig. 2).

Statistical Analysis

A study of Fig. 2 indicated that the subjects who, without exercise, had the highest plasma turbidity showed the greatest change in plasma turbidity after exercise. The correlation coefficient between these two sets of values was calculated to be $r = 0.85$, which is highly significant.

As the differences in magnitude (effect of exercise) of the plasma turbidity varied with the initial value, the

FIG. 1.—Clearing of alimentary lipaemia of six subjects (group 1).

FIG. 2.—Relation of plasma turbidity after fatty meal to decrease in plasma turbidity after exercise. The four cases in which plasma turbidity rose in test after exercise have been omitted.

Results in the Three Groups

Subject	Sex	Group (See Text)	Amount of Fat in Meal (g.)	Time of Blood Sample (Hours After Meal)	Type of Exercise	Plasma Turbidity (Optical Density)		Difference (Effect of Exercise) (B-A)	% Difference $\frac{B-A}{A}$
						Without Exercise (A)	With Exercise (B)		
1	F	1	75	7	Walking	0.15	0.14	-0.01	-6.7
2	M	1	75	7	"	0.30	0.16	-0.14	-46.6
3	F	1	75	7	"	0.28	0.52	+0.24	+85.7
4	F	1	75	7	"	0.17	0.15	-0.02	-11.8
5	M	1	75	7	"	0.51	0.33	-0.18	-35.3
6	M	1	75	7	"	0.34	0.22	-0.12	-35.3
7	M	2	60	6	"	0.30	0.14	-0.16	-53.3
8	M	2	60	6	"	0.09	0.09	0	0
9	M	2	60	6	"	0.16	0.19	+0.03	+18.8
10	F	2	60	6	"	0.12	0.10	-0.02	-16.7
11	F	2	60	6	"	0.17	0.13	-0.04	-23.5
12	F	2	60	6	"	0.21	0.24	+0.03	+14.3
13	M	2	60	6	"	0.23	0.39	+0.16	+69.6
14	M	2	60	6	"	0.09	0.06	-0.03	-33.3
15	M	2	60	6	"	0.20	0.20	0	0
16	M	2	60	6	"	0.15	0.10	-0.05	-33.3
17	F	2	60	6	"	0.35	0.11	-0.24	-68.6
18	F	2	60	6	"	0.34	0.15	-0.19	-55.9
19	M	2	60	6	"	0.31	0.12	-0.19	-61.3
20	M	2	60	6	"	0.17	0.17	0	0
21	F	3	75	7	Cycling	0.32	0.14	-0.18	-56.2
22	F	3	75	7	"	0.29	0.10	-0.19	-65.5

percentage differences were used for the statistical analysis instead of the absolute values—that is,

$$\frac{\text{value with exercise} - \text{value without exercise}}{\text{value without exercise}} \times 100,$$

these values are shown in the Table.

Thus the proportional effect of exercise was measured. This method apparently reduced the change in plasma turbidity due to exercise in those subjects with the highest plasma turbidity.

The test used was the "t" test of the differences, and the value of t obtained ($t = 2.73$) was significant between the 1% and 2.5% levels of probability—in other words, the decrease in plasma turbidity due to exercise was a significant one.

Discussion

The turbidity of plasma after a fatty meal bears a close relation to its neutral fat content and to the chylomicron count (Osmon, Zinn, and Wharton, 1957). This lipaemia is obviously a function of fat-absorption and the clearance of chylomicrons from the blood. The effect of exercise may be to impede absorption from the gut or to increase fat-clearance. If our findings were due to diminished absorption during exercise we would expect that the students in group 1 would show decreased plasma turbidity at three and five hours after the meal, but increased turbidity at seven hours, as they had been resting between the tests at five and seven hours after the meal. As this was not the case the suggestion is that the effect was due to increased clearing.

Schwartz *et al.* (1952) found that patients with ischaemic heart disease exhibited more intense and prolonged turbidity of the serum after a meal of fat than normal controls. Becker *et al.* (1949) measured the chylomicron count in young and old subjects after a standard meal. They found increased and prolonged lipaemia in the old people. Barritt (1956), in a careful study, confirmed the findings of Schwartz *et al.* He found that the greatest difference between the normal and abnormal groups occurred at seven hours after the meal—that is, there appeared to be a delay in clearing lipaemia in patients with ischaemic heart disease.

Moreton (1947) suggested that lipaemia might be the underlying cause of the intimal lipid deposition in human

atherosclerosis. If this is so, then physical exercise, if it reduces lipaemia, may delay the development of atherosclerosis. If persons who clear lipaemia slowly have a particular tendency to develop atherosclerosis, then physical exercise might be specially beneficial for them.

Stocks (1951) suggested that class differences in the incidence of ischaemic heart disease might be related to the physical demands of occupation. This suggestion has been amplified by the epidemiological studies of Morris and his associates (1953, 1958), which support the hypothesis that physical activity is a protection against ischaemic heart disease. To explain this observation various proposals based on experimental studies have been put forward.

Eckstein (1957) found that exercise promoted the growth of collateral anastomoses of the coronary arteries of dogs. By observations on human volunteers Mann and his associates (1955) found that increased physical activity prevented the rise in serum cholesterol and lipoproteins that resulted from overfeeding. McDonald and Fullerton (1958) found that physical exercise abolished the increase in blood coagulability that occurs after a meal of fat. If changes in the clearing of alimentary lipaemia affect the cholesterol-lipoprotein system and the blood-coagulation mechanism, our observations may be related to those of other investigators.

Summary

The effect of physical exercise on the clearing of lipaemia has been investigated. The plasma turbidity of 22 student volunteers was measured at various times after a standard meal containing either 75 or 60 g. of fat. During one test the students rested, but during another similar test they took exercise, either walking or cycling. In a statistically significant number of cases the plasma turbidity was less after exercise than after resting.

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Medical Memoranda

Dietary Deficiency of Vitamin B₁₂

In non-tropical areas of the world, dietary deficiency of vitamin B₁₂ is rare: even tropical nutritional macrocytic anaemia is primarily due to folic acid deficiency (Das Gupta *et al.*, 1953). Vegans—namely, people who do not eat any form of animal protein—are liable to develop dietary vitamin-B₁₂ deficiency, because vegetable proteins, apart from seaweed and ground-nuts, contain negligible quantities of this vitamin. Wokes *et al.* (1955a, 1955b) have presented a full account of this problem in vegans. They showed that, even in this group, vitamin-B₁₂ deficiency takes some years to develop, and, in fact, may not necessarily occur. On the other hand, a number of cases of megaloblastic anaemia due to dietary deficiency have been described, but many of these cases were investigated before vitamin B₁₂ had been discovered and many before sternal-marrow examination was a routine procedure. Some of these recorded cases could be regarded as showing manifestations of vitamin-B₁₂ deficiency due to an inadequate diet, but many had other possible causes of the anaemia or such blunderbuss therapy that proof of dietary vitamin-B₁₂ deficiency is uncertain.

As far back as 1927, O'Hara and Grewal described a case which they said had pernicious anaemia. Their patient was a 14-year-old boy living on bread, milk, potatoes, and "candy." He was anaemic, with a megaloblastic marrow and achlorhydria, and responded to oral liver. Other similar cases, some well investigated and others poorly investigated, were described by Aykroyd (1930), Kern (1931), and Longcope (1934). Groen and Snapper (1937), in a very sound study of two cases, pointed out the lack of "extrinsic" factor in diets sadly lacking in meat, milk, and eggs. Their patients had free acid, and one responded to a full diet but the other was given intramuscular liver. Ungley (1933) described two cases, but probably one of them was receiving anticonvulsant drugs, and we now know that these drugs can produce a megaloblastic anaemia (Badenoch, 1954; Hawkins and Meynell, 1958). The same is true of the case he described later (Ungley, 1938). Still, we must agree that all three patients were on a diet grossly deficient in animal protein and therefore vitamin-B₁₂ deficiency was possible. Townsend and Begor's (1942) case was probably a true case of dietary vitamin-B₁₂ deficiency, and we must similarly accept the case of Badenoch (1954), and of Harrison *et al.* (1956), and the three cases of Mollin and Ross (1954).

We feel that to prove that a case of macrocytic anaemia is due to dietary vitamin-B₁₂ deficiency the following criteria are necessary: (1) megaloblastic bone-marrow; (2) normal vitamin-B₁₂ absorption by one of the techniques using radioactive cyanocobalamin; (3) normal fat-absorption; (4) the absence of complicating factors such as the taking of anticonvulsant drugs (Hawkins and Meynell, 1958), pregnancy, or gastric operations; (5) low serum level of vitamin B₁₂; (6) it would be helpful but not absolutely necessary to find free acid in the stomach; and (7) conversion of the megaloblastic marrow to normoblastic by small oral doses of vitamin B₁₂.

The New South Wales Parliament has given a first reading to a Bill to combat air pollution. The Bill provides for the establishment of a central organization to investigate the causes of air pollution and to give expert advice to industry and municipal authorities. (*Radio Australia News*, April 8.)