taining finely granular intracytoplasmic lipoid material (xanthoma cells), giant cells, and endothelial and fibroblastic elements. The various forms of xanthoma cannot be identified on the histological findings alone, and classification is therefore based partly on the morphological-clinical picture and partly on the biochemical findings (Beaumont 1950, Froehlich 1951, Thannhauser 1958, Caplan and Curtis 1961).

Xanthoma tuberosum multiplex is often found in patients with essential familial hypercholesterolæmia (Müller 1938, Alvord 1949) and, according to a comprehensive genetic study by Wilkinson et al. (1948) and a later investigation by Epstein et al. (1959), these cases seem to indicate that a single dominant gene bearing the disease causes a lesser degree of familial hypercholesterolæmia with a tendency to the usual atheromatous complications at more or less the normal age, whereas doubling of this gene causes more advanced hypercholesterolæmia in association with the xanthoma tuberosum and an accelerated early death from complications. But xanthoma tuberosum multiplex also appears in persons with hypercholesterolæmia in the absence of any significant familial history. Moreover, many people have pronounced hypercholesterolæmia in the absence of xanthoma tuberosum, which suggests that other factors besides hypercholesterolæmia may be decisive, the most important of these probably being a simultaneous disturbance of the colloid dispersion of serum-lipids (Allen 1954).

As regards therapy, even as late as 1948 Lomholt wrote that the only treatment was excision of the most troublesome nodules, which in my patient would have been quite impossible. More recently a blood-cholesterol-lowering diet has been accepted as a rational form of therapy (Caplan and Curtis 1961), but there are only a few reports of satisfactory results (Herzberg 1962).

Summary

The clinical manifestations in a patient with advanced xanthoma tuberosum multiplex disappeared completely after 4 months of rigorous dietetic therapy for lowering the elevated blood-cholesterol level. There has been no relapse in a follow-up period of 21 months on the diet.

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Preliminary Communications

THE PANTOTHENIC ACID METABOLISM OF RHEUMATOID ARTHRITIS

VERY little is known at present about the pantothenic acid content of human blood. We are aware of only three papers specifically dealing with this subject,[1–3] and none of these is helpful, because unsuitable methods of hydrolysis were employed. The values found by these investigators, which varied between 20 and 40 μg. per 100 ml. whole blood, are significantly lower than ours.

MATERIALS AND METHODS

For hydrolysing the blood-samples we used the now accepted method of hydrolysis of Neilands and Strong,[4] later modified by Clegg [5] and Barton-Wright,[6] in which a mixture of an alkaline phosphatase and an enzyme prepared from dried pigeon's liver is employed. We examined a number of different commercial preparations of these enzymes, and we found that the dried pigeon-liver enzyme and alkaline calf-intestinal phosphatase (especially prepared for us by Messrs. Seravac Ltd., of Colnbrook, Bucks.) were approximately ten times more active than others and these were invariably employed.

The pantothenic acid was assayed microbiologically, using the lactic organism *Lactobacillus plantarum* (formerly *L. arabinosus* 17/5) and the pantothenic-acid-free basal medium described by one of us.[6]

The bound and free pantothenic acid of blood were both assayed in the initial stages of this investigation, but later only the total pantothenic acid content was determined, since it was found that the free pantothenic acid level was low and variable (4·0–9·2 μg. per 100 ml. whole blood) and conformed to no definite pattern.

RESULTS

The mean level of the whole blood pantothenic acid values of the following groups were:

Group 1.—Subjects consuming a normal balanced diet including meat: 107·7 μg. per 100 ml. whole blood. Number tested = 20, $s = 8{\cdot}32$.

Group 2.—Vegetarians (not vegans): 262·2 μg. per 100 ml. whole blood. Number tested = 9, $s = 115{\cdot}0$.

Group 3.—Rheumatoid arthritics (consuming a normal balanced diet): 68·7 μg. per 100 ml. whole blood. Number tested = 56, $s = 9{\cdot}28$.

Group 4.—Vegetarian arthritics (corresponding to group 2): 69·8 μg. per 100 ml. whole blood. Number tested = 10, $s = 8{\cdot}02$.

Statistical examination of the results in these four groups shows:

	Healthy		*Arthritics*	
	Non-vegetarian	*Vege-tarians*	*Non-vegetarian*	*Vege-tarians*
n	20	9	56	10
Mean pantothenic-acid level (μg. per 100 ml. whole blood) = $\bar{x}$	107·7	262·2	68·7	69·8
s	8·32	115·0	9·28	8·02
Variance = s^2	69·22	13,225	84·65	64·33

Since the two arthritic groups are clearly so similar in mean and standard error, they can and should be treated as one group. Thus, for the whole group of 66 arthritics (56 + 10) we have:

$$\bar{x} = 68{\cdot}9,\ s^2 = 83{\cdot}05$$

The significance of the difference in mean pantothenic acid level between the blood of healthy non-vegetarian subjects ($\bar{x} = 107{\cdot}7$ μg. per 100 ml.) and arthritics ($\bar{x} = 68{\cdot}9$ μg. per 100 ml.) was tested by the t test. The difference is 38·8, and its standard error is 2·28. The value of t is 17·0, and the corresponding value of P (84 degrees of freedom) is much less than 0·001 (i.e., 0·1%). Thus, the difference is highly significant.

The difference in pantothenic acid levels between healthy non-vegetarians and healthy vegetarians (262·2 and 107·7 μg.) cannot be tested in the same way because the variances of the two groups are so very different. However, we have applied the approximation proposed by Cochran and Cox,[7] in which an estimate of the 5% and 1% level of the ratio (difference/standard error) is computed from the weighted mean of the two values of t for degrees of freedom = 19 and degrees of freedom = 8, the weights being the variances of the two means. In practice, the results are very close to the t values for 8 degrees of freedom, which are 2·31 (P = 0·05) and 3·36 (P = 0·01). The value of the ratio in our case is 4·06, and it is therefore apparent that this difference also is highly significant.

DISCUSSION

It is difficult to account for the high blood pantothenic acid level of vegetarians compared with those of people who consume a normal balanced diet. It is possible that the intestinal bacterial flora is different in the two groups, and

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that the bacterial flora of vegetarians contains actively pantothenic acid synthesising organisms.

It seems clear from our findings that freedom from rheumatoid arthritis is correlated in some way with a blood pantothenic acid level of 0·95–1·0 μg. per ml. of whole blood, and that if the value falls below 0·95 μg. per ml. symptoms of rheumatoid arthritis make their appearance. This view is confirmed by the fact that the lower the level of the pantothenic acid in the blood, the greater is the severity of the symptoms of rheumatoid arthritis. For example, it was found that patients with a blood pantothenic acid level of 40–50 μg. per 100 ml. whole blood were in nearly every case badly crippled, and in two cases bedridden.

Small-scale clinical trials have been initiated and the results are briefly summarised below:

1. Daily intramuscular injections into 20 patients of group 3 of calcium-*d*-pantothenate (50 mg., pH 4·6) gave temporary alleviation after seven days' treatment. The blood-level of pantothenic acid rose in every case to 100–110 μg. per 100 ml. whole blood. There was, however, no further improvement in condition, even when the injections had been continued for another 21 days (i.e., total time of treatment=28 days). After treatment was discontinued, the blood pantothenic acid level gradually fell over a period of a month to its initial value, with concomitant reappearance of symptoms.

These results indicate that some other essential factor(s) is involved in rheumatoid arthritis, failure of which leads in turn to a breakdown in pantothenic acid metabolism and to inability to maintain the pantothenic acid level of the blood at its normal value of 0·95–1·0 μg. per ml.

Townsend et al.[8] have shown that the injection of royal jelly or of 10-hydroxy-Δ^2-decenoic acid in citrate buffer (pH 4·6) affords complete protection against transplantable mouse leukæmia. Royal jelly, the larval food of the queen bee, contains 10-hydroxy-Δ^2-decenoic acid as a major constituent (2·0% dry weight), and it has the highest known pantothenic acid content of any known natural product. We have found that the *whole* of the pantothenic acid content of royal jelly is in the free state:

Free pantothenic acid	..	554 μg. per g. (dry weight)
Total „ „	..	557 μg. per g. (dry weight)

(Mean of 10 different samples.)

The possibility that 10-hydroxy-Δ^2-decenoic acid might be the second factor concerned was therefore investigated, and this appears to be so. We prefer to call this substance the fatty-acid factor (F.A. factor), because there is the possibility that other 10-carbon straight chain fatty acids—e.g., sebacic acid—might act in a similar capacity.

2. Daily intramuscular injections into 5 patients (group 3) of royal jelly alone (50 mg., pH 4·6) for twenty-eight days proved ineffective. There was no improvement in their condition, and no increase in the blood pantothenic acid level.

3. Daily injections into 20 patients (group 3) of a mixture of royal jelly and pantothenic acid (50 mg. royal jelly+50 mg. Ca-*d*-pantothenate, pH 4·6) led to a gradual rise in the blood pantothenic acid level and when the value reached 110–130 μg. per 100 ml. whole blood (twenty-eight days), there was in the case of 14 patients (70%) an improvement in general condition and mobility of joints, and a fall in the erythrocyte-sedimentation rate. Improvement, however, was not permanent. After treatment had been discontinued, the blood pantothenic acid level was found to fall gradually over two months to its initial figure, with reappearance of the symptoms of rheumatoid arthritis. On retreatment (6 cases), there was once again improvement in the general condition and mobility, and a fall in sedimentation-rate when the blood-level of pantothenic acid reached 100 μg. per 100 ml. whole blood.

4. Daily injections into 10 vegetarian arthritics (group 4) of a mixture of royal jelly and pantothenic acid (50 mg. royal jelly+50 mg. Ca-*d*-pantothenate, pH 4·6) produced rapid disappearance of symptoms in all cases (fourteen days) with concomitant increase in the blood pantothenic-acid level to 130–160 μg. per 100 ml. whole blood. Of the 10 patients treated after fifteen months, only one has returned showing a slight recurrence of symptoms.

Injection treatment has not proved uniformly successful. A number of patients objected to daily injections, and others (about 12%) showed a distinct erythema at the site of injection. In view of this, the possibilities of oral treatment are now being explored, and the preliminary results have proved encouraging. Further experiments are also being carried out with 10-hydroxy-Δ^2-decenoic acid, both by mouth and by intramuscular injection.

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DONOR SELECTION IN HUMAN ORGAN TRANSPLANTATION

A Possible Screening Test

THE vigour of the immunological reaction provoked by homotransplanted living tissue depends to a major degree on the genetic difference between the two subjects concerned. Work done largely with genetically standardised inbred strains of mice has shown that the genetically determined histocompatibility antigens are multiple, and that differences between subjects may be in respect of strong or weak characters.[1] This designation depends upon their relative potency in calling forth the full destructive machinery of the host. Almost no information exists about the human population in this regard, but if humans are similar to laboratory animals, one would expect man to be endowed with some strong and some weak histocompatibility factors which are independent of one another. With co-isogenic resistant lines of mice developed by Snell, which differ only at weak (non-H^2) loci, grafts of tumour and normal tissues survive longer than when host and donor differ at the strong (H^2) locus.[2,3] Actively acquired immunological tolerance is easier to produce when the barrier is weak, both in the neonatal period[4] and in adult life.[5] It is also easier to procure long-term survival of homografts after irradiation and homologous bone-marrow replacement,[6] or by means of immunosuppressive drugs,[7] if weak barriers only are to be overcome.

It is therefore a matter of some urgency to develop a test, readily applicable to man, that might provide information as to the relative histocompatibility differences

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