

pyruvic acid molecules, the diminution of hydrogen ion would be only 0.2 μ mole per mmole of pyruvic acid transformed. Consequently, in a lactic acidotic condition the extra hydrogen load imposed on the blood would be reduced by only about 0.02%. The effect is too small to be called homeostatic.

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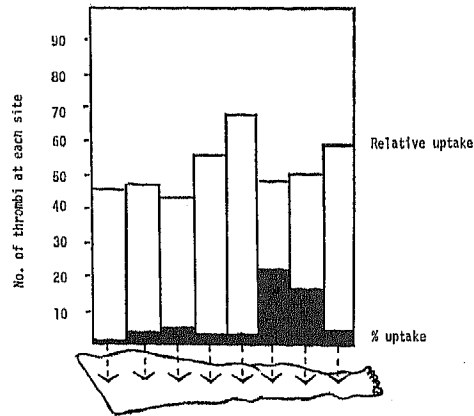
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SITE OF ORIGIN OF VENOUS THROMBI

SIR,—Opinions on the site of origin of venous thrombosis have undergone several changes since the time of Virchow, when thrombi were thought to originate in the iliofemoral segment. On the basis of clinical observations (in particular by Homans,¹ Frykholm,² and Bauer³), the site of a venous thrombosis was localised to the calf, since it was here that clinical signs and symptoms first appeared. But careful pathological studies⁴⁻⁷ cast doubt on this concept and returned the origin of thrombus formation to the deep veins of the thigh. In McLaughlin's series⁴ of patients 73% of the thrombi started in the veins of the thigh and pelvis, while Sevtitt and Gallagher⁵ established six sites along the length of the venous tree at which thrombi originated, the incidence being only slightly higher in the calf than in the thigh. They established that thrombi often started at multiple sites and coalesced by proximal and distal extension. With the development of thrombus-labelling by radioactive fibrinogen, emphasis has again been placed on the calf as the seat of thrombus formation. Kakkar,⁸ using this technique, showed that in surgical patients the majority of thrombi start in calf veins, and proximal extension occurs in only just over 20%. Similar findings were reported^{9,10} in medical patients. Maurer¹⁰ found 44 affected limbs in a series of 100 patients, and of these 41 were mid-calf and 2 were lower-calf in origin.

In our own series of 100 patients, with conventional criteria for the radioactive detection of thrombi,¹¹ our findings correspond to previous reports. There was an incidence of 27% with a distribution of thrombi throughout the limb, as shown in the accompanying figure, which shows a predilection for the calf. When, however, the data obtained on these patients were analysed by the relative uptake method,¹² a different pattern emerged. Firstly, there was a greater total incidence of thrombosis. Of the 100 patients, 69 had thrombi, in a total of 118 affected limbs. The distribution of these thrombi is shown in the figure. This pattern conforms closely to the findings of Sevtitt and Gallagher,⁵ in that the incidence in the thigh is only slightly less than in the calf. We found a peak incidence at the knee and ankle joints. In 62 of the limbs there was a single site of origin, in 49 limbs a double site, and in 7 limbs there were three independent sites of origin.

The presence of these thrombi was not subjected to



Distribution of venous thrombi.

phlebographic confirmation, since we believe this would impose limitations on the sensitivity of the method which it is designed to overcome. However, by observing the blood clearance of radioactive fibrinogen in these patients, a complete correlation with the findings of the relative uptake method has been obtained.^{13,14}

If thrombi are present in the deep veins of the thigh as often as they are in the calf, the importance of venous stasis in their pathogenesis is seriously undermined. Also, the presence of large numbers of subclinical thrombi in the veins of the thigh must raise the possibility of a high incidence of subclinical embolisation in patients after surgery.

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VITAMIN C AND DEEP-VEIN THROMBOSIS

SIR,—I am not deterred by the findings of Dr Andrews and Dr Wilson (July 7, p. 39), because I have been able to demonstrate that vitamin C has a powerful protective action against thrombosis. It has been known for many years that this substance was responsible for the health of the capillaries. I am now entirely convinced that it is responsible for the health of the arteries. It would therefore be logical for it to be responsible for the veins also.

A double-blind trial, using vitamin C and a placebo, has been done on patients who were vulnerable to deep-vein thrombosis.

They consisted of 21 patients who had had retropubic prostatectomies (ages 55-84), 19 who had had hip arthroplasties (ages 35-78), 20 with atherosclerotic episodes, 17 who had had an acute myocardial infarction, 3 a cerebral infarction (1 had both), and 1 an internal-carotid-artery occlusion (ages 48-70), and 3 patients with carcinoma, who had undergone surgical removal.

The prostatectomy patients, all of whom were admitted with acute urinary retention, were given vitamin C (1 g. daily) or placebo tablets from the day of admission until 2 weeks after operation. Preoperative treatment varied from 1 to 20 days. The carcinoma patients were treated similarly, once it had been decided to operate on them, until 2 weeks postoperatively: preoperative treatment lasted for 1, 2, and 19 days respectively. Arthroplasty patients were given the same medication from the time they were seen in the outpatient clinic until 2 weeks postoperatively. Preoperative treatment varied from 1 to 42 days.

Medical patients were also treated in this way from admission, as soon as the diagnosis had been established, for 2 weeks.

Since the legs were scanned with ¹²⁵I-fibrinogen (Radio-

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INCIDENCE OF DEEP-VEIN THROMBOSIS

		Total no. of patients	Positive cases					Negative cases				
			Ages	Pre-op. treatment (days)	No.	Signs	Pulmonary embolism	Ages	Pre-op. treatment (days)	No.	Signs	Pulmonary embolism
Atherosclerosis	Vitamin C	9	48-70	..	3 (3 legs)	0	0	52-69	..	6	0	0
	Placebo	11	53-66	..	4 (7 legs)	3	2	55-62	..	7	0	0
Arthroplasty	Vitamin C	11	59-78	10, 25, 42	3 (3 legs)	1	0	35-77	5-36	8	0	0
	Placebo	8	56-72	0-21	6 (8 legs)	3	0	63, 77	5, 28	2	0	0
Prostatectomy	Vitamin C	9	64-76	8-12	4 (4 legs)	0	0	59-68	1-7	5	0	0
	Placebo	12	63-84	1-20	8 (13 legs)	5	1	55-79	1-7	4	0	0
Carcinoma	Vitamin C	1	63	19	1	0	0
	Placebo	2	55, 85	1, 2	2 (2 legs)	1	0

chemical Centre), potassium iodide (120 mg. daily) was given from the day before injection for 3 weeks. In all cases, the consent of the patient was obtained after the nature of the trial had been explained.

The randomisation of the tablets was done by hospital pharmacists, and nobody in the study saw the code until the trial was completed.

Scanning was done on a scaler, using a collimated scintillation counter. Readings were taken over the heart (average of two readings) and at eight marked positions on each leg, approximately 4 in. apart, over the course of the main venous supply. Scanning was done on alternate days, from the day after injection, for 10-12 days, and the readings were expressed as a percentage of the heart count.

In the surgical patients, the ¹²⁵I-fibrinogen was injected as soon as the patient returned from the operating-theatre. In the medical patients, it was given on the day after admission—i.e., the day after the first dose of potassium iodide.

A rise of more than 15% between two adjacent readings on the same leg, or between similar positions on the two legs, or at the same position on two successive readings, which was sustained for at least two further readings, was regarded as positive.

The overall results were:

	Vitamin C	Placebo	P value
Total no.	30	33	
Positive	10 (33%)	20 (60%)	<0.05
2 legs affected	0	10	<0.001
Pulmonary embolism	0	3	>0.05
Physical signs	1	12	<0.001
Average of peak readings in affected legs (% of heart count)	81	153	Interest only

The incidence of deep-vein thrombosis in the placebo group was 60%, compared with 33% in the vitamin-C group. There was a striking reduction in the presence of physical signs in the vitamin-C group. The signs taken as significant were swelling and tenderness in the calf, a positive Homan's sign, and an unexplained temperature. (In only 1 case was a temperature found without other signs.)

The "average of peak readings in affected legs" was an attempt to show the big difference in the degree of activity in the two groups. Since this was presumably related to the extent of thrombus formation, it showed that there was much less thrombus formed in the vitamin-C group. Indeed, 6 of these patients had increases of 25% or less, compared with 2 such patients in the placebo group.

A more detailed analysis is shown in the accompanying table. The incidence and severity of deep-vein thrombosis was reduced in all groups to roughly the same degree.

Virchow described three factors as necessary for the production of a deep-vein thrombosis: (1) venous stasis (generally speaking, early mobilisation has minimised

this); (2) alterations in the blood-vessel walls (vitamin C provides the ground substance for the blood-vessel walls); and (3) alterations in the coagulability of the blood.

According to Hawkey,¹ animals are hypercoagulable compared with humans. Carnivorous animals are not troubled with atherosclerosis (they synthesise their own vitamin C). She therefore concluded that the coagulation changes in atherosclerosis were not primary, but were secondary to the blood-vessel changes and the fatty changes. Vitamin C is responsible for the proper metabolism of fat.²⁻⁵ Thus, if the blood-vessel changes and the fatty changes can be reversed by vitamin C, the coagulation changes will also be reversed. In other words, the two factors in Virchow's triad which at present cannot be treated are both controlled by vitamin C.

Sokoloff et al.,³ in their studies with vitamin C in elderly atherosclerotic patients, found that it was about 3 months before the lipoprotein lipase activity, and therefore the triglycerides, started to return to normal levels. This would suggest that in order to secure absolute protection from a deep-vein thrombosis, at least 3 months' treatment would be needed.

It is now just over 6 months since this trial was completed. Since that time, some of our general and orthopaedic surgeons have been giving vitamin C, 500 mg. daily, routinely in their wards. During this period, in six wards, we have had a total of 3 cases of clinical deep-vein thrombosis and 3 of pulmonary embolism (2 slight).

I am now recommending that the dose be increased to 1 g. daily, in the hopes of eliminating even this small number. In the Regional Burns Unit at this hospital, vitamin C (1 g. daily) has been given routinely to all patients, in the interests of promotion of healing, since the unit was opened more than seven years ago. Only 1 death from pulmonary embolism has been recorded, and no cases of clinical deep-vein thrombosis have occurred for at least 5½ years (159 patients over the age of 40 years).

This suggests that Dr Andrews and Dr Wilson were not giving a sufficiently large dose of vitamin C to protect their geriatric patients from thrombotic episodes.

I am indebted to E. Merck Ltd. for sponsoring this trial and for providing the statistical analysis. I should also like to thank radiographers Miss E. Clark, Mrs P. Holland, and Mrs P. Taylor for the leg scanning; Mr A. F. Cox and Mrs M. Fisher,

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regional physicists, for the loan of their apparatus, and for their constant help and support; Mr G. Bird, Mr C. Denley Clark, Dr R. Fletcher, Mr J. Patrick, and Mr C. Robertson for allowing me to study their patients; and the nursing staff for all their cooperation.

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SERUM-CHOLESTEROL AND WHOLE-BLOOD ASCORBIC ACID IN CHILDREN

SIR,—Little information is available on the specific dietary factors thought to be responsible for the metabolism of cholesterol. Of the nutritional factors postulated to be involved in cholesterol metabolism, ascorbic acid (vitamin C) has been shown to reduce raised serum-cholesterol concentrations in subjects who have a seasonal deficit of vitamin C.¹ In subjects not deficient in vitamin C—e.g., those who had received supranormal doses of vitamin C—the influence of the vitamin on cholesterol metabolism was questionable. As an example of the lack of agreement, several reports²⁻⁴ support the therapeutic value of ascorbic acid in the treatment of cholesterolæmia and atherosclerosis, while others deny it.⁵⁻⁷

To the best of our knowledge, no reports of the relationship between blood levels of ascorbic acid and serum-cholesterol concentrations in normal children have appeared. We now present data which describe this relationship in young children not receiving ascorbic-acid supplements.

A nutritional biochemistry survey of 284 Mexican-American children in Santa Cruz County, Arizona, ranging in age from 36 to 72 months, was completed in February, 1973. Total serum-cholesterol determinations performed on these children gave a mean concentration of 172 ± 35 mg. per 100 ml., with a range of 79–400 mg. per 100 ml. Whole-blood ascorbic-acid (w.B.A.A.) determinations on trichloroacetic-acid-stabilised samples⁸ showed a mean concentration of 1559 ± 395 μ g. per 100 ml., with a range of 370–3020 μ g. per 100 ml. Both w.B.A.A. and serum-cholesterol concentrations demonstrated normal (gaussian) distributions.

A linear correlation coefficient computed for the above w.B.A.A. and serum-cholesterol concentrations ($r = 0.016$ [$r_{0.05} = 0.113$ for $n = 300$]) revealed no significant correlation between concentrations of w.B.A.A. and their associated (paired) serum-cholesterol concentrations. In order to increase the probability of detecting an association between w.B.A.A. and serum-cholesterol, values of w.B.A.A. falling within the upper and lower portions of the normal distribution were chosen for further statistical treatment. w.B.A.A. values falling above or below one standard deviation from the mean were paired with their associated serum-cholesterol values; linear correlation coefficients were then computed for the two groups of data. For the group low in vitamin C ($n = 37$), the linear correlation coefficient for cholesterol was -0.054 ($r_{0.05} = 0.325$), while for the group high in vitamin C ($n = 35$) it was -0.076 ($r_{0.05} = 0.325$). Thus, at either end of the w.B.A.A. distribution no significant association between w.B.A.A. and cholesterol could be detected. The means of the two cholesterol distributions associated

with the low and high vitamin-C groups, 169 ± 27 mg. per 100 ml. and 173 ± 23 mg. per 100 ml., respectively, were not significantly different ($t = 0.620$; $t_{0.05} = 1.960$).

From these observations one may conclude that concentrations of w.B.A.A. within the normal range do not influence serum-cholesterol concentrations. Presumably, significant effects of ascorbic acid on cholesterol metabolism may be found only at very high or very low blood concentrations of the vitamin.

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URINARY OXALATE AND VITAMIN-C SUPPLEMENTS

SIR,—It has been known for several years that ascorbic acid is metabolised by the human body partly to oxalic acid, some of which is excreted in urine.^{1,2} Previous studies have shown that the average percentage change in 24-hour urinary oxalate increases in proportion to the dose of vitamin C, though there are considerable individual differences.³ As high-dose vitamin-C supplementation is being used and recommended with increasing frequency,⁴⁻⁶ we have organised a study to reinvestigate the magnitude of individual differences in oxalate production from ascorbic acid. We have encountered a surprising result.

One of our volunteers was a healthy young man of 21. Eating his usual mixed diet, which is free of oxalate-rich foods, he has received two courses of vitamin-C supplementation at 4 g. daily in divided doses ($\times 4$ daily). His 24-hour urinary oxalate before supplementation was 58 mg., but rose to 622 mg. and 478 mg., respectively, at the end of each course of vitamin C (7 and 4 days). The usual 24-hour increase in urinary oxalate in other subjects we have studied after 4 g. ascorbic acid daily for several days has been about 12 mg.

We feel that the massive increase in urinary oxalate in this young man places him in danger of renal calcification if vitamin-C supplements were to be continued. It is likely that individuals with high capacity to convert ascorbic acid to oxalate are rare, but unless they are identified vitamin-C supplementation at high doses could have very undesirable results.

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REDUCED ASCORBIC-ACID EXCRETION AND ORAL CONTRACEPTIVES

SIR,—There is increasing evidence that ascorbic acid in sufficient but as yet undefined amounts may reduce the incidence and perhaps the severity of the common cold.^{7,8} If ascorbic acid indeed is prophylactic against the common cold, the amounts are certainly in excess of the levels required to prevent scurvy, and are considerably in excess of the recommended intake for adults suggested by most Western medical authorities, but in this context subclinical

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