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VITAMIN A *in* RHEUMATIC FEVER

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INTEREST in the significance of vitamin A status in rheumatic fever has been aroused by investigations by Coburn and other workers, and has followed two distinct lines of development. Firstly, it has been suggested that deficiency of vitamin A, and other forms of malnutrition, may be among the conditioning factors which cause a small proportion of patients with streptococcal infection of the throat to develop rheumatic fever. In support of this claim there is evidence that a good diet may reduce the incidence or rate of recurrence of rheumatic fever in children, although there has been no clear demonstration that special importance should be attached to vitamin A.[1,2] Secondly, it has been shown that in rheumatic fever the metabolism of vitamin A is abnormal, as indicated by its greatly reduced level in the blood plasma.[3] Again, the question arises whether special attention should be paid to this abnormality, since other metabolites are certainly affected. Harris *et al.*,[4] for example, have shown that in acute rheumatic fever the excretion of vitamin C is greatly diminished. Rheumatic fever, moreover, is not unique in reducing the concentration of vitamin A in the plasma; the level tends to fall in pyrexia of any origin.[5]

These considerations make it difficult to decide whether vitamin A plays an active part in supporting the body's resistance to rheumatic fever, or whether it merely suffers unspecific side effects in common with many other metabolites. Even if the second alternative should prove correct, however, the severity of the losses of vitamin A which are sustained clearly deserves study. Recovery from a single short period of pyrexia is usually accompanied by a prompt return of the plasma vitamin A to within normal limits, the vitamin presumably being mobilised from the large reserves stored in the liver. It might be considered, therefore, that after recovery from rheumatic fever the vitamin A status might well be left alone to correct itself. It must be borne in mind, however, that attacks of this disease tend to recur, and that even if cardiac complications are avoided the period of convalescence is often prolonged. In face of such sustained demands, even the substantial reserves originally present in the liver might eventually prove inadequate. It was thought desirable, therefore, to investigate the levels of vitamin A and carotenoids in the blood plasma of patients at various stages during and after acute rheumatic fever, and to relate the values obtained with data for body temperature and erythrocyte sedimentation rate (E.S.R.). For purposes of comparison, similar observations have also been made in patients with certain other diseases.

Earlier data at our disposal on the vitamin A reserves of the liver have been searched for information on the vitamin A reserves present

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at autopsy in the livers of subjects who had died from heart diseases which were presumably of rheumatic origin.

Experimental

Material and Methods

Serial specimens of blood plasma from patients with rheumatic fever, and from patients with certain other diseases, for purposes of comparison, were obtained during the years 1945–48 from Paddington Hospital and the Whittington Hospital, London. The patients with rheumatic fever were given sodium salicylate during the acute stage in doses ranging from 6 to 10 Gm. daily, according to the severity of the condition and age of the patient. As the clinical condition improved the dosage was reduced, but a maintenance dose of 3–4 Gm. daily was given for at least 3–4 weeks after complete disappearance of all clinical symptoms and signs. During the whole period of illness the patients had ordinary hospital diet with a liberal allowance of milk.

Vitamin A and carotenoids were estimated by a modification of Kimble's[6] method, with correction for the contribution of carotenoids to the antimony trichloride reaction.

The effects of disease on the vitamin A and carotenoid contents of the plasma were measured by comparison with normal values reported by Moore and Leitner.[7] In confirmation of general experience, a wide range of values was found for both substances in healthy adults and in hospital patients with diseases not known to affect their vitamin A metabolism. The average vitamin A for mixed sexes in the London area was assessed at 120 I.U. per 100 ml. and total carotenoids at 150 "I.U." (0.6 μg. units without reference to biological activity).

The Plasma Vitamin A and Carotene in Relation to Body Temperature

In Table I the average levels of vitamin A and carotenoids found in 100 patients with acute rheumatism have been arranged according to arbitrary ranges of body temperature. The patients examined were equally divided in sex, and ranged in age from 5 to 60 years, with an average of 20.5 years and with 64 per cent of the patients between the ages of 5 and 19 years. It will be seen that the levels of vitamin A were reduced at raised body temperatures. This reduction was found in the temperature range 98.9–100°, and in acute

TABLE I

Carotenoids, Vitamin A and E.S.R. in Relation to Body Temperature. Patients from Hospitals in Paddington and Archway Group

Temperature Range	No. estimations	Carotenoids	Vitamin A	E.S.R.
° F.		*I.U./100 ml.*	*I.U./100 ml.*	*mm./hr.*
Acute rheumatism (100):*				
Below 98.0	170	105	105	17.7
98.0–98.8	381	104	104	22.6
98.9–100.0	44	113	74	53.5
Over 100	28	71	50	83.6
Pneumonia (21):				
Below 98.0	12	91	88	20.0
98.0–98.8	27	97	98	25.7
98.9–100.0	13	90	65	51.8
Over 100	2	152	34	—
"Subacute rheumatism" (20):				
Below 98.0	22	109	119	16.2
98.0–98.8	48	117	100	11.9
98.9–100.0	10	113	118	13.7
Over 100	1	60	90	13
Pleural effusion (22):				
Below 98.0	24	97	97	24.5
98.0–98.8	52	130	86	34.8
98.9–100.0	20	136	73	40.0
Over 100	9	103	55	52.9
Rheumatoid arthritis (16):				
Below 98.0	36	116	103	49.4
98.0–98.8	59	109	96	59.7
98.9–100.0	11	77	67	79.0
Over 100	5	72	49	106.0
Erythema nodosum (12):				
Below 98.0	9	136	112	15.1
98.0–98.8	18	120	104	31.5
98.9–100.0	7	87	68	55.5
Over 100	0	—	—	—
Acute tonsillitis (18):				
Below 98.0	5	141	108	9.5
98.0–98.8	19	128	88	10.1
98.9–100.0	6	124	63	25.7
Over 100	2	103	58	32.5

* Figures in parentheses indicate the number of patients in each group.

rheumatism a further reduction was observed at temperatures of over 100°. In the other diseases, in which the patients examined were of both sexes but not necessarily in equal numbers, the average values for vitamin A also tended to fall as the range of body temperature was increased.

	No. estimations	Carotenoids	Vitamin A	E.S.R.
		I.U./100 ml.	I.U./100 ml.	mm./hr.
Acute rheumatism:				
Below 98°	170	105	105	18
98.0–98.4°	338	103	103	22
Above 98.4°	113	89	76	50

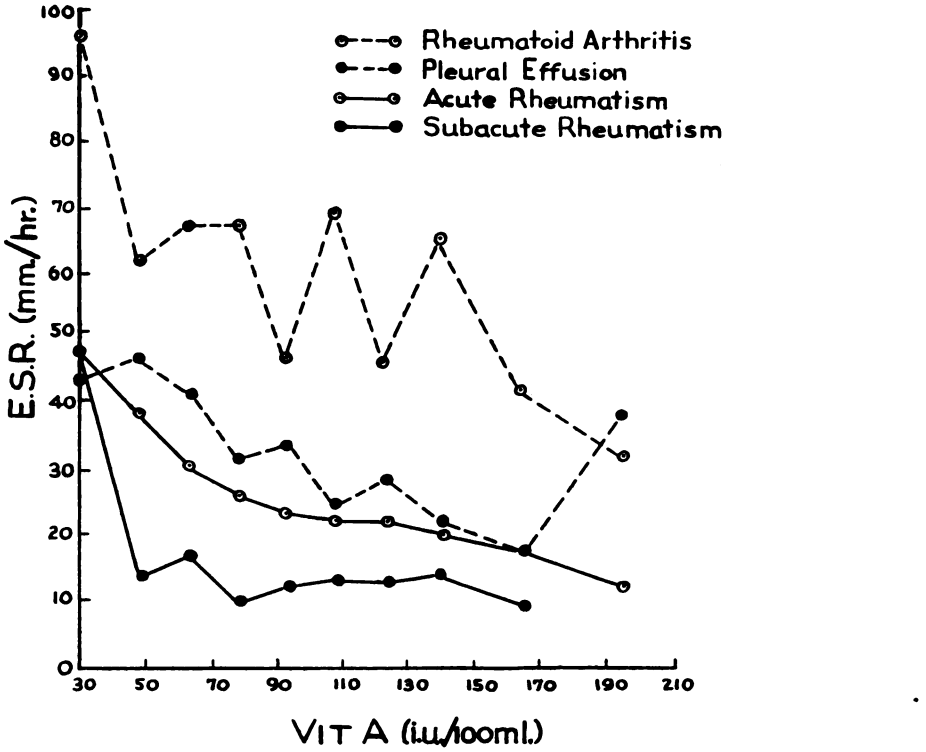

Fig. 1. E.S.R.—Vitamin A curves

Carotenoid levels tended to respond less noticeably to temperature increases. In the range 98.9–100° reduced levels were found only in rheumatoid arthritis and erythema nodosum. At temperatures of over 100°, however, carotenoids were reduced in acute rheumatism. It will be noticed that even at normal temperatures the carotenoid levels remained below those found in health.

In choosing the arbitrary ranges of temperature shown in Table I the main purpose was to demonstrate the relation between temperature and vitamin A. The ranges taken, however, are obviously less appropriate as a guide to rheumatic activity, and on Dr. B. E. Schlesinger's advice our data may for this purpose be rearranged as follows:

Vitamin A in Relation to E.S.R.

Mean values for E.S.R. at the various temperature intervals are included in Table I. The data were also regrouped according to arbitrary vitamin A ranges, and the corresponding mean E.S.R.'s calculated. These are shown in graphical form in Figure 1. In each disease a tendency for vitamin A to fall with increasing E.S.R. was observed, as might be expected from the association between E.S.R. and body temperature. At corresponding vitamin A levels the E.S.R., however, was much higher in rheumatoid arthritis than in acute rheumatism, subacute rheumatism and pleural effusion. This observation is in accordance with the well-known tendency for

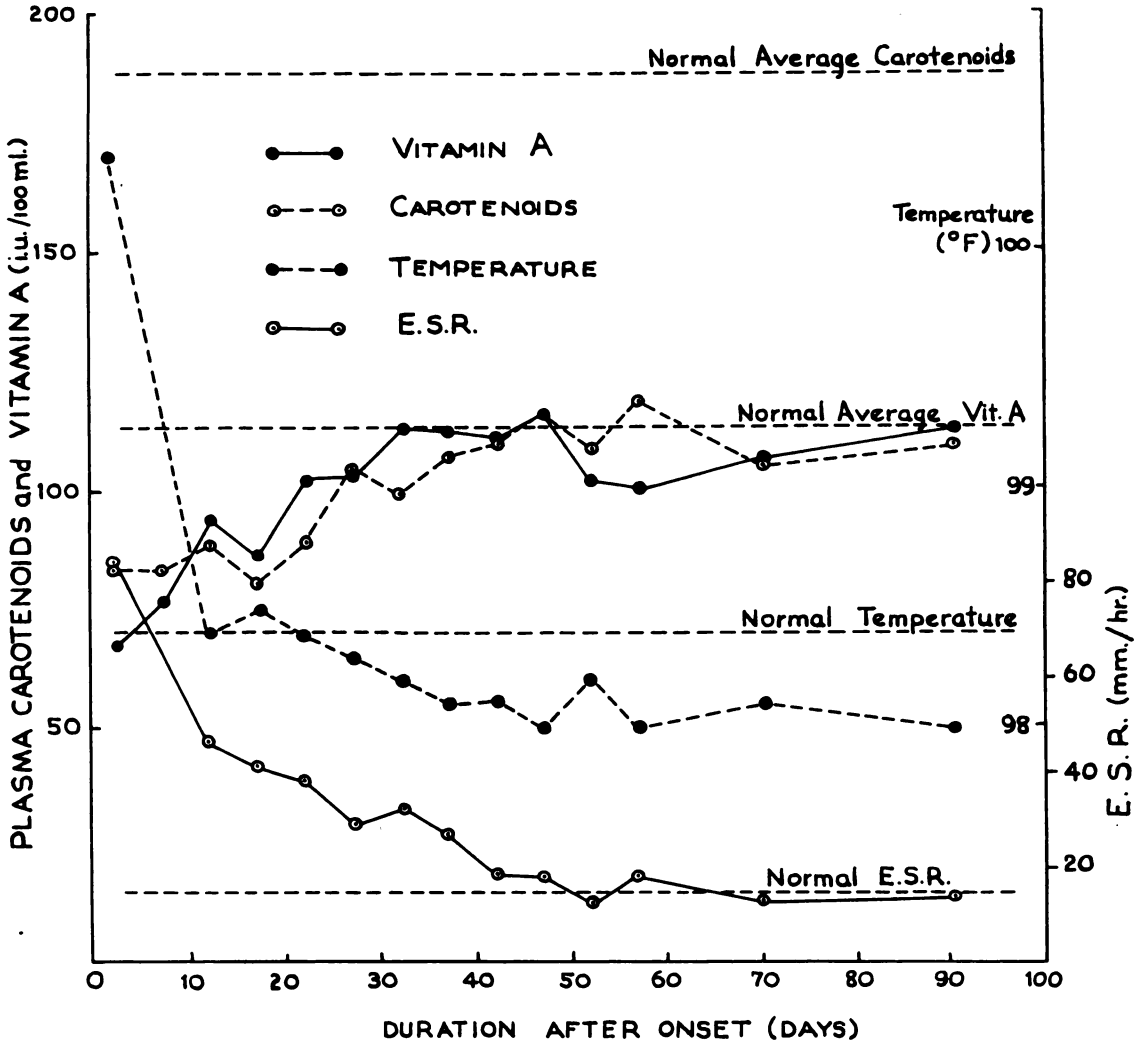

Fig. 2. Changes in vitamin A, carotenoids, body temperature, and E.S.R. in patients (100) recovering from acute rheumatism

the E.S.R. to be high in rheumatoid arthritis, even in the absence of pyrexia.

Changes in Vitamin A, Carotenoids, Temperature, and E.S.R. in Relation to the Time after the Inception of Rheumatic Fever

Figure 2 was obtained by arranging data for the 100 rheumatic fever cases according to the time after the inception of the disease at which the observations were made. It will be seen that the mean temperature returned to normal after 2–3 weeks, and was afterwards subnormal. Vitamin A rose, and the E.S.R. fell, with decreasing rapidity in the later stages of recovery, until after 7 weeks the levels in each instance were almost normal.

Total carotenoids showed increases parallel to those in vitamin A, but the maximum levels reached remained well below the normal average. A similar degree of subnormality, however, was observed in nonfebrile patients suffering from other diseases.

Vitamin A in the Plasma of Patients Shortly before Death

The data so far presented have indicated that the mean vitamin A for large numbers of patients falls when the body temperature

TABLE II

Fatal Cases Showing Low Premortal Vitamin A Values

Patient	Age	Disease or cause of death	Days before death	Temperature	E.S.R.	Carotenoids	Vitamin A
				° F.	mm./hr.	I.U./100 ml.	I.U./100 ml.
A. B.	59	Carcinoma bronchi	25	98	10	42	80
A. F.	37	Femoral thrombosis (embolic lung abscess)	14	98	53	43	43
S. J.	59	Syphilitic aortitis	13	?	—	46	54
J. S.	21	Mitral stenosis congestive failure (rheumatic origin)	12	97.2	6	68	29
G. B.	69	Pyogenic arthritis	12	97.6	72	55	28
E. B.	34	Uraemia	9	?	—	79	49
H. B.	23	Pneumonia, congestive heart failure	6	97.8	18	65	13
F. M.	10	Chronic rheumatism. Dyspnoea. Lung collapse	5	97	68	144	64
C. H.	52	Acute rheumatism	5	99	98	36	21
Mean	40		11	—	—	64	42

rises. It must be emphasised, however, that this inverse relationship did not always hold good in individual patients, in many of whom inconsistent changes were observed. These irregularities were seen in many patients who eventually recovered, but a low level of vitamin A without elevated body temperature occurred with noticeable frequency in patients examined shortly before death. Data were collected from only one such patient with acute rheumatism and from two others with diseases which were presumably of rheumatic origin, and in Table II additional data have been added which relate to patients who died from other diseases, and from whom specimens were received during the period while the present investigation was proceeding. The values given are the last observed before death. It will be seen that low levels were invariably found, although the body temperatures were usually normal or subnormal.

The Vitamin A Reserves of the Liver in Fatal Cases of Juvenile Heart Disease

No specimens of liver were taken from patients who died in the present investigations. It may be of interest, however, to record the individual values found by Ellison and Moore (1937) in children who had died from heart diseases, mostly of rheumatic origin. From Table III it will be seen that the range of values found in heart disease, with a mean of 28 I.U. per Gm., was much lower than in accidental death, mean of 129 I. U.

Moore (1937) also examined the vitamin A contents of the liver in adults dying of heart disease, and found that vitamin A was completely or almost absent in 20 per cent of the patients with valvular lesions.

Discussion

The present observations confirm and extend previous findings that the metabolism of vitamin A is disturbed in rheumatic fever. It remains difficult, however, to decide how far the vitamin need be taken into account in explaining the progress of the disease, or in planning treatment. Obviously there are many possibilities to be considered beyond the simple conception that dietary deficiency of the vitamin may reduce resistance to the disease. Thus the disease may cause a reduced consumption of food containing the vitamin, or may interfere with the absorption of the vitamin from such food as is consumed. A conditioned deficiency can thus be visualised which might reduce resistance to the further progress of the disease. Possibly the rate of expenditure of the vitamin in the tissues may be increased, and the stores present in the liver may be immobilised by failure of the regulatory mechanism which releases the vitamin into the blood. Without attempting to discriminate

TABLE III

Vitamin A Reserves in the Livers of Children Dying from Heart Disease, as Compared with Those Found in Accidental Death

	Name	Sex	Age	Place	Post-mortem report	Vitamin A
						I.U./Gm. liver
Heart cases	CW	M	13	L	Simple endocarditis	0
	AL	F	11	B	Congenital heart disease	3
	MP	F	12	G	Subacute rheumatic endocarditis	3
	GGS	M	6	L	Rheumatic endocarditis	9
	JEM	F	8	L	Rheumatic heart disease	12
	JR	M	14	G	Chronic rheumatic endocarditis	23
	JC	M	14	G	Rheumatic endocarditis	37
	CN	M	7	B	Acute rheumatism and rheumatic carditis	60
	SM	F	4/12	B	Rheumatic carditis	105
					Mean	28
Accident cases	EM	M	7	G	Fractured skull	3
	FM	F	3	G	Fractured skull. Meningitis	15
	MH	F	12	B	Ruptured spleen	30
	MP	F	1 6/12	G	Lysol burn	75
	RN	M	4	Lo	Fractured skull	87
	GE	M	3	G	Burns	150
	WM	M	7	G	Fractured pelvis	150
	CF	F	7	G	Fractured skull	150
	IM	F	6	G	Fractured skull	150
	TS	M	11	G	Fractured skull	150
	DC	M	5	G	Fractured skull	300
	MO	F	7/12	?	Burns	300
					Mean	129

B = Belfast, G = Glasgow, L = Leeds, Lo = London.

between these possibilities, however, it is clear that in acute rheumatic fever the level of vitamin A in the plasma is reduced, while in chronic heart disease of rheumatic origin the liver reserves of vitamin A often reach vanishing point.

The prescription of diets in convalescence from rheumatic fever should obviously be based on the assumption that the metabolism of many nutrients may be affected, and dosing with vitamins should not be considered an effective substitute for nutritious and appetising food. In view of the clear evidence that vitamin A metabolism is affected, however, it would seem a reasonable insurance to provide halibut liver oil, or some other potent concentrate, at a dose providing an intake considerably in excess of the adult's requirement of 2500 I.U. per day. Doses of 40,000–50,000 I.U. would appear to be reasonable.

Summary

(1) Vitamin A was estimated in the blood plasma of 100 patients with rheumatic fever, and the results were averaged according to arbitrary ranges of body temperature, or according to the time after the commencement of the disease.

(2) Vitamin A was considerably reduced during the febrile stage of the disease, but equally severe reductions were found in smaller groups of patients with pneumonia, pleural effusion, rheumatoid arthritis, erythema nodosum or acute tonsillitis.

(3) During convalescence the mean body temperature first reached normal, followed by vitamin A and by E.S.R.

(4) The changes in the mean carotenoid contents of the plasma were less clear-cut than those in vitamin A, but there was a consider-

able reduction when the body temperature exceeded 100°.

(5) The inverse relation between body temperature and vitamin A was not always observed in individual cases. Very low vitamin A values were found in specimens collected from nonfebrile patients with various diseases within 14 days of death.

(6) A re-examination of earlier data indicated that the vitamin A reserves found in the livers of children who had died from heart diseases, mainly rheumatic in origin, were much lower than in children who had died by accident.

(7) No claim can be made either that rheumatic fever differs from other febrile diseases in its effect on vitamin A metabolism, or that vitamin A is the only nutrient affected. The danger that the prolonged course of rheumatic fever may eventually exhaust the vitamin A reserves in the liver, and so produce a conditioned deficiency of vitamin A, should not, however, be ignored.

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RESUMEN

Vitamina A en la fiebre reumática

Se determinó la vitamina A en el plasma sanguíneo de 100 pacientes afectos de fiebre reumática, y de las cifras resultantes se sacaron promedios basados o en límites arbitrarios de temperatura corporal o en tiempo trascurrido desde el aparecer de la condición.

La vitamina A fué notablemente reducida durante el período febril de la enfermedad, pero unas reducciones igualmente severas se notaron en grupos menores de pacientes afectos de neumonía, efusión pleural, artritis reumatoide, *erythema nodosum*, o angina tonsilar aguda.

Durante la convalescencia el promedio de la temperatura corporal alcanzó por primera vez lo normal, seguido por la normalización de la vitamina A y de la velocidad de sedimentación globular.

Las alteraciones en el contenido promedio de los carotenoides del plasma fueron menos claras que las de la vitamina A, pero hubo una notable disminución cuando la temperatura corporal excedió de 100 grados.

La relación inversa entre temperatura corporal y vitamina A no siempre se observó en casos individuales. Muy pocos valores bajos de vitamina A se hallaron en las muestras obtenidas de pacientes no febriles con diversas enfermedades durante los 14 días antes de su fallecimiento.

Una nueva examinación de hallazgos anteriores indicó que las reservas de vitamina A en los hígados de niños muertos de cardiopatías, las más de origen reumático, fueron muy inferiores a las de niños muertos de accidentes.

No se puede pretender que la fiebre reumática difiera de otras enfermedades febriles en cuanto a su efecto sobre el metabolismo de la vitamina A, ni que la vitamina A sea el único factor nutricional afectado. Hay que no olvidar, sin embargo, el peligro de que el curso prolongado de la fiebre reumática pueda al fín agotar las reservas hepáticas de vitamina A y así conducir a una deficiencia condicionada de vitamina A.