XVIII. VITAMIN A AND CAROTENE

XIII. THE VITAMIN A RESERVE OF THE ADULT HUMAN BEING IN HEALTH AND DISEASE

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THE determination of a value for the vitamin A reserve which may be considered typical for the normal human being constitutes a problem of considerable importance in nutritional research. It is equally important to discover whether in any ordinary diseases, as opposed to acknowledged deficiency diseases, low vitamin A reserves are prevalent. Wilson [1927] made the first attempt to answer these questions by determinations of the vitamin A content of specimens of liver obtained at autopsy. Similar investigations have since been carried out by Wolff [1929; 1932], Kerppola [1931], Moore [1932; 1934], Green [1932], Fox [1933], Breusch & Scalabrino [1934], Muller & Suzman [1934] and Crimm & Short [1935].

The main vitamin A reserve of the body is located in the liver and may be readily assayed by the antimony trichloride reaction without the necessity for biological tests. The collection of data is therefore less laborious than for most other vitamins. On the other hand, several serious difficulties must be faced in the interpretation of results. (1) Even in normal subjects the vitamin A reserve varies over a wide range. In studying the relationship between disease and low vitamin A reserves, therefore, results obtained upon individual cases are of little significance. Valid deductions can only be drawn from data obtained on large groups. (2) When low vitamin A reserves are observed in any particular disease it may be difficult to decide whether the subnormality is a cause or an effect of the disease. (3) If we have reasons for believing that low vitamin A reserves in any disease are of aetiological significance we have no justification for assuming that vitamin A deficiency is the only, or indeed the most important, defect involved. Diets deficient in this vitamin would probably be deficient in other factors, e.g. in vitamins C and D.

It is plain therefore that observations of vitamin A reserves at autopsy cannot be expected to provide an immediate and comprehensive solution of the whole problem of the significance of vitamin A in human nutrition, although data so obtained may be of real value in affording a first indication of those diseases in which low vitamin A reserves are most frequently encountered and in indicating profitable fields for future research.

Of the 950 cases investigated in the present work about 320 formed the bases of the earlier preliminary communication mentioned above [Moore, 1932].

EXPERIMENTAL PROCEDURE, TECHNIQUE AND EXPRESSION OF RESULTS

Collection of specimens. Specimens of human liver were obtained through the kindness of Prof. J. Shaw Dunn, Royal Infirmary, Glasgow; Dr W. M. Elliott, Ruchill Fever Hospital, Glasgow; Prof. E. H. Kettle, St Bartholomew's Hospital,

London; Prof. J. R. Marrack, London Hospital; Prof. R. Muir, Western Infirmary, Glasgow; Dr Dorothy Russell, London Hospital; Prof. M. J. Stewart, General Infirmary, Leeds; Prof. H. M. Turnbull, London Hospital; Dr C. G. L. Wolf, Addenbrooke's Hospital, Cambridge; and Prof. J. S. Young of the Queen's University, Belfast.

During the early stages of the work, which was extended over several years, specimens were obtained from cases dying from all types of diseases. Later the collection of specimens was restricted to those diseases which appeared to show subnormal reserves.

Technique. 5 g. portions of liver were taken at autopsy, placed in small wide-necked stoppered bottles, covered with 10 ml. of 5% aqueous KOH, and sent to this laboratory. Vitamin A was assayed by the antimony trichloride method using the technique of Davies [1933]. Control experiments indicated that no deterioration of the vitamin was to be expected during the time necessary for dispatch and assay, and also that samples of liver taken from different lobes gave identical results.

Expression of results. Individual vitamin A reserves were first calculated in blue units per g. of wet liver,¹ and then converted into international units per g. by multiplying by 0.6.

Whilst an accurate conversion of blue units into international units is not possible at our present stage of knowledge the obvious advantages of the expression of results in this form must outweigh any criticism of want of accuracy. The conversion factor given above was calculated as follows: 1 B.U. per g. (Moore) = Carr-Price value $0.0182 = E_{1\text{cm.}}^{1\%} 328\text{m}\mu \cdot 0.000373 = 0.60$ I.U. per g. The conversion of B.U. per g. (Moore) into Carr-Price value depends on the definition of the two scales. The factor for converting Carr-Price value into $E_{1\text{cm.}}^{1\%} 328\text{m}\mu$ has been calculated from data relating to a rich vitamin A concentrate [Carr & Jewell, 1933]. For converting $E_{1\text{cm.}}^{1\%} 328\text{m}\mu$ into I.U. per g. the factor 1600 provisionally recommended by the Medical Research Sub-Committee on vitamin A standardization has been adopted.

The results in groups of cases were summarized by dividing each group into three equal sub-groups ("low, medium and high") according to ascending vitamin A reserves and then taking the mean of each sub-group. The mean of the middle sub-group is described as the "median" and is taken as the main criterion of the vitamin A range of the whole group. The mean of the whole group is also given to facilitate comparison of the present results with those of previous workers.

This method is not claimed to be ideal, but has been adopted after giving serious consideration to many other possible methods. The essential difficulty in arriving at a satisfactory method of summarizing results lies in the enormous spread of values which occurs even in health. The ordinary method of taking the mean for the whole group is open to the objection that the mean may sometimes be unduly influenced by the inclusion of very high values. Thus one case with a very high value might cancel the effect of 10–20 cases having low reserves. In a previous communication [Moore, 1932] a graphical method was adopted for the expression of results. This method is however very laborious and does not seem to make the results any clearer than the simpler method adopted in the present paper. The mean of the middle third of cases is preferable to the actual median value, defined simply as the value of the middle case, in view of the susceptibility of the latter to fortuitous irregularity in the grading of cases.

¹ In calculating the vitamin A reserve per g. of wet liver the author has followed the course adopted in previous work. In some circumstances, and notably in diseases involving marked change in the size of the liver, it might be considered preferable to give the total reserve of the whole organ. The former plan however has the advantage of giving a value that is independent of the size of the subject, and is considered adequate for its purpose at the present stage of the research.

Table I

	No. of cases	Cause of death	Age group	Mean age	Vitamin A reserve (i.u. per g. liver. Means of lowest, middle and highest thirds)			
					L.	M. (median)	H.	Mean
Group 1, accidental death	40	Death within 7 days of injury	15-59	33	75	220	590	290
	16	" "	Over 60	67	18	100	330	150
	73	Death at any time after injury*	All ages	37	41	150	480	220
Group 2, poisoning	13	Death within 7 days from poisoning	15-59	39	94	170	360	210
Group 3, alimentary tract diseases	43	Gastric and duodenal ulceration	15-59	45	40	110	300	150
	9	" "	Over 60	64	43	110	240	130
	19	Appendicitis	15-59	37	28	110	490	210
	11	Enteritis and colitis	15-59	38	9	74	390	160
	12	Peritonitis	15-59	34	31	75	220	110
	10	Hernia, intestinal obstructions, faecal fistulas	15-59	40	90	160	470	230
	7	" "	Over 60	69	34	95	300	140
	13	Gall bladder diseases	15-59	48	49	110	250	130
	7	" "	Over 60	68	90	100	280	150
Group 4, respiratory diseases	22	Pneumonia (lobar and broncho)	15-59	36	5	63	200	88
	12	Empyema	15-59	37	9	60	240	100
	12	Bronchiectasis, chronic bronchitis	15-59	40	18	82	250	120
Group 5, endocrine diseases	15	Diabetes	15-59	42	89	300	870	520
	8	" "	Over 60	66	240	540	750	520
	9	Thyroid diseases	15-59	44	90	310	530	310
Group 6, heart and circulatory diseases	56	Valvular diseases of the heart	15-59	37	7	60	230	96
	26	Cerebral haemorrhage resulting from high blood pressure	15-59	47	25	120	370	170
	20	Coronary diseases	15-59	51	28	100	320	140
	14	" "	Over 60	67	25	76	230	100
Group 7, tuberculosis	36	Tuberculosis, all forms	15-59	31	24	96	380	170
Group 8, cancer	76	Cancer, all forms	15-59	46	43	110	320	160
	36	" "	Over 60	67	23	110	210	110
Group 9, syphilitic diseases	27	Syphilitic aortitis, aortic aneurisms, periarteritis nodosa, syphilitic cirrhosis	15-59	48	23	95	390	170
Group 10, diseases of the kidney and urinary tract	48	Chronic nephritis	15-59	42	5	25	150	59
	10	Sub-acute nephritis	Over 60	66	6	23	120	47
	12	Kidney and bladder infections	15-59	35	9	75	350	140
	13	Prostate diseases	15-59	39	3	19	320	110
	23	Head and spine infections, otitis, antrum and sinus infections, cerebral abscesses, mastoiditis, meningitis	All ages	64	7	40	230	86
Group 11, septic diseases	52	Other infections—abscesses, septicaemia, osteomyelitis, septic arthritis	15-59	31	10	73	260	110
	35	Septic, ulcerative, malignant, subacute endocarditis	15-59	36	9	51	270	110
Group 12, diseases of blood generation, etc.	33	Anaemia, leucaemia, purpura haemorrhagica, Hodgkin's disease, pernicious anaemia, Banti's disease	15-59	37	22	90	250	120
Group 13, thrombosis and embolism	31	Thrombosis and embolism	15-59	38	19	130	520	220
Group 14, nerve and spinal cord diseases	23	All types of nerve degeneration	15-59	47	13	89	240	110
Group 15, diseases of women	13	Hysterectomy, abortion, puerperal septicaemia etc.	15-59	36	22	110	560	220
	15	" Including the 56 cases given above.	15-59	32	29	96	270	130

* Including the 56 cases given above.

Classification of cases. Cases have been classified according to the primary disease causing death. Thus cancer cases have been classed as such although the immediate cause of death might be pneumonia or peritonitis. No very logical system in the order of tabulating results can be claimed. As a general rule diseases have been grouped according to the physiological system effected. Some exceptions to this rule have however been made, notably in grouping together all cases of tuberculosis, neoplasms and syphilis, irrespective of the system sustaining the lesion.

Age limits. Previous work [Wolff, 1929; Breusch & Scalabrino, 1934] has suggested that, except in early infancy, the vitamin A reserve shows no significant variation with age. In the present work it was found that, although very high reserves were often observed in individual cases, the medians for groups over 60 were usually lower than for corresponding groups of younger subjects. Whilst the evidence available is not sufficiently weighty to permit a decision on this point it has been thought desirable to rule out any complicating factors that might arise through the effects of old age by excluding data on subjects over 60. The exclusion was effected half-way through the work by ceasing to collect specimens from cases over 60. In those diseases for which a large number of cases had already been collected values have been calculated separately. Unless otherwise stated the data given refer to subjects between the age limits 15-59.

Disease level median. In the present work the vitamin A ranges in almost all diseases were considerably below the level found in accidental death (220 I.U. per g.). It is not certain how far the disparity can be correlated with the existence of disease *per se*, and how far with other factors, such as changes in dietary habits during hospital treatment. It is plain, however, that some standard of comparison is needed in order to distinguish between those diseases which show only the ordinary depression below the accident level and those showing very low reserves. For this purpose the median observed in cancer (110 I.U. per g.) has been chosen, as being typical of a chronic disease which does not appear to have any connexion with vitamin A deficiency, and for which adequate data are available. Working on an arbitrary basis, only those diseases with median less than 80 % of the cancer median (i.e. less than 88 I.U. per g.) have been regarded as showing significant subnormality.

The results obtained are given in Table I.

It may be pointed out that the antimony trichloride method is accurate to 5-10 % for values obtained in the same laboratory, while a larger degree of error might sometimes occur in results obtained on the same specimen in different laboratories. For individual cases therefore values can only be considered accurate within these limits. When, however, the mean of a number of cases is taken one might expect, by compensation of errors, that the margin of error might be reduced. In Table I results have been "rounded off" to show two figures. The second figure is of questionable significance when the first figure is large. Values under 10 have been given as the nearest integer.

DISCUSSION

The vitamin A reserve in health

The typical vitamin A reserve of the normal adult. To establish the extent of the vitamin A reserves in health it is necessary to resort to data obtained on cases of accidental death. No assurance can be given that all the cases were in perfect health, but the accident group appears to afford a reasonable cross-section of subjects in "ordinary health". Since the reserve varies over a wide range (even in this group) (lowest individual value 10, highest 1500) it is not

permissible to speak of a "normal" reserve.¹ The median (220) of this group may, however, be taken as the "typical" vitamin A reserve in health. This result is somewhat higher than that previously given (130 I.U. per g. [Moore, 1932]), the increase being mainly due to the restriction of the age limits (15-59) and to the omission of cases dying more than 7 days after injury. In Table II the results obtained in the present work are compared with previous findings, the same factor (0.6) for the conversion of blue units into international units being employed in each instance. In view of the difficulty of ensuring a reliable comparison of results obtained by colorimetric methods in different laboratories it is enough to note that the values obtained by all three workers are of much the same order.

Table II. *Accidental death*

Worker	No. of cases	Subjects	Mean	Median
Fox [1933]	14	African native mine workers	180	110
Moore [1932]	23	British (all cases)	200	130
Moore (1937)	73	British (all cases)	220	150
Moore (1937)	40	British (age 15-59)	290	220
Wolff [1932]	78	Dutch	160	ca. 110

Time equivalent of the typical human reserve. Davies & Moore [1935] have estimated the physiological requirements of the rat at 2 B.U., or 1.2 I.U. per g. of liver per day. By analogy with this admittedly rough estimate the typical human reserve, assuming equal expenditure per g. of liver, should be sufficient to support life for about 6 months. The prediction of the time of survival is made difficult, however, by the fact that the vitamin A reserve, especially if high, may sometimes be dispersed at a rate greater than that demanded by apparent physiological requirements.

Vitamin A reserves in disease

Relation between the vitamin A reserve and general state of nutrition. As already mentioned one of the chief difficulties in the interpretation of data relating to liver reserves lies in the difficulty of deciding whether low reserves when observed in any disease represent a factor of aetiological significance or are merely a secondary effect. No satisfactory answer to this question can yet be given, but ample evidence is available to show that the vitamin A reserve bears no essential relation to the general state of nutrition. Thus Wolff [1929] found no difference in the vitamin A reserves of lean, medium and fat human subjects. In the rat Dann & Moore [1931] found that the extreme emaciation caused by vitamin B deficiency had no effect on the vitamin A reserve. In the present work high reserves were observed in cases of cancer showing severe emaciation. These results suggest that any effect of illness on the vitamin A reserve must be due either to a reduced intake of foods rich in the vitamin, or to the direct influence of the disease in causing either increased expenditure of existing stores of the vitamin or decreased assimilation of the alimentary supplies. There is no reason to suppose that failure in general nutrition in itself should cause low vitamin A reserves.

Diseases showing high vitamin A reserves. Vitamin A reserves above the "level in health" were found in diabetes (ages 15-59, 300, over 60, 540 I.U. per g.). High values in this disease have been reported by other workers and appear to be mainly due to the adoption of vegetable dietaries. Whether this simple

¹ There appears to be no objection to the use of the term normal, or subnormal, in referring to ranges of reserves as opposed to individual values.

explanation represents the whole story is not certain. According to Ralli *et al.* [1935] the ingestion of carotene by diabetics results in a more intense carotenaemia than administration of the same amount of carotene to a normal subject. The observation of high vitamin A reserves in the livers of subjects dying from diabetes must rule out the suggestion that there is any serious impairment of the power of the liver to convert carotene into vitamin A. It is possible, however, that a general slowing down of the metabolism of both carotene and vitamin A takes place, with consequent accumulation of both substances in the organism.

High reserves were also found in thyroid diseases (all types), although the small number of cases available (9) makes the authenticity of this result more questionable. It may be noted, however, that Wolff found a high average for 5 cases of exophthalmic goitre, while Breusch & Scalabrino observed the highest value in their 72 cases in a man 98 years old suffering from a swollen thyroid.

Diseases showing moderate vitamin A reserves. The two groups with reserves most nearly approaching those found in accident cases were poisoning (170) and hernia (160), in both of which death had presumably occurred after a short, or no, illness. It may be noted that two out of three poisoning cases with fatty degeneration of the liver gave quite high values. This finding is in agreement with the work of Lasch [1935], who found that the vitamin A reserve of the rat is not reduced as a result of phosphorus poisoning and deduced from this result that the reticulo-endothelial system of the liver, and not the parenchyma, is concerned with the storage of the vitamin. The median (110) for the cancer group, which as stated has been taken as providing a value typical for disease, was about half the level in accidental death. A list of diseases with medians falling within 20 % variation from the cancer level is given in the summary.

Diseases showing low vitamin A reserves. To avoid misunderstanding it may be emphasized that in no disease were the vitamin A reserves uniformly low in all cases. Thus the highest values in diseases showing low medians were always higher than the lowest values in diseases showing high medians. Moreover, in referring to "low" reserves we are making a comparison with values found in other diseases, without any implication that the reserves were low in an absolute sense.¹ Bearing these points in mind we may gain a good idea of the striking subnormality observed in certain diseases by comparing median values. Low medians were found in the following diseases:

Respiratory diseases (non-tubercular). (Bronchiectasis and chronic bronchitis 80, pneumonia 63, empyema 60.) As Fox has pointed out, all workers are agreed that in pneumonia the vitamin A reserve tends to be lower than in health. Data obtained by Wolff on a large number of cases suggest, however, that the results in the present work may have been unusually low.

Intestinal diseases. (Enteritis and colitis 74.)

¹ Since in the young rat the signs of avitaminosis-A do not develop until the liver reserve has been completely exhausted it might be argued that any measurable reserve must indicate that the immediate requirements of the organism are satisfied. Recently however evidence has become available which suggests that a state of avitaminosis may sometimes be reached before the colour reaction of the liver is completely negative. Thus Guilbert & Hart [1934] have observed night blindness in cows whose livers at autopsy still gave a faintly positive antimony trichloride reaction. Reactions of similar intensity have been observed by Guilbert & Hinshaw [1934] in the livers of turkeys killed when the first signs of avitaminosis become evident. The writer has observed faintly positive reactions in the livers of adult rats which have been allowed to accumulate stores of the vitamin and have then been restricted to a diet deficient in the vitamin for long periods until death supervened.

Valvular diseases of the heart (60). Results for this group are of interest in view of the extremely high proportion of cases (about 20 %) which gave negative, or almost negative, vitamin A reactions. (Note the very low mean (7) for the lowest third of the group.) This finding gains interest in view of the observation of a very low median (15) in a group of nine children dying from heart disease [Ellison & Moore, 1937]. Although Wolff did not separate valvular lesions from other heart diseases he observed a decidedly low mean in a large group of heart cases of all types.

Septic diseases. (Head and spine infection 73, other infections—septicaemia, cellulitis, carbuncles, osteomyelitis, septic arthritis, visceral abscesses—51.) The work of Mellanby and his colleagues [Green & Mellanby, 1928; 1929; Green *et al.* 1931] has focused attention on the anti-infective action of vitamin A. The results obtained in the present work confirm the previous finding [Moore, 1932] that severe infections may often occur in subjects having adequate, or even high vitamin A reserves. At the same time the low ranges of reserves found in septic diseases lend colour to the view that vitamin A deficiency, although it cannot be regarded as a sole cause predisposing to infection, may nevertheless be of aetiological significance in a large proportion of cases. The accumulation of additional data has supported earlier evidence [Moore, 1932] that low vitamin A reserves are to be found in the group described as "other infections". Moreover, the head and spine infections group, which previously gave a median at the ordinary disease level, is now included among those diseases showing low reserves. Septic endocarditis, however, continues to show a median (90) just above the arbitrary level taken as indicating subnormality.

Differences in the grouping of cases make a comparison of these results with those of other workers very difficult. Wolff reported reserves of varying degrees of subnormality in erysipelas, phlegmons, sepsis¹ and chronic suppurations. In otitis media and acute meningitis however no subnormality was observed. The total number of septic cases was about half those examined in the present work. Kaufmann & Drigalski [1933] found no difference in the reserves of pooled livers from 35 infectious and 35 non-infectious cases. Details as to the nature of the cases selected were not given.

Diseases of the urinary system. (Subacute nephritis 75, prostate diseases 40, chronic nephritis 25, kidney and bladder infections 19.) In this group the lowest ranges of reserves encountered in the present work were observed. Unfortunately only small groups of cases of subacute nephritis and kidney and bladder infections were collected, but the data on prostate diseases and chronic nephritis were obtained on groups of 23 and 48 cases respectively. The degree of subnormality observed in chronic nephritis, in which the cases were almost all of the interstitial, azotaemic type, may be realized from the calculations that the median reserve should suffice for some 3 weeks, as opposed to the 6 months in the healthy subject. For the lowest third of cases the mean reserve should be sufficient for only 4 days.²

In regard to chronic nephritis the authenticity of the low reserves seems to be beyond question. Wolff found a low mean for a large group of kidney disease

¹ Wolff's results for this group afford a striking example of the susceptibility of the mean to undue influence by the inclusion of cases having unusually high values. For 23 cases the mean was 196.2. When one case having a value of 2112 was omitted the mean for the remaining 22 cases fell to 109.2.

² A brief report on the low vitamin A reserves found in kidney diseases has already appeared [Moore, 1934].

cases (mostly chronic nephritis). Aschoff [1934] has also reported depleted reserves in chronic nephritis. In uraemia Breusch & Scalabrino [1934] found negative reserves in 3 out of 4 cases,¹ while low values in 7 cases of this condition were also reported by Kerppola [1931]. On the other hand, Wolff observed a high mean for 8 cases of prostate hypertrophy. It may be noted that at least 14 out of the 23 prostate cases examined in the present work were septic.

Diseases involving liver degeneration. Both Wolff and Breusch & Scalabrino have reported that low, and often zero, vitamin A reserves are frequently observed in cirrhosis of the liver. The number of cases of this disease examined in the present work was insufficient to justify the inclusion of a separate group in Table I, but the individual results may be quoted as affording support to the conclusions of the above workers. In 7 cases in which cirrhosis of the liver was the main lesion values of 0, 3, 6, 6 (child), 90, 375 and 525 were observed. In 2 cases of syphilitic aortitis involving cirrhosis of the liver values were 0 and 6. These results suggest that in cirrhosis the vitamin A reserve often falls to vanishing point, although in other cases, possibly of different aetiology, substantial reserves may be observed. The two instances of low reserves in syphilitic cirrhosis are of interest in view of Wolff's observation of a very low mean for tertiary and quaternary syphilis. In the present work the syphilitic group as a whole, which included cases of aneurisms of presumably syphilitic origin, gave a median (95) not significantly different from the ordinary disease level.

The significance of low vitamin A reserves

From the above evidence it is apparent that low vitamin A reserves occur frequently in a number of quite common diseases. As already emphasized the significance of this finding is open to question. On the one hand, it may be argued that since vitamin A reserves are lowered in almost all diseases the extent of the subnormality will depend merely on the duration and severity of the disease. Thus chronic nephritis and valvular disease of the heart, in which low reserves are observed, are diseases which run a very long course and in which there is marked dyspepsia. In support of this view Wolff has found the mean reserve for a large group of cases of various chronic diseases to be slightly lower than the mean for a group of acute diseases.

Approaching the problem from a slightly different angle it appears certain that in some diseases the power of the liver to store vitamin A must be impaired. Thus the low reserves found in some cases of cirrhosis of the liver, and particularly in syphilitic cirrhosis, appear to be an effect, and not a cause, of the liver injury. Similarly in the chronic venous congestion caused by mitral stenosis low values might be expected, both on account of the impairment of the functions of the liver and the reductions of the amount of actual liver tissue per g. of the organ on account of its engorgement with blood. Moreover, Green [1932] has reported instances of puerperal cases, treated unsuccessfully with large doses of vitamin A concentrate, which showed only meagre stores of the vitamin in the liver at autopsy. On the basis of this evidence one might be tempted to assume that the explanation of low reserves observed in all diseases not recognized as being

¹ These workers have suggested, apparently without putting the matter to direct test, that their negative results in uraemia may have been due to the presence of a substance inhibiting the antimony trichloride reaction rather than to the absence of this vitamin. The present author was unable to confirm this view in the case of a liver specimen taken from a subject dying from nephritis and having a very low vitamin A reserve. No inhibitory action was observed when the extract was added to a solution of vitamin A concentrate from an external source.

specifically due to vitamin A deficiency might lie in the reduced power of the liver to absorb the vitamin, or to effect its synthesis from carotene. It may be mentioned, in support of this latter explanation in the case of chronic nephritis, that the extracts from many of the specimens were deeply yellow in colour, suggesting a preponderance of unconverted carotene.

On the other hand, it may be mentioned in favour of the aetiological significance of low vitamin A reserves, that many of the diseases showing low reserves are also among the most common terminations to experimental vitamin A deficiency in animals. No one would suggest that all cases of pneumonia, sepsis, kidney disease etc. are due to vitamin A deficiency, and this self-evident conclusion is confirmed by the observation of cases with adequate reserves even in those groups giving the lowest median values. The question to be answered, however, is not whether all cases of these diseases are due to vitamin A deficiency, but whether in a significant proportion of cases (e.g. even 5–10%) vitamin A deficiency, or the general nutritional subnormality which it may imply, is a contributory cause of the disease. No solution of this difficult problem can be reached at the present stage of research.

SUMMARY

1. Vitamin A has been determined by the antimony trichloride method in about 1000 specimens of adult human liver obtained at autopsy. The results have been arranged in groups according to the cause of death.

2. Since the individual vitamin A reserve varies over a wide range both in health and disease, conclusions cannot be drawn from individual cases. The ordinary method of taking the mean for groups is also open to objection. The results for the cases of each group have therefore been arranged in order of ascending vitamin A reserves, and the "median" value for the group calculated by taking the mean for the middle third of cases.

3. The median value for 40 cases of accidental death in subjects between 15 and 59 years of age, dying within 7 days of injury, was 220 I.U. per g. of wet liver. This value may be taken as a "typical" value for the healthy adult of this country. The value for 73 cases of accident of all ages, and dying at any time after injury, was 150 I.U. per g.

4. In almost all diseases the vitamin A median was lower than in accidental death. For the purpose of distinguishing those diseases showing outstandingly low reserves the median of the cancer group (110 I.U. per g.), and not the accident median, has been taken as a basis of comparison. The following were the results obtained (all data refer to cases between the age limits 15–59 years):

Diseases with vitamin A reserves at autopsy above the health level. Thyroid diseases (all types, 9 cases only, median 310 I.U. per g.). Diabetes (300).

Vitamin A reserves slightly below the health level. Poisoning (170). Hernia (160).

Vitamin A reserves at the "ordinary disease level" (within 20% variation from the cancer median). Diseases of blood generation (130). Cerebral haemorrhage, high blood pressure (120). Cancer (110). Appendicitis (110). Gall bladder diseases (110). Nerve and spine diseases (110). Gastric and duodenal ulceration (110). Coronary disease (100). Tuberculosis (96). Diseases of women (96). Syphilitic diseases (95). Septic endocarditis (90). Thrombosis and embolism (89).

Vitamin A reserves below the "ordinary disease level". Bronchiectasis and chronic bronchitis (80). Subacute nephritis (75). Peritonitis (75). Enteritis and colitis (74). Head and spine infections (73). Pneumonia (63). Empyema (60).

Valvular diseases of the heart (60). Septic diseases (51). Prostate diseases (40). Chronic nephritis (25). Kidney and bladder infections (19). Cirrhosis of liver (insufficient cases for calculation of median).

5. The interpretation of these results is complicated by the difficulty of deciding in any given disease whether low vitamin A reserves, or the general nutritional subnormality which they might imply, are a factor of aetiological significance or merely a secondary effect of the disease. It is clear that in some diseases the power of the organism to absorb the vitamin is impaired. On the other hand, it is noteworthy that many of the diseases showing low reserves in the human being are also frequent terminations to experimental vitamin A deficiency in the animal.

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