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KYNURENINE IN DISEASE, WITH PARTICULAR REFERENCE TO CANCER*

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THE TECHNICAL and physiological limitations affecting the significance of kynurenine determination in human urine have been discussed elsewhere.[1, 2] The analysis would be useful if it could be proved that disease affects the findings much more than, for instance, ordinary variations in the average man's diet. Such investigations are the subject of the present study.

MATERIALS AND METHODS

Twenty-four hour specimens of urine were used except in the cases of poliomyelitis with a case number over 22. No standardization of diet was attempted. This means that most of the advanced cancer patients were on a light diet with little tryptophan content. Most of the poliomyelitis patients, being children, were on the customary children's regimen. Other patients were taking whatever is usual in the respective condition.

Kynurenine was determined by a procedure described elsewhere.[1]

RESULTS

Table I gives the data obtained in this survey. These were used to compare averages for the different groups of diseases (Table II) and to compare percentages of "abnormal" results. Figures were considered abnormal when they were above the average[2] for normal adults over 30 years of age plus the mean deviation from this average, i.e. above 0.32 mgm. per 100 ml. The much lower normal range for young adults (0.096 ± 0.041 mgm. per 100 ml.) is used for comparison in the group of poliomyelitis cases. Even this will give too high a percentage of abnormal results in this group because a considerable proportion were not adults.

The patients themselves were divided into four groups. Group I includes cases of malignant tumour which were either not yet treated, inoperable, or fit only for palliative treatment. Treated cases were also included where the diagnosis was definitely established but no evidence was obtained suggestive of at least a temporary cure. The table is arranged in subgroups according to the site of the tumour. Group II (cases marked with an asterisk) comprises several cases in which malignancy was only suspected. The majority were in patients after supposedly complete removal of an accessible tumour. Regional metastases, where diagnosed, had been extensively irradiated. Group III are poliomyelitis patients. About half had been ill for less than three weeks and the rest were being treated for sequelæ. Those over 30 years of age are shown in sub-group IIIa. Group IV: miscellaneous diseases including tuberculosis (IVa) form the last group.

Table II shows in all groups except I and III essentially the same average urinary concentration of kynurenine as in normal adults over 30 years. Group III (poliomyelitis) comprises children and young adults. The nearest comparable normal group is one previously reported,[2] of students about 20 years old; the two give practically the same average (0.070 mgm. per 100 ml. for Group III and 0.095 mgm. for the students).

When we consider the influence of age it is obvious that, on the average, urinary concentrations of kynurenine are normal in most common diseases except cancer. The average in malignant disease is nearly twice that found in the other diseases and well outside the previously defined range of normal values.

There is a very marked difference between groups I and II, the latter giving a normal average, whereas the average in the former is more than twice that in normal persons. These findings indicate that there is a relationship between malignancy and urinary kynurenine.

DISCUSSION

The number of observations is certainly too small to allow comparison between different types of tumours on the basis of average figures alone, and it will be attempted later using further considerations. The statistical approach is, of course, inferior to an experimental study, and it is only used here *faute de mieux*. The validity of any conclusions based on consideration of average findings is put in doubt as soon as we examine Table I more closely. The high averages obviously result from comparatively few exceedingly high figures, the majority of cases being within the normal range in all groups (except the small sub-group of cancer of the prostate).

Figures illustrating this observation are given

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TABLE I.

URINARY EXCRETION OF KYNURENINE IN DISEASE (IN MGM. PER 100 ML.)

Groups I and II. Malignant diseases. (Group II is marked with an asterisk.)

No.	Mgm.
Carcinoma of rectum or sigmoid	
1.	0.14
2.	0.10
3.	0.11
4.	0.13
5.	0.20
6.	0.31
7.	0.44
8.	0.52
9.	0.70
10.	2.37
11.*	0.42
12.*	0.35
13.*	0.12
14.	0.47
15.	0.45
16.	0.11
Average:	0.434
Carcinoma of lung	
1.*	0.09
2.	0.06
3.	0.19
4.	0.27
5.	0.74
6.	0.84
Average:	0.365
Carcinoma of breast	
1.	0.07
2.	0.08
3.	0.10
4.	0.11
5.	0.12
6.	0.19
7.	0.19
8.	0.20
9.	0.24
10.	0.42
11.	0.18
12.	0.28
13.	0.35
14.	0.80
15.	0.80
16.*	0.47
17.*	0.12
18.*	0.11
19.*	0.11
20.*	0.14
21.*	0.09
Average:	0.245
Carcinoma of prostate	
1.	0.07
2.	0.10
3.	0.07
4.	0.12
5.	0.24
6.	0.50
7.	0.49
8.	0.55
9.	1.06
10.	1.66
11.	1.38
12.	0.27
13.*	0.26
14.	0.57
Average:	0.524

No.	Mgm.
Carcinoma of uterus	
1.	0.08
2.	0.10
3.	0.13
4.	0.17
5.	0.19
6.	0.25
7.	0.27
8.	0.54
9.	0.44
10.*	0.06
11.*	0.12
12.*	0.34
Average:	0.224
Leukaemia, Lymphosarcoma, Hodgkin's disease	
1.	0.20
2.	0.22
3.	0.18
4.	0.45
5.	1.52
6.*	1.16
Average:	0.622
Miscellaneous carcinomas	
1.	0.07
2.	0.13
3.	0.16
4.	0.19
5.	0.16
6.	0.23
7.	0.24
8.	0.11
9.	0.38
10.	0.41
11.	0.35
12.	0.21
13.	0.28
14.	0.34
15.	0.19
16.	0.27
17.	0.45
18.	1.77
19.	2.50
20.*	0.07
21.*	0.05
22.*	0.14
23.*	0.15
24.*	0.21
25.*	0.08
26.*	0.09
27.*	0.10
28.*	0.12
29.*	0.12
30.*	0.29
31.*	0.47
Average:	0.333

Group III.

No.	Mgm.
Poliomyelitis	
1.	0.00
2.	0.00
3.	0.16
4.	0.10
5.	0.13
6.	0.10
7.	0.07
8.	0.10
9.	0.09
10.	0.13
11.	0.09
12.	0.06
13.	0.03
14.	0.06
15.	0.15
16.	0.06
17.	0.19
18.	0.03
19.	0.13
20.	0.12
21.	0.16
22.	0.05
23.	0.06
24.	0.12
25.	0.12
26.	0.07
27.	0.05
28.	0.05
29.	0.14
30.	0.10
31.	0.24
32.	0.14
33.	0.10
34.	0.15
35.	0.05
36.	0.06
37.	0.15
Average:	0.098

Group III-a

Poliomyelitis	
1.	0.00
2.	0.06
3.	0.07
4.	0.14
5.	0.34
6.	0.90
Average:	0.252

Group IV.

No.	Mgm.
Miscellaneous Diseases	
1.	0.03
2.	0.08
3.	0.13
4.	0.14
5.	0.18
6.	0.03
7.	0.11
8.	0.03
9.	0.09
10.	0.13
11.	0.14
12.	0.07
13.	0.06
14.	0.19
15.	0.20
16.	0.20
17.	0.17
18.	0.21
19.	0.22
20.	0.25
21.	0.28
22.	0.30
23.	0.29
24.	0.30
25.	0.33
26.	0.43
Average:	0.177

Group IV-a

Pulmonary tuberculosis	
1.	0.05
2.	0.07
3.	0.07
4.	0.10
5.	0.12
6.	0.14
7.	0.13
8.	0.11
9.	0.15
10.	0.17
11.	0.28
12.	0.36
13.	0.69
14.	0.23
15.	0.26
Average:	0.195

in Table II. Even if Group I alone is considered significant, we obtain a rather low percentage (40%) of abnormal findings in malignancy. This percentage of "abnormal" results is, however, significantly higher than the 13% for all other diseases combined.

The low percentage of positive results may be due to several causes. It must be remembered that the survey includes few patients examined before any treatment was started. Possibly even group I includes a number of cases with insufficient malignant tissue to affect the metabolism. This point could only be decided by a study of cases followed up during treatment. It seems unlikely that a standardization of diet would affect the statistics, although it undoubtedly should be done in assessing an individual case.

TABLE II.

AVERAGE KYNURENINE CONCENTRATIONS (IN MGM. PER 100 ML.) AND INCIDENCE OF ABNORMAL RESULTS IN DIFFERENT DISEASES

Group	*I*	*II*	*III*	*III-a*	*IV*	*IV-a*	*All tumours (I and II)*	*III, IV & IV-a*
Average urinary kynurenine	0.412	0.217	0.098	0.252	0.177	0.195	0.362	0.192
% of abnormal results	39	11	11	33	8	13	32	13
Number of cases	79	27	37	6	26	15	106	47

TABLE III.

URINARY KYNURENINE AFTER ADMINISTRATION OF TRYPTOPHAN (IN MGM. PER 100 ML.)

*No.**	*Site of carcinoma*	*Kynurenine before tryptophan*	*Kynurenine after tryptophan*	*Increase*
7.	Rectum	0.44	0.75	0.31
15.	,,	0.45	1.00	0.55
16.	,,	0.11	2.83	2.72
5.	,,	0.20	0.47	0.27
2.	Lung	0.06	1.75	1.69
1.	Lymphosarcoma	0.20	0.40	0.20
12.	Breast	0.28	0.69	0.41
14.	Colon	0.47	2.60	2.13
5.	Uterus	0.19	0.28	0.09
–	,,	0.27	1.56	1.29
–	Prostate	0.10	0.22	0.12
5.	,,	0.24	1.05	0.81
–	,,	0.08	0.79	0.71
–	,,	1.66	3.51	1.85
–	Œsophagus	0.28	1.27	0.99
14.	Maxilla	0.34	0.77	0.43
–	Prostate	0.07	1.30	1.23
				Average: 0.93

*The numbers correspond with those in Table I.

The figures suggest on the whole that there is considerable overlapping of findings between the normal and malignant groups. Setting the "normal" values at a lower level would probably be to some extent justified, as the average figure for diseases other than cancer was actually lower than for the small group of normal persons,[2] and so was the incidence of "abnormal" values. Also, the cancer patients had on the whole a lower dietary tryptophan intake than others. But even setting the normal limit at the probable rather than the observed level does not remove the overlapping.

It remains to test the hypothesis that only certain types of malignancy give "positive" results. As far as our few observations allow any conclusion, Tables I and II hold out a hope that this may be true; cancer of the prostate gave both a rather high average kynurenine value and a high incidence of positive results, whereas the corresponding figures are low for cancer of the uterus. This does not, of course, constitute a conclusion; another attempt was made in which ten cases with conspicuously high kynurenine levels over 0.6 mgm. per 100 ml. were collected to see whether they had anything in common. The types observed were: carcinoma of prostate (3 cases), carcinoma of bladder (1 case), carcinoma of breast (2 cases), carcinoma of rectum (2 cases), and carcinoma of lung (2 cases).

Apparently no single type was prevalent. They were all patients with infiltrating growth and/or metastases; in other words, advanced cases. Two lived on a vegetarian diet, showing again that dietary tryptophan is not the only, perhaps not even the most important, source of kynurenine.

The present study does not explain the high kynurenine values in malignancy. Kynurenine certainly is not the causative agent in cancer. The possibility which seems most likely is that the kynurenine is formed mainly from endogenous tryptophan, originating from the destruction of tissue proteins. This has been long known to occur in malignancy to a greater extent than in health. The apparently very malignant character of tumours where kynurenine values were highest somewhat supports this hypothesis.

It is also possible that some tissue of patients with tumours converts tryptophan into kynurenine more readily than in health. Such patients, if offered tryptophan, should excrete more kynurenine than normal persons. The average increase of kynurenine concentration in 12-hour specimens after 1.5 gm. of L-tryptophan was calculated from data published elsewhere[2] as 0.38 mgm. per 100 ml. urine. Similar tests in

malignancy (Table III) gave an average of 0.93 mgm. per 100 ml. The increase was more than 0.40 mgm. in 11 out of the 17 cases, apparently irrespective of the original concentration of kynurenine. More extensive studies will elucidate the significance of these findings.

CONCLUSIONS

The average concentration of urinary kynurenine in 106 patients with malignant tumours is about twice as high as the average either for healthy people or for patients suffering from any of the diseases investigated. The latter included poliomyelitis (43 cases), pulmonary tuberculosis (15 cases), and 26 patients with miscellaneous diseases.

A concentration of more than 0.32 mgm. per 100 ml. is considered abnormal. Such concentrations occurred in 32% of all cancer patients and 39% of cases presenting some indication of severity. The average incidence of abnormal results in all other diseases was 13%.

The average increase in urinary kynurenine after administration of tryptophan in patients with tumours was more than twice that in a small group of cancer-free persons. An "abnormally" high increase was found in the majority of cancer cases.

The incidence of abnormal results either before or after tryptophan appears too low to make the determination of kynurenine in the urine a test for malignancy. Nevertheless the findings indicate that there is a connection between malignant disease and the metabolism of tryptophan.

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ROTATOR CUFF TENDONITIS AND BICIPITAL TENOSYNOVITIS*

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THE PROCESSES OF ATTRITION, as they affect the mechanics of functioning joints in the musculoskeletal system, occur most frequently, as might be expected, in those articulations subjected to weight-bearing stress. However, similar changes also occur in other joints not primarily in the weight-bearing axis of the body. In these latter instances, the supporting soft tissues usually bear the brunt of the functional stresses rather than the actual skeletal framework, and consequently demonstrate the pathological changes which are to be eventually responsible for the production of symptoms.

In the upper limb the shoulder is most subject to this type of disorder, due in large part to the great range of movement through which the joint may be activated in circumduction and the resultant friction to which the ensheathing soft tissues are subjected as they are repeatedly compressed between bony and ligamentous structures or affected by the moving end of the humerus lying immediately subjacent to the musculotendinous cuff. Actually, with heavy physical work, the strain imposed upon this inadequately articulated joint will of necessity throw a very great load indeed upon its muscular supports.

Being due to the constant wear and tear of such occupational stresses, the resulting diseases might be expected to become apparent as aging occurs, and this is certainly true. Apart from the occasional patient who, at a young age, indulges in activities entailing an unusual amount of muscular activity of the arm in above-shoulder-level positions (e.g. tennis players, baseball pitchers, painters, and carpenters), these lesions produce symptoms with increasing frequency after the age of 40 years. The coincidental loss of elasticity in the same structures as a result of senescent processes undoubtedly accelerates the

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