

A FURTHER NOTE ON "STATUS THYMICO-LYMPHATICUS."

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IN 1927 Hilda M. Woods and I contributed to this *Journal*¹ a study of some aspects of a syndrome called "Status Thymicus," "Status Thymico-Lymphaticus" or simply "Status Lymphaticus." We were moved by three considerations: (1) that Prof. H. M. Turnbull had placed at our disposal a long series of weighings of the Thymus, the alleged principal villain of the piece; (2) that every year a not inconsiderable number of deaths are put to the account of *this syndrome*; (3) that the first volume of Prof. J. A. Hammar's monograph on the Thymus had recently been published. Since our publication, the annual quota of victims shows no signs of diminution (Table I) and the second volume of Prof. Hammar's work has appeared².

Table I. *Deaths from Status Lymphaticus in England and Wales and deaths under anaesthetics in which Status Lymphaticus was noted. (These are not included in all deaths from Status Lymphaticus.)*

		1925		1926		1927		1928	
		Male	Fe-male	Male	Fe-male	Male	Fe-male	Male	Fe-male
Deaths under anaesthetic	Ages 0-	85	54	88	41	68	48	80	48
		9	5	20	6	9	3	12	5
" " "	5-	4	2	9	1	8	7	10	3
		3	1	9	5	8	2	5	5
" " "	10-	6	2	4	5	3	2	8	4
		2	3	1	1	5	3	—	—
" " "	15-	2	3	5	3	3	—	6	3
		1	2	2	—	2	—	3	—
" " "	20-	3	3	1	2	3	2	1	2
		2	—	1	1	—	1	3	—
" " "	25 and up	2	3	3	4	5	4	3	5
		3	4	3	1	3	4	—	3
" " "	All ages	102	67	110	56	90	63	108	65
		20	15	36	14	27	13	23	13
		(204)		(216)		(193)		(209)	

These facts justify a further short note upon an episode not very much to the credit of the medical profession. In the previous study Woods and I showed: first, that the mean weight and variability of the thymus in cadavera which revealed no pathological changes were such that to base any diagnosis merely on weight was unreasonable; secondly, we gave reason to think that sudden and inexplicable death did not overtake persons with heavy thymi more frequently than others; thirdly, we noted that Hammar, on the basis of

¹ *J. Hygiene* (1927), 26, 305-26.

² *Die Menschenthymus in Gesundheit und Krankheit*. Teil II. *Das Organ unter Anormalen Körperverhältnissen*, pp. 1,114. Akademische Verlagsgesellschaft, Leipzig, 1929.

numerically less extensive but more closely analysed data, had also reached the conclusion that gravimetric criteria of abnormality were worthless. Lastly, by means of historical analysis we showed that the concept of a status or diathesis "explained" by an abnormality of the thymus was, not merely in our opinion, but in that of more learned students such as Hart and Hammar, a mere farrago of random assertion and debased tradition.

So far as the gravimetric problem is concerned, I have nothing to add to what was then published. The few people who have attempted to defend the current doctrine by rational argument have taken the line that weight is only *one* of the criteria of thymic abnormality and that the diagnosis of Status Thymico-Lymphaticus rests upon a broader basis. The data of Hammar's second volume are suitable for a quasi-statistical test of these assertions. This author has devoted a special chapter to the study of forty-four cases in which the diagnosis of Mors thymica or Status Lymphaticus was made, or no sufficient explanation of the death was revealed at autopsy. The conclusions reached by him are these.

1. In fatal cases of this class, the thymus is not usually enlarged. Statements to the contrary which are so frequent in the literature depend upon an underestimate of the weight of the normal thymus which, up to now, has been customary. All theories, whether of pressure or hyperthymism, based on such a belief must be rejected.

2. A separate hyperplasia of the medulla does not occur. In only two instances was the medulla found to be hyperplastic and in these there was a still greater hyperplasia of the cortex.

3. Again, a hyperplasia of the medulla in Schridde's sense, *i.e.* a subnormal Index¹, does not characterise these organs. Indeed, the Index rather tends on the average to be supra-normal.

4. Lastly, the conjecture one occasionally hears, *viz.* that in these cases of inexplicable death one has to do with infective-toxic factors, finds no support in this thymus material. Neither an accidental involution nor the new formation of Hassall corpuscles, which is characteristic of such influences, is usually present. We have here a quite different picture. In a thymus with more or less abundant but not supra-normal parenchymatous content and a high index, with no signs of accidental involution, we find a low, sometimes a subnormal number of small Hassall corpuscles. My material, which is fairly abundant, brings out the same shifting of structural form for the most part within the range of normal variation, which I recorded in my earlier communications. At the same time the previously emphasised occurrence of individual cases deviating from this type has received confirmation by means of the normal material which has since accumulated. Hammar, *op. cit.* II, 811-12.

Hammar concludes his chapter with these words:

States of special physical—or psychical—sensitivity of the organism occur which find expression in the thymus by a reduction, possibly a cessation, of the new formation of Hassall corpuscles. Sometimes these manifestations are associated with a strong development of the whole of the lymphoid tissue. What fundamental cause or causes may be at the back of these relations we do not yet know. Nothing suggests that we should seek them in the thymus. This is, as is clear, really a crystallisation of the conclusions to which I was led along another path by an analysis of normal thymus material with reference to the "Status Thymicus." *Op. cit.* II, 860.

¹ Ratio of cortex to medulla.

In other words, Hammar believes—what, I suppose, most of us believe—that there are persons whose deaths cannot be “explained” in terms of obvious pathological findings. He thinks that this peculiar lability is, or may be, the expression of some physiological abnormality perhaps of the endocrine system (see Hammar, 1, 489) and that stigmata may be found in the histological structure of the thymus. But these stigmata have only a statistical or, as he would probably prefer to call it, a numerical significance. As means of individual diagnosis these criteria will be difficult of application even by a master of the histological technique; in ordinary clinical or medico-legal practice they will be inapplicable.

Such seem to me to be the conclusions deducible from this record of a research which should command the admiration of all who value the spirit of exact scholarship. It is not, perhaps, probable that Prof. Hammar will secure a wide circle of readers. Those medical men who neither certify deaths to be due to Status Lymphaticus nor, as expert witnesses, explain the apparently inexplicable to the laity, are under no moral obligation to peruse some 1600 pages of minute description and cautious inference. The minority who do take upon themselves such responsibilities are, I conceive, under such an obligation; that they will recognise it, only an incorrigible optimist could bring himself to believe. So far, then, as practical affairs are concerned, we may be quite confident that Status Thymico-Lymphaticus, etc., is a mere legal fiction. *There is, however, some academic interest in seeking to express numerically the evidence which led Hammar to his conclusions.*

I shall therefore examine some of Hammar's data arithmetically, the problem submitted being this: We form two *groups*, by the criterion that all individuals of one group shall have this in common, that death occurred in circumstances such that no adequate objective explanation, either in the condition found at autopsy or in the overt circumstances of the death, was forthcoming. We then determine, with respect to each individual of both groups, numerical characteristics of the structure of the thymus and we inquire whether in respect of all or any of such characteristics the groups are significantly differentiated.

The primary division was made by taking all the normal children of Hammar's first volume whose ages were between 1 month and $5\frac{1}{4}$ years, and all the children assigned in the second volume to the classification “Sudden death with negative or trivial post-mortem indications.”

The numerical characteristics of the thymus used were: (1) Gross weight in grammes. (2) Index, or ratio of cortex to medulla. (3) The ratio of the number of Hassall bodies the diameters of which were from $26-50\mu$ to the number of such bodies with diameters $10-25\mu$. (4) The ratio of the number of Hassall bodies with diameters $51-100\mu$ to that of those with diameters $26-50\mu$.

Of course (2) is plainly an important criterion of the make-up of the organ; while (3) and (4) are regarded by Hammar (1, 448) as indices of the progressive or regressive changes occurring within the organ. With respect to each of these

variables, I shall enquire whether the groups are differentiated (*a*) by significant differences between the means, (*b*) by significant differences of variation around the means. The biological distinction is important. Assuming the original criterion to be well applied, the two groups are obviously differentiated. If then the function or structure under study be of importance to the well-being of the organism, it is reasonable to entertain the hypothesis that here too there will be differentiation. If, and only if, the differentiation comprises (*a*) as well as (*b*) is a presumption created that the group differentiation might, under favourable circumstances, be of value for *individual* differentiation. A differentiation of the form (*b*) merely implies that the group is less true to type and probably less biologically stable than a normal group—which we already knew—and gives no reason to suggest that the organic criterion we have selected has any special value in or relevance to the primary differentiation.

The data used are set out in Table II. Table III contains the means and coefficients of variation with their respective standard errors.

Table II. *Normal and "Abnormal" data.*

Normals						"Abnormals"					
Catalogue no.	Age (months)	Thymus wt. in gm.	Index	1st ratio	2nd ratio	Catalogue no.	Age (months)	Thymus wt. in gm.	Index	1st ratio	2nd ratio
1000	1	22.5	4.8	3.3	0.3	1524	1.5	56.0	3.0	6.2	0.5
1416	4	20.2	3.8	3.8	0.6	1489	5.0	51.34	4.2	7.8	0.8
813	5	25.0	3.2	2.3	0.4	431	16.0	51.5	6.1	11.1	0.4
910	5	31.0	3.6	3.4	0.3	976	5.0	35.0	3.2	1.8	0.7
721	23	31.0	4.5	2.0	0.3	1841	4.0	45.0	4.3	3.9	0.6
1087	24	8.0	1.1	3.1	0.3	953	2.0	30.0	3.6	13.3	0.4
1450	24	18.49	3.5	2.5	0.4	997	12.0	32.5	2.4	2.4	0.3
624	24	23.0	1.8	2.0	0.9	944	2.5	28.0	3.9	3.6	0.1
918	30	24.0	2.7	4.0	0.9	811	4.0	27.0	5.0	4.0	0.5
1492	36	13.5	1.2	3.2	0.5	1406	3.5	25.36	3.0	4.1	0.4
1801	36	18.5	3.2	2.2	0.8	1445	12.0	27.5	2.6	1.7	0.2
1871	36	29.0	2.9	2.0	0.6	1618	1.5	25.0	3.3	9.2	0.5
1094	36	35.5	1.9	1.6	0.4	955	2.25	26.0	4.3	14.6	0.4
1616	48	18.6	3.2	4.2	1.0	787	3.0	25.3	4.6	6.8	0.5
1738	48	20.6	1.6	1.7	0.9	780	2.5	25.0	3.4	8.3	0.7
1046	48	22.0	1.5	3.9	0.4	779	7.0	26.0	4.2	4.3	0.6
757	48	25.9	4.2	2.7	0.6	781	2.0	22.0	6.6	4.6	0.4
956	48	32.85	2.4	8.7	0.6	939	12.0	21.06	3.6	5.5	0.4
1799	51	28.0	2.9	4.8	0.5	1723	24.0	22.14	1.8	3.0	0.9
1429	60	18.0	2.3	2.7	0.5	444	1.75	21.6	5.5	4.0	0.4
1776	60	25.0	2.2	5.3	0.5	946	1.0	20.0	5.1	20.7	0.7
1583	60	28.0	2.5	2.6	0.4	947	1.0	20.0	3.1	7.1	0.2
1803	60	30.0	2.7	2.4	0.5	808	2.0	20.0	5.1	2.8	0.5
814	60	31.0	3.4	3.9	0.3	1531	9.0	22.0	2.9	3.4	0.2
1417	60	36.0	3.4	1.8	0.6	952	3.0	18.0	4.8	—	0.8
699/6	60	48.0	2.6	5.8	0.7	1530	2.0	19.0	2.8	1.9	0.4
1615	64.5	29.67	2.4	2.4	0.4	964	3.0	15.2	3.4	16.4	0.6
						1529	1.0	14.0	2.6	1.7	0.4
						741	4.0	15.0	1.7	2.4	0.4
						1544	1.3	13.14	2.5	25.2	0.7
						1506	1.0	10.0	3.1	2.2	0.3
						1507	1.0	9.5	4.2	2.6	0.2
						943	16.0	53.5	3.1	5.7	0.3
						949	10.5	28.0	4.7	8.2	0.4
						776	60.0	28.9	2.6	2.9	1.0

Table III.

	Normals	"Abnormals"	Difference
	Gross weight		
Mean	25.68 ± 0.80	26.56 ± 1.40	- 0.88 ± 1.61
Coefficient of variation	22.49 ± 2.17	44.31 ± 4.22	- 21.82 ± 4.75
	Index		
Mean	2.80 ± 0.13	3.72 ± 0.14	- 0.92 ± 0.19
Coefficient of variation	33.48 ± 3.40	30.80 ± 2.71	+ 2.68 ± 4.35
	1st ratio		
Mean	3.27 ± 0.21	6.57 ± 0.67	- 3.30 ± 0.70
Coefficient of variation	46.49 ± 5.11	84.44 ± 10.76	- 37.95 ± 11.91
	2nd ratio		
Mean	0.54 ± 0.03	0.48 ± 0.03	+ 0.06 ± 0.04
Coefficient of variation	37.75 ± 3.93	43.36 ± 4.10	- 5.61 ± 5.68

Gross weight.

Even taken as they stand, it is evident that the means are not differentiated and, in fact, the comparison exaggerates the difference. The "normal" group consists mainly of older children than those of the "abnormal" group; if the mean of the "normals" is corrected for age by means of the equation connecting age and weight given in Table III of Greenwood and Woods' paper (Greenwood and Woods, *op. cit.* p. 318) the mean is increased by a little more than 1 gm. and thus becomes sensibly that found for the "abnormals." This result is in complete agreement with Hammar's statement. On the other hand, there is differentiation of variability. The "abnormals" are significantly more variable than the normals. We might amend the discredited tradition by saying that those who die suddenly are indeed likely to have heavier thymi than normal persons, but they are also likely to have lighter thymi than others.

Index.

Here there is *prima facie* evidence of differentiation of means. But correction for age affects this appreciably. In the "normal" series the correlation of age with index is -0.347 ± 0.121 ; in the "abnormal" series it is -0.240 ± 0.112 . If one bases correction on the "normal" series, using the regression equation: $\text{Index} = 3.4487 - 0.0166 \text{ times Age (in months)}$, the expected index for a child of the mean age of the "abnormal" series is 3.99, actually greater, although insignificantly greater, than the observed value. The variabilities of the two groups do not differ appreciably.

First Hassall ratio.

Here both means and variabilities are differentiated. There is no indication of a sufficiently stringent association between age and ratio for age correction to affect the issue.

Second Hassall ratio.

This measure is not differentiated with respect to mean or variability.

These results confirm the four conclusions of Hammar cited above. The practical outcome is that an enumeration of the Hassall bodies *might* be of

some value for group-differentiation, were the operation carried out with the technical thoroughness which distinguishes Hammar's work; as the measure has, in a normal series, a variability little short of 50 per cent. of its mean value, its futility as an individual criterion is obvious. To this little measure does the imposing clinico-juridical concept of Status Thymicus shrink.

Since it is now obvious that we shall not find in the thymus any touchstone—still less the cause—of instability, the right course would seem to be to return to the question proposed by Paltauf and seek other criteria. These numerical analyses do no more than confirm the conclusions reached by Hammar. The suggestion is that the thymus, if examined as few men are likely to examine it, might afford differentiae of the groups which interest us, so that, almost hidden by the masses of nonsense and bad observation which forms the bulk of the literature of Status Thymico-Lymphaticus, a little truth may be discerned. What has not been shown or even made faintly probable is that an equally painstaking study of other organs or functions (bodily or psychic) would not have revealed at least as clear cut group differentiae.

(MS. received for publication 26. v. 1930.—Ed.)