AN ASSOCIATION BETWEEN THE RHEUMATIC DISEASES AND THE RETICULOSES

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It has previously been shown (Abbatt and Lea, 1958) that there is an association between the rheumatic diseases and leukaemia. Because of the inter-relationships between the various pathological conditions described as reticuloses it appeared possible that the association with rheumatic diseases might be found to apply to the whole group.

Material and Methods

The material consisted of all cases of reticuloses which occurred in males in the Armed Forces between September 4, 1939, and December 31, 1958, and for which application for pension was made to the Ministry of Pensions and National Insurance, and in which there was no evidence of exposure to either therapeutic or industrial radiation before the first signs and symptoms of the reticulosis. A total of 1,356 cases was obtained, but there may have been others. Some cases are always missed from such a series because of the method of coding, etc., but no grounds have been found for suggesting that such omissions are due to selective factors. These 1,356 cases comprised 735 of leukaemia (all types), 200 of lymphosarcoma, 377 of Hodgkin's disease, and 44 of other reticuloses (myelomatosis, Hodgkin's sarcoma, leucosarcoma, etc.).

For each case the year and place of birth, date of first signs or symptoms of reticulosis, type of reticulosis, and date of death or duration of disease were recorded. In addition, the following factors were recorded only when they clearly antedated any signs or symptoms which could be attributed to the reticulosis: fractures, injuries other than fractures, sulpha drugs, antibiotics, chronic sepsis, the rheumatic diseases, other diseases. The definitions of these factors were exactly the same as those given for the leukaemia series (Abbatt and Lea, 1958). The control series* was that used in the previous

investigation (Abbatt and Lea, 1958) and consisted of 1,378 cases for which the same details were recorded as for the reticuloses series.

The reticulosis and control series were then divided in two ways:

- (1) By age at onset into three groups: 15-24, 25-34, and 35 years and over;
- (2) By years of onset from 1940 to 1958 inclusive.

The reasons for these two methods of division were:

(1) For the factors fractures, injuries other than fractures, chronic sepsis, rheumatic diseases, and other diseases, it is obvious that the longer a man has lived before developing a reticulosis or the control condition the greater is the probability that he has met with one or more of them. Division into age groups at onset is therefore essential.

(2) Sulpha drugs and antibiotics have come into general use only since 1939, and the probability of having received them will therefore vary, other things being equal, with the year in which the reticulosis or the control condition was treated. Direct comparison of the incidence of these drugs in two groups of cases, one developing some condition in 1940 and the other in 1958, would clearly be absurd (for the present purposes). For these factors the reticulosis and control series have therefore been compared year by year.

Comparisons were made between the various types of reticulosis, between each type and the control series, and between all reticuloses and the control series, for all these factors.

Results

No significant differences between the four groups of reticuloses were found for the possible factors fractures, injuries other than fractures, and chronic sepsis. The data from the four groups were then combined to give "all reticuloses" and these were compared with the control series (for method of comparison see Appendix). The results are shown in Table I (opposite).

* The question of control groups for the 1958 investigation was discussed in the first place with Dr. C. A. B. Smith at the Galton Laboratory. The points specifically made were:

- (1) the vexed question of whether leukaemia and the reticuloses generally are true neoplasms;
- (2) if the reticuloses are neoplasms, whether a control series made from other neoplasms would be adequate.

It was decided that at least two control series would be necessary in view of the present state of ignorance of the nature of these diseases, one series of what are generally agreed to be neoplasms but excluding the reticuloses, and the other of all diseases and injuries. Then, if these two series showed no significant differences between them, they could be combined and we should have a series of adequate size for our purpose and demonstrate at the same time that there was a difference between the reticuloses and the "other neoplasms". This actually did happen in the course of the investigation.

TABLE I

COMPARISON OF ALL RETICULOSES AND CONTROLS FOR THE FACTORS FRACTURES, OTHER INJURIES, AND CHRONIC SEPSIS

Factors	Series	* Age Groups (yrs)			Sum of Differences in Proportion
		15-24	25-34	35 and Over	
Fractures	All Reticuloses	50(14·0)	84(16·7)	87(17·5)	0·0244 ± 0·0412 less than s.e. not significant
	Controls	53(11·2)	75(15·3)	80(19·3)	
Other Injuries	All Reticuloses	49(13·8)	111(22·1)	124(24·9)	0·0438 ± 0·0458 less than s.e. not significant
	Controls	71(15·0)	108(22·0)	92(22·2)	
Chronic Sepsis	All Reticuloses	16 (4·5)	36 (7·2)	31 (6·2)	0·0457 ± 0·0245 1·9 times s.e. not significant
	Controls	18 (3·8)	23 (4·7)	20 (4·8)	
All Cases	All Reticuloses	356	503	497	1,356
	Controls	474	490	414	

* Figures in brackets are percentages of that age group.

It will be seen that none of the observed differences is significant. The incidence of antibiotics in the reticulosis and control series was compared for each year, and the sum of the differences in proportion found to be $0·0086 \pm 0·2524$, *i.e.* much less than its standard error. In addition, there were four negative values of the differences in proportion, so that there was no evidence whatever to incriminate antibiotics as a factor in the production of reticuloses.

The position with sulpha drugs was not so clear. These again were compared year by year, and the sum of the differences in proportions was found to be $0·8844 \pm 0·2946$, three times the standard error. This in itself was significant at the 0·01 level, but the data showed no consistency, the differences were negative for four of the years, and the significance was due to the events of one year, 1953. Without the contribution of this year the sum of the differences in proportion was only 1·7 times its standard error. Sulpha drugs cannot be dismissed as unconnected, but the evidence is certainly not strong enough to incriminate them. Further investigation is required.

The position of the rheumatic diseases will be given in detail. They are here defined as all those conditions at present classified under this heading with the exception of arthritis following trauma. This factor was recorded in two ways:

- (1) Those cases in which there was hospital investigation of the rheumatic disease with positive findings,

- (2) All cases including those with only a history of rheumatic disease.

The incidence of rheumatic disease, divided in this way, by age groups, for the various reticuloses, for all reticuloses, and for the control series, is shown in Table II (overleaf).

The results of comparing the incidence of rheumatic disease, "all" and "confirmed", within the group of reticuloses is shown in Table III (overleaf). In no instance was the sum of the differences of proportion as great as its standard error.

The different reticuloses were then compared with the control series for this factor (Table IV, overleaf).

With the exception of the group of "Other Reticuloses", in which there were only 44 cases, the observed excess of the rheumatic diseases in the reticuloses was very highly significant, the probability of its being due to chance being less than 1 in 1,000 in each group.

Having established that there were no significant differences in the incidence of the rheumatic diseases within the group of reticuloses, it was now possible to combine the evidence from them and compare it with the control series. The results of this comparison were:

- (a) for *All Rheumatic Diseases*, the sum of the differences in proportion was $0·1889 \pm 0·0300$ (6·3 times s.e., *P* less than 10^{-9})
- (b) for *Confirmed Rheumatic Diseases*, the sum of differences in proportion was $0·1368 \pm 0·0224$ (6·1 times s.e., *P* less than 10^{-8}).

TABLE II
THE INCIDENCE OF THE RHEUMATIC DISEASES IN RETICULOSES AND CONTROL SERIES

Series		* Age Groups (yrs)			Totals
		15-24	25-34	35 and Over	
<i>Leukaemia</i>	All rheumatic disease	14(6·7)	21 (8·0)	45(17·0)	80(10·9)
	Confirmed rheumatic disease ..	5(2·4)	13 (4·9)	32(12·1)	50 (6·8)
	All cases	208	263	264	735
<i>Lymphosarcoma</i>	All rheumatic disease	1(2·6)	9(11·1)	12(15·0)	22(11·0)
	Confirmed rheumatic disease ..	1(2·6)	5 (6·2)	8(10·0)	14 (7·0)
	All cases	39	81	80	200
<i>Hodgkin's Disease</i>	All rheumatic disease	3(2·9)	12 (8·4)	21(16·2)	36 (9·5)
	Confirmed rheumatic disease ..	2(1·9)	5 (3·5)	12(10·0)	20 (5·3)
	All cases	104	143	130	377
<i>Other Reticuloses</i>	All rheumatic disease	0(0·0)	1 (6·3)	5(21·7)	6(13·6)
	Confirmed rheumatic disease ..	0(0·0)	0 (0·0)	4(17·4)	4 (9·1)
	All cases	5	16	23	44
<i>All Reticuloses</i>	All rheumatic disease	18(5·1)	43 (8·5)	83(16·7)	144(10·6)
	Confirmed rheumatic disease ..	8(2·2)	23 (4·6)	57(11·5)	88 (6·5)
	All cases	356	503	497	1356
<i>Controls</i>	All rheumatic disease	10(2·1)	16 (3·3)	25 (6·0)	51 (3·7)
	Confirmed rheumatic disease ..	1(0·2)	5 (1·0)	14 (3·4)	20 (1·5)
	All cases	474	490	414	1378

* Figures in brackets are percentages of that age group.

TABLE III
COMPARISON OF THE RETICULOSES WITH EACH OTHER FOR THE FACTOR RHEUMATIC DISEASES

Rheumatic Diseases	Comparison	Sum of Differences in Proportion	Significance
<i>All</i>	Leukaemia with Lymphosarcoma	0·0309 ± 0·0728	less than s.e. not significant
	Leukaemia with Hodgkin's Disease	0·0430 ± 0·0557	less than s.e. not significant
	Leukaemia with Other Reticuloses	0·0377 ± 0·1556	less than s.e. not significant
	Lymphosarcoma with Hodgkin's Disease	0·0125 ± 0·0735	less than s.e. not significant
	Lymphosarcoma with Other Reticuloses	0·0068 ± 0·1411	less than s.e. not significant
	Hodgkin's Disease with Other Reticuloses	0·0057 ± 0·1353	less than s.e. not significant
<i>Confirmed</i>	Leukaemia with Lymphosarcoma	0·0073 ± 0·0566	less than s.e. not significant
	Leukaemia with Hodgkin's Disease	0·0404 ± 0·0447	less than s.e. not significant
	Leukaemia with Other Reticuloses	0·0207 ± 0·1136	less than s.e. not significant
	Lymphosarcoma with Hodgkin's Disease	0·0331 ± 0·0574	less than s.e. not significant
	Lymphosarcoma with Other Reticuloses	0·0134 ± 0·1208	less than s.e. not significant
	Hodgkin's Disease with Other Reticuloses	0·0197 ± 0·1049	less than s.e. not significant

Discussion

The problem of retrospective evidence of the type used here was debated by the Medical Section of the Royal Statistical Society in 1956, and the following conclusion was reached: "routine medical records have a real part to play in research, provided too much is not expected of them" (Royal Statistical Society, 1956).

The validity of evidence obtained from records of this type, and of retrospective surveys in general was fully discussed in a previous paper (Abbatt and

Lea, 1958). The arguments used there apply equally to this evidence. However, two points in particular need special consideration in the present context.

(1) Cases in which none of the factors were recorded before the onset of the reticulosis should clearly decrease in numbers with advancing age. This is well shown in the combined reticulosis series, the proportions of such cases in the age groups 15-24, 25-34, and 35 years and over being respectively 36·5, 16·1, and 12·3 per cent.

TABLE IV

COMPARISON OF THE RETICULOSES WITH THE CONTROLS SERIES FOR THE FACTOR RHEUMATIC DISEASES

Rheumatic Diseases	Comparison	Sum of Differences in Proportion	Significance
<i>All</i>	Leukaemia with Control Series	0.2034 ± 0.0332	6.1 times s.e. very highly significant
	Lymphosarcoma with Control Series	0.1725 ± 0.0469	3.7 times s.e. very highly significant
	Hodgkin's Disease with Control Series	0.1600 ± 0.0387	4.1 times s.e. very highly significant
	Other Reticuloses with Control Series	0.1657 ± 0.0954	1.7 times s.e. not significant
<i>Confirmed</i>	Leukaemia with Control Series	0.1485 ± 0.0245	6.1 times s.e. very highly significant
	Lymphosarcoma with Control Series	0.1362 ± 0.0300	4.5 times s.e. very highly significant
	Hodgkin's Disease with Control Series	0.1081 ± 0.0265	4.1 times s.e. very highly significant
	Other Reticuloses with Control Series	0.1278 ± 0.0529	2.4 times s.e. not significant

(2) It is to be expected that the incidence of rheumatic diseases will increase with advancing age, and that the significance of the differences between the reticulosis and control groups will also vary in the same way. The internal structure of the differences between the combined reticuloses and the control series was therefore investigated (Table V).

It will be seen that the expected effect is very well shown, for both "all" and "confirmed" rheumatic disease. The presence of this effect is of particular importance as it would not be expected to occur if the rheumatic diseases in these series represented merely a "rheumatoid" type of onset of the reticulosis.

The evidence demonstrates a very definite association between the reticuloses and the rheumatic diseases. This association means that the presence of a rheumatic disease in an individual increases the probability that one of the reticuloses will develop. The evidence does not allow of any explanation of this association between these two ill-defined disease groups, nor does it provide any fresh information on their nature. It does not seem likely that evidence of this type will help to solve these problems.

Summary

Two series of cases have been obtained from the records of the Ministry of Pensions and National Insurance. One consisted of 1,356 cases of reticulosis, the other of 1,378 cases of diseases, injuries, and neoplasms other than the reticuloses. The incidence in these series of factors alleged or thought possibly to be involved in the production of the reticuloses was compared.

Associations between the reticuloses and the rheumatic diseases were found. The probability that these associations were due to chance was, in all cases, less than one in one thousand. The evidence does not permit of an explanation of this association.

I am greatly indebted to Dr. John D. Abbatt, who was unfortunately prevented from collaborating in this paper, for permission to use the control and other series prepared in association with him and also for helpful advice and criticism. I also thank the Chief Medical Officer of the Ministry of Pensions and National Insurance for permission to publish data taken from the records of the Ministry.

TABLE V

INTERNAL STRUCTURE OF DIFFERENCES BETWEEN COMBINED RETICULOSES AND CONTROL SERIES IN THE INCIDENCE OF THE RHEUMATIC DISEASES

Rheumatic Diseases	Age Group (yrs)	Sum of Differences in Proportion	Significance
<i>All</i>	15-24	0.0295 ± 0.0141	2.1 times s.e., not significant
	25-34	0.0528 ± 0.0141	3.7 times s.e., $P < 10^{-3}$
	35 and Over	0.1066 ± 0.0224	4.8 times s.e., $P < 10^{-5}$
<i>Confirmed</i>	15-24	0.0204 ± 0.0100	2.0 times s.e., not significant
	25-34	0.0355 ± 0.0100	3.6 times s.e., $P < 10^{-3}$
	35 and Over	0.0809 ± 0.0173	4.7 times s.e., $P < 10^{-5}$

REFERENCES

Abbatt, J. D., and Lea, A. J. (1958). *Lancet*, 2, 880.
Royal Statistical Society (1956). *Brit. med. J.*, 2, 1479.

APPENDIX

The method of comparison used was suggested by Dr. C. A. B. Smith and is derived from a consideration of the Fisher-Irwin-Yates exact treatment of 2×2 tables. For example, if, in any age group, the number of men developing a reticulosis was n_a and of these x_a had suffered from one of the rheumatic diseases before the onset of the reticulosis and y_a had not, and, similarly, in the same age group n_b men developed the control condition, x_b having had one of the rheumatic diseases previously and y_b not, then a Table can be constructed as follows:

	Rheumatic Disease	No Rheumatic Disease	Totals
Reticulosis . .	x_a	y_a	n_a
Control condition . .	x_b	y_b	n_b
Totals . .	X	Y	N

It can be then shown that the difference between the two series in the proportion of men with rheumatic disease is

$$\frac{x_a}{n_a} - \frac{x_b}{n_b} \text{ with variance } \frac{XY}{(N-1)n_a n_b}$$

This process is repeated for each age group and the differences in proportion summed, also the

variances. The standard error of the sum of the differences in proportion is then given by the square root of the sum of the variances, so that finally we have:

Sum of Differences in Proportion

$$= S\left(\frac{x_a}{n_a} - \frac{x_b}{n_b}\right) \pm \sqrt{S\left(\frac{XY}{(N-1)n_a n_b}\right)}$$

Une association entre les maladies rhumatismales et les réticuloses

RÉSUMÉ

On a recueilli deux séries de cas parmi les fiches du Ministère des Pensions et de l'Assurance Nationale. Une série consistait en 1,356 cas de réticulose et l'autre en 1,378 cas de maladie, accident ou néoplasme autre que réticulose. On a comparé dans ces deux séries l'incidence des facteurs qu'on présumait ou soupçonnait de jouer un rôle dans la production des réticuloses. On a trouvé des associations entre les réticuloses et les maladies rhumatismales. La probabilité que ces associations soient due au hasard était, dans tous les cas, moins d'une sur mille. On ne trouva pas de données pouvant expliquer cette association.

La asociación entre las enfermedades reumáticas y las reticulosis

SUMARIO

Se recogieron dos series de casos en los registros del Ministerio de Pensiones y de Seguro Nacional. Una serie comprendía 1,356 casos de reticulosis y la otra 1,378 casos de enfermedad, accidente o neoplasia otra que reticulosis. Se comparó en ambas series la incidencia de los factores, alegados o sospechados, que hubieran podido jugar un papel en la producción de reticulosis. Se encontraron asociaciones entre las reticulosis y las enfermedades reumáticas. La probabilidad de que estas asociaciones sean debidas al azar era, en todos los casos, inferior a uno por mil. No hay datos para explicar esta asociación.