Blood Groups and Diabetes Mellitus

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Aird, Bentall and Roberts' discovery[1] of a relationship between the incidence of gastric carcinoma and blood group A promoted a number of studies on the relationship between blood groups and various diseases, such as duodenal ulcer, gastric ulcer, gastric carcinoma, pernicious anemia, cancer of the colon and rectum, cancer of the breast, cancer of the lung, and diabetes.[8] In the three first-mentioned diseases the evidence supplied by the different investigators appears to be so strong and consistent that it seems fairly certain that a relationship exists between duodenal and gastric ulcer and Group O as well as between gastric carcinoma and Group A. There are marked indications also that Group A persons are particularly apt to develop pernicious anemia.

There is fairly strong evidence that diabetes mellitus is commoner in people of Group A, but as to the other diseases mentioned the results are negative.

In 1955 and 1956 two papers on the distribution of blood groups among diabetics were published. Craig and Wang[4] performed ABO blood groupings on 817 diabetic patients treated at the Victoria Infirmary, Glasgow. The series as a whole, as well as classified by sex, age, and weight when diabetes was diagnosed, showed no significant differences from a control series of blood donors. By dividing the series into various subgroups, the authors succeeded in demonstrating that all overweight patients, as well as patients with a family history of diabetes or obesity, showed a significantly reduced frequency of Group O as compared with all other blood groups combined. This was particularly marked when both factors were combined. Conversely, all nonobese diabetics and all male diabetics without a family history of diabetes showed a significant predominance of Group O compared with all other blood groups. The authors conclude that without confirmation from other series the divergences which they found cannot be interpreted as more than possible factors in "the natural history of diabetes mellitus."

In an analysis of 1,333 patients with diabetes mellitus from Liverpool and Oxford, McConnell, Pyke, and Roberts[3] found that among male diabetics there was a marked increase in the relative number of Group A persons compared with the control series which consisted of donors from the respective areas. Diabetic women, on the other hand, did not show significant divergences from the control series. Among the males the excess of Group A was greatest among the young patients whose diabetes began before the age of thirty, but the difference between this group and the other groups was not significant. On the other hand, both groups, combined as well as separately, differed significantly from the control series. The excess of Group A among the males was far more marked in cases where a close relative also suffered from diabetes. On the basis of these findings, the authors advance the hypothesis that the excess of Group A among the males may be characteristic of a special type of diabetes rather than of the disease as a whole. They do not consider the difference in the distribution as definitely proved, and only submit it for further trial.

The Oxford series was also investigated from the point of view of the distribution of Rh positive and Rh negative as well as MN types which did not differ significantly from the control series.

Since the results of these two British investigations are to some extent conflicting, it was decided to study a Danish series of diabetics to find out whether the ABO groups among Danish diabetics differ from those among the general Danish population. In addition, it was decided to investigate the frequency of the Lewis group Le(a+) in the Danish diabetic series to ascertain whether a relationship exists between diabetes and the secretor status Le(a+) persons are nonsecretors of blood group substances A, B, and H. Lastly, it was considered expedient to combine the ABO grouping with a routine Rh grouping.

PRESENT INVESTIGATION

Diabetic Series. The series comprises 992 diabetics treated at the Hvidøre Hospital, Copenhagen, during the period Aug. 20, 1956, to Sept. 20, 1958. The diagnosis was based on considerably elevated fasting blood sugar or a glucose tolerance curve of a diabetic type. A relatively large proportion of the patients, viz. 46 per cent, were under thirty years of age at the onset of diabetes. Classification by residence was evenly distributed over the whole of Denmark.

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Control series. As control material we used primarily a medicolegal series of 12,122 blood samples.[5] In this series, which is derived from all parts of Denmark, but with some preponderance for the cities, particularly Copenhagen, the distribution of the blood groups is given separately for males and females. Moreover, we used another five series comprising 27,332 donors from all Denmark, but with some preponderance for Copenhagen, and 9,682 patients, mainly from Copenhagen. In these five series the blood groups are not stated separately for males and females. The six series do not differ significantly from each other so far as the distribution of the ABO groups is concerned (table 1).

TABLE 1
Control series

Origin of material and author	No.	O	A	B	AB
All Denmark, paternity cases (males), Gürtler[5]	7,122	41.4	44.6	10.4	3.6
All Denmark, paternity cases (females), Gürtler[5]	5,000	41.9	43.5	10.1	4.5
Copenhagen, 2,784 donors, 6,754 patients, Jordal[6]	9,538	42.0	43.5	9.8	4.7
Copenhagen, donors, Bryde-Andersen[2]	14,304	40.6	44.0	10.9	4.5
Fifteen provincial towns, donors, Sørensen[9]	9,200	41.4	41.2	11.3	6.1
Sønderborg County Hospital, donors, Sørensen[9]	1,044	40.4	41.7	12.1	5.8
Sønderborg County Hospital, patients, Sørensen[9]	2,928	43.1	43.2	10.0	3.7
Total material	49,136	41.4	43.3	10.6	4.7

The distribution of the ABO groups in the total control series must be considered representative of the ABO distribution in Denmark.

As a control on the distribution of the Rh groups, Rh positive (D positive) and Rh negative (D negative) in the diabetic series we used Lyndrup's series of 4,319 Rh groupings[7] which consisted of 2,701 mothers and 1,618 men, mainly from paternity cases. This series is derived from all parts of Denmark. The mothers and the men, each category considered separately, must be regarded as random samples of the population as far as the distribution of blood groups is concerned. Lyndrup found 81.4 per cent Rh positive and 18.6 per cent Rh negative.

As a control on the distribution of the Lewis groups Le(a+) and Le(a—) in the diabetic material we used Jordal's series from 1957[6] consisting of 5,208 blood samples from adult men and women studied in connection with paternity cases. These samples were derived from the whole of Denmark and, according to Jordal, they did not differ significantly in regard to ABO distribution from values reported by Gürtler[5] and Andersen.[2]

TECHNIC AND RESULTS

All the blood groupings were carried out in the Blood Group Department of Statens Seruminstitut on blood samples drawn by venipuncture. Two drops of test serum were mixed with one drop of a 3-4 per cent suspension of red cells in saline in a round-bottomed tube (10 x 70 mm.). After two hours' incubation at 20°C. (ABO and Lewis grouping) or at 37°C. (Rhesus grouping) the readings were taken with the naked eye while cautiously shaking the tubes. All the test sera used contained "complete" or saline-agglutinating antibodies. The results are given in table 2.

ABO System. Table 3 shows a preponderance of Group O in male as well as female diabetics compared with the control series. Although there is no difference between the ABO groups of males and females, the males showed a significantly larger number of Group O persons than did the controls ($P<1$ per cent).

In table 4 the diabetic series is classified into groups, age at the onset of diabetes and the frequency of Group O compared with the frequency of the other three groups combined in each age group.

Table 4 shows that there is a tendency for the excess of Group O to manifest itself especially in cases with early onset of diabetes. If the series is divided according to whether the disease set in before or after the thirtieth year of age, as did Craig and Wang[4] and McConnell, Pyke, and Roberts,[3] there is a significant excess of Group O in males as well as females with an onset of diabetes prior to the age of thirty. That the ABO distribution in the total female series does not differ significantly from the controls may be due to the fact that a large proportion of the women did not develop diabetes until after the thirtieth year of age. The men as a whole showed a significant excess of persons with Group O. In those whose diabetes had not set in until after the thirtieth year of age, however, this excess of Group O persons was not significant compared with the control series.

There is no correlation between a family history of diabetes and the distribution of ABO blood groups, either for the entire series, or for the separate age groups. A family history of diabetes was elicited in about half the cases, evenly distributed over all four ABO groups (table 5).

Further subdivision of the series according to the nature of treatment or the presence of complications was not believed to serve any purpose.

TABLE 2

Distribution of ABO, Rh, and Le(a+) groups in 992 diabetics

	O		A		B		AB		Rh-positive		Rh-negative		Le(a+)		Le(a—)	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Males	246	48.34	203	39.88	44	8.64	16	3.14	425	83.50	84	16.50	114	22.40	395	77.60
Females	217	44.93	198	40.99	50	10.35	18	3.73	398	82.41	85	17.59	117	24.22	366	75.78
Both sexes	463	46.67	401	40.42	94	9.48	34	3.43	823	82.96	169	17.04	231	23.29	761	76.61

TABLE 3

ABO distribution in the diabetic series compared with the control series

Males	Observed distribution	Computed distribution I*	Computed distribution II†	χ^2 test I*	χ^2 test II†
O	246	210.73	210.73	5.903	5.903
A	203	220.40	227.01	1.374	2.539
B	44	53.95	52.94	1.835	0.294
AB	16	23.92	18.32	2.632	0.294
Total	509	509.00	509.00	11.744	9.030

Females	Observed distribution	Computed distribution I	Computed distribution II	χ^2 test I	χ^2 test II
O	217	199.96	202.38	1.452	1.056
A	198	209.14	210.11	0.593	0.698
B	50	51.20	48.78	0.028	0.031
AB	18	22.70	21.74	0.973	0.643
Total	483	483.00	483.01	3.046	2.428

*Computed on basis of combined control series using the following ABO distribution: O: 41.4; A: 43.3; B: 10.6; AB: 4.7.

†Computed on the basis of Gürtler's series, with the following separate distribution of ABO groups: *Males*: O: 41.4; A: 44.6; B: 10.4; AB: 3.6. *Females*: O: 41.9; A: 43.5; B: 10.1; AB: 4.5.

Rhesus System. As evident from table 2, eighty-four out of 509 male diabetics (16.50 per cent) were Rh negative, whereas the corresponding value for the females was eighty-five out of 483 or 17.59 per cent. In the control series of 4,319 males and females (not specified) 18.6 per cent were Rh negative. The deviation from the control series was 1.16 times the mean error for the males and 0.54 times the mean error for the females. In other words, the distribution of Rh positive and Rh negative persons in the diabetic series does not differ significantly from the control series.

Lewis System. Out of the 509 male diabetics 114 or 22.40 per cent were Le(a+) and the females 117 of 483 or 24.22 per cent. Jordal's findings[6] were as follows: 530 out of 3,070 males or 17.26 per cent and 392 out of 2,138 females or 18.33 per cent. Comparison between the diabetic and the control series gave the result that for the males the deviation was 2.79 times the mean error and for the females 2.96 times the mean error.

For the males as well as the females there was an increased frequency of Le(a+) group as compared with the control series. These differences were highly significant ($P = .0003$).

The Lewis group determinations were not carried out by the same technic in the diabetic series and in the control series. Jordal[6] used a slide technic, one drop of test serum and one drop of a 5 per cent suspension of red cells mixed on a glass slide and left in a moist chamber for twenty minutes. Jordal states that only definitely positive reactions were designated as positive. Since frequently divergences in the incidence of the Le(a+) group are explicable by weak reactions, presumably due to "cross reaction" with "strong" Le(a—b+) cells, the diabetic series was analyzed to ascertain whether the 231 Le(a+) reactions included some which might be characterized as weak. We found twenty which were weaker than the other 211. Out of these twenty, ten were A_1 and the remainder O or A_2. Since the A_1 character exerts an epistatic action upon the Le(b+) character on the blood

TABLE 4

ABO distribution in the different age groups of the diabetic series

	Males					Females				
Age	No.	Group O		Groups A+B+AB		Age	No.	Group O		Groups A+B+AB	
		No.	Per cent	No.	Per cent			No.	Per cent	No.	Per cent
0- 9	55	30	54.5	25	45.5	0- 9	52	30	57.7	22	42.3
10-19	107	53	49.5	54	50.5	10-19	97	48	49.5	49	50.5
20-29	95	47	49.5	48	50.5	20-29	52	25	48.1	27	51.9
30-39	83	37	44.6	46	55.4	30-39	42	17	40.5	25	59.5
40-49	88	45	51.1	43	48.9	40-49	70	29	41.4	41	58.6
50-59	56	26	46.4	30	53.6	50-59	110	46	41.8	64	58.2
60 and over	25	8	32.0	17	68.0	60 and over	60	22	36.7	38	63.3
Total	509	246		263			483	217		266	

TABLE 5

Distribution of Group O in the different age groups, subdivided according to familial predisposition

Age	Males						Females					
	With family predisposition			Without family predisposition			With family predisposition			Without family predisposition		
	Total No.	Group O No.	Group O Per cent	Total No.	Group O No.	Group O Per cent	Total No.	Group O No.	Group O Per cent	Total No.	Group O No.	Group O Per cent
0- 9	27	13	48.1	28	17	60.7	24	15	62.5	28	15	53.6
10-19	60	28	46.7	47	25	53.2	50	25	50.0	47	23	48.9
20-29	44	22	50.0	51	25	49.0	23	11	47.8	29	14	48.3
30-39	40	17	42.5	43	20	46.5	28	11	39.3	14	6	42.9
40-49	53	24	45.3	35	21	60.0	38	19	50.0	32	10	31.3
50-59	21	12	57.1	35	14	40.0	63	24	38.1	47	22	46.8
60 and over	5	3	60.0	20	5	25.0	30	10	33.3	30	12	40.0
Total	250	119		259	127		256	115		227	102	

cells there were presumably only the ten O and A_2 samples which may have reacted with anti-Le^a due to a "cross reaction" with a "strong" Le(b+) receptor. Even after exclusion of the ten weak O and A_2 Le(a+) samples, there is still a significant difference between the diabetic series and the control series ($P = 0.02$ for both male and female diabetics).

DISCUSSION

Unlike the studies on the ABO distribution in duodenal ulcer, gastric ulcer, and gastric carcinoma with fairly consistent results from the different countries, the diabetic series show marked divergences. What is most difficult to explain is the finding of McConnell[3] and his associates that the divergence concerns particularly Group A, whereas Craig and Wang[4] and the present authors found Group O to differ most from the control series.

McConnell and his associates mention the possibility that the Group A excess may be a characteristic of a special "type" of diabetes, differing "genetically" from other forms of diabetes. If so, the Group O excess might be characteristic of another "type" of diabetes, reduced frequency of Group O without a simultaneous excess of Group A characteristic of a third "type," etc. If differences in the distribution of the ABO groups reflect differences in genetic "types" of diabetes, these different "types" must int. al. be of a different geographical distribution. The "type" characterized by the excess of Group A would in that case be very uncommon in Scotland and Denmark, but common around Liverpool and Oxford. Both McConnell and his associates as well as the present authors have shown that the distribution of ABO groups in diabetics differs significantly from the control series only in the case of the males, whereas the ABO distribution in female diabetics does not differ significantly from the control series. Then, the women, at any rate after the age of thirty, might be particularly sensitive to a special "type" of diabetes independent of the ABO system and equally widespread in the different geographic areas. This entire theory that persons of different ABO groups might possess a different sensitivity to a special "type" of diabetes is very interesting. At our present stage of knowledge, however, it must be considered a purely speculative attempt at explaining certain incongruities between the findings.

Other factors too may influence the ABO distribution in a diabetic series. If the diabetics are closely related, the material will show a variation too marked in relation to the theoretical variation determined by the binomial distribution. In our series, only ten patients were known to be related. Our diabetic series comprises all social classes and is derived from all parts of Denmark. Since the distribution of social groups and geographic areas in the diabetic and control series is not known, a divergence in the ABO distribution may occur between the two materials, if social or geographic factors influence the ABO distribution. It is not known whether this is so in Denmark.

As mentioned above, the Rh distribution did not differ significantly from the distribution in the controls. In this respect, it conforms with the Oxford series.

The difference between the total diabetic series and the control series in respect to the Lewis group, Le(a+), was highly significant. Le(a+) persons are nonsecretors of blood group substances A, B, and H which are excreted by the secretors int. al. in the saliva parallel to the occurrence of the corresponding antigen on the blood cells. This secretor function is dependent upon a gene, called the Se gene with the corresponding inactive allele se. The Lewis group on the blood cells is the result of an interaction between genes on several loci, int. al. the secretor genes. The Lewis group Le(a+) presupposes that the person concerned is homozygotic with regard to the gene se, viz., that he is a nonsecretor. Thus, it seems as if the nonsecretor status favors the development

of diabetes, independently of the ABO group.

The genetic composition of the population is probably not in equilibrium, and this applies to diabetes as well as to blood groups. It may be imagined, therefore, that in fact the blood group distributions found are "snapshots" of a dynamic process. The conflicting results from the three areas, Glasgow, Liverpool-Oxford, and Denmark, might indicate that the diabetic-genetic and blood group-genetic evolution of the population has reached different steps in the three areas. One of the factors which might be imagined to interfere with the diabetic-genetic development is insulin therapy. It must be assumed, however, that insulin therapy has been initiated at approximately the same time and with approximately the same efficacy in all three areas. Incidentally, it is so fairly recent that its influence upon the diabetic-genetic composition of the population cannot have left its mark except on the younger age groups. In this connection it is perhaps of importance that in all three materials the most marked divergences in ABO distribution as compared with the control series were found in patients whose diabetes had set in prior to the thirtieth year of age.

The results of the attempts to elucidate the genetic background of diabetes by means of blood group studies are so conflicting and so inexplicable, however, that they can only lead to the conclusion that no regularity has been demonstrated in the relationship between diabetes and the ABO blood group system.

The excess of Le(a+) group in male as well as female diabetics of the present series indicates a possible relationship between diabetes and the nonsecretor status. It must be tested, however, on new and larger series to learn whether nonsecretor status is tantamount to increased sensitivity to diabetes.

SUMMARY

A total of 992 diabetics from Denmark were studied with regard to ABO, Rh and Le(a+) groups.

Compared with the control series there was a significant excess of Group O among the male diabetics. In diabetic females, too, there was an excess of Group O, but not significant.

The distribution of Rh positive and Rh negative persons did not differ significantly from the control series.

A significant excess of Group Le(a+) was found in male as well as female diabetics. Since Le(a+) persons are nonsecretors of A, B, and H substance, these results indicate that possibly the nonsecretor status means an increased susceptibility to diabetes.

Comparison with the divergences within the ABO system found in other series showed results so conflicting that they must lead to the conclusion that so far no regularity in the relationship between diabetes and the ABO system has been demonstrated.

SUMMARIO IN INTERLINGUA

Gruppos de Sanguine e Diabete Mellite

Un total de 992 diabeticos ab omne partes de Danmark esseva studiate con respecto al gruppos de sanguine ABO, Rh, e Le(a+).

In comparation con le series de controlo, diabeticos mascule includeva un excesso de representantes del gruppo O. Inter le diabeticos feminin il etiam habeva un excesso de representantes de gruppo O, sed iste excesso non esseva statisticamente significative.

Le distribution de subjectos Rh-positive e Rh-negative inter le diabeticos non differeva significativemente ab le correspondente distribution in series de controlo.

Un excesso significative de representantes del gruppo Le(a+) esseva trovate inter le masculos si ben como inter le femininas diabetic. Viste que personas del gruppo Le(a+) es non-secretores de substantia A, B, e H, iste resultatos suggere que possibilemente le stato de non-secretor significa un augmentate susceptibilitate a diabete.

Un comparation del divergentias intra le systema ABO trovate in altere series produceva resultatos de character si contradictori que on debe concluder que al tempore presente nulle regularitate ha essite demonstrate in le relationes inter diabete e le systema ABO.

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