

Blood Groups and Lung Cancer

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Analyses of the relative frequencies of the major blood groups in a series of patients suffering from various disease states have helped to indicate the genetic component which, to a greater or lesser extent, is present in most human illnesses. This study is directed to a consideration of the ABO and Rhesus groups in cases of carcinoma of the lung.

Material

The ABO and Rhesus blood groups were determined in 1257 men with lung cancer; in 802 instances there was sufficient histological material available for the tumour to be classified as differentiated or undifferentiated and for the type of differentiation to be determined; in most of the remaining cases the diagnosis was made on clinical and radiological evidence. The proportions of men with the several blood groups were compared with a control series which consisted of 9649 individuals from this part of South West Wales whose blood groups were determined in this laboratory (Ashley and Davies, 1966a).

Results

The findings in the case of the ABO blood groups are set out in Table I. In the over-all series, which included many patients in whom the diagnosis was made on clinical and radiological grounds only, without histological confirmation, no significant differences in blood group frequencies from the control population were noted. There was a low frequency of blood group O and a high frequency of blood group A in the patients whose lesions were proximal and could be seen at bronchoscopy, and a high frequency of blood group O and a low frequency of blood group A in the patients whose lesions were more distally situated.

The two subgroups of patients with proximal and distal lesions were compared. The frequency of blood group O was significantly lower (χ^2 5.8; $p < 0.02$) in the patients with proximal lesions than in the patients with distal lesions: the frequency of

TABLE I

ABO BLOOD GROUPS IN PATIENTS WITH LUNG CANCER

	Total	O		A	
		Obs.	Exp.	Obs.	Exp.
Control series	9649	4479		3860	
Total cases	1257	581	583.5	506	502.9
Operable	334	153	155.0	129	133.6
Inoperable	923	428	428.5	377	369.2
Bronchoscopy positive	693	299	321.7	297	277.2
Bronchoscopy negative	564	282	261.8	209	225.6
Operable bronchoscopy positive	136	54	63.1	57	54.4
Operable bronchoscopy negative	198	99	91.9	72	79.2
Inoperable bronchoscopy positive	557	245	258.6	240	222.8
Inoperable bronchoscopy negative	366	183	169.9	137	146.4

blood group A was significantly higher (χ^2 4.3; $p < 0.05$) in the patients with proximal lesions than in those with distal lesions.

No significant differences were observed when the two groups of patients with operable and inoperable lesions were compared.

Each of the subgroups operable and inoperable was in turn subdivided according to whether the lesion was proximal or distal in situation. In each group there was a low frequency of group O and a high frequency of group A in the patients with proximal lesions, and a high frequency of group O and a low frequency of group A in the patients with distal lesions. These differences did not reach the 5% level of statistical significance. No significant differences in respect of blood group B were found in this series.

Blood groups were recorded in the cases of 802 men who had lung cancer which was confirmed by histological examination. These were divided into three groups: 206 men had undifferentiated tumours, 407 men had tumours showing squamous differentiation, and 126 had tumours showing glandular differentiation (Table II). When the blood group proportions were compared with those in the control series, there was an excess of group O and a deficiency of group B among the men with

TABLE II
ABO BLOOD GROUPS AND
HISTOLOGICAL TYPES OF LUNG
CANCER

	O	A	B	A B	Total
Undifferentiated	118	71	9	8	206
Squamous	218	193	40	19	470
Glandular	53	51	21	1	126
	389	315	70	28	802

undifferentiated tumours, and an excess of men of group B in the group with tumours showing glandular differentiation. These three differences were significant at the 1% level.

The frequencies of the three major blood groups O, A, and B were compared in the three histological groups which were taken in pairs. The frequency of group O was significantly higher in the men with undifferentiated tumours than in the men with squamous cell tumours (χ^2 6.31; $p < 0.02$) and in the men with glandular tumours (χ^2 6.65; $p < 0.01$). The frequency of men of group B was higher in the group with glandular tumours than in those with squamous cell tumours (χ^2 7.39; $p < 0.01$) and in those with undifferentiated tumours (χ^2 12.93; $p < 0.01$).

The proportion of patients who were Rhesus (D) negative was slightly below that to be expected (Table III). No significant differences were found between subgroups with operable or inoperable lesions or with proximal or distal lesions. The proportion of patients with differentiated lesions who were Rhesus negative was lower than was expected, but the proportion in men with undifferentiated lesions was higher than was expected. These differences were not statistically significant.

TABLE III
PROPORTIONS OF RHESUS NEGATIVE
MEN WITH LUNG CANCER

	No.	Rh Negative	
		Observed	Expected
Total	1257	200	206.3
Operable	334	57	54.8
Inoperable	923	143	151.5
Proximal	693	109	113.7
Distal	564	91	92.6
Differentiated	596	87	97.8
Undifferentiated	206	37	33.8

Discussion

Examination of the ABO and Rhesus blood group distributions showed initially that there was no significant deviation from the frequencies expected from a large survey of the blood groups of

men in this area (Ashley and Davies, 1966a). Though the control series was used to demonstrate a difference in blood group frequencies between those with Welsh and those with non-Welsh surnames, the grand total was used as control, as no difference in the distribution of lung cancer was seen in men with Welsh and non-Welsh surnames (Ashley and Davies, 1966b).

The frequency of men whose Rhesus blood group was negative (D negative) did not differ significantly from that in the control series. There was a small, non-significant, deficiency of Rhesus negative men in the whole series, and especially in those with differentiated tumours, while there was a small excess of Rhesus negative patients in the men with undifferentiated tumours. These findings confirm those of McConnell, Clarke, and Downton (1954, 1955) who were unable to find a significant difference between lung cancer patients and other hospital patients in respect of the frequency of Rhesus negative patients. When the three series, that of McConnell, that of Aird (Aird *et al.*, 1954), and the present series are combined, a total of 372 Rhesus negative men is found in a total population of men with tumours of 3345; 396.5 Rhesus negative men would have been expected. This difference is small and is not statistically significant. The combined results suggest that if there is an association between the Rhesus factor and this disease it is a weak one.

The over-all frequencies of the ABO blood groups corresponded closely to those in the control series. This observation confirms those of other workers (Aird *et al.*, 1954; McConnell *et al.*, 1954; Roberts, 1956/7; Parker and Walsh, 1958; Rennie and Haber, 1961; Jakoubková and Májský, 1965). All those series have been combined and the numbers of individuals of groups O and A compared with the numbers expected in those groups: 1620 were of blood group O, 1611.4 were expected; 1410 were of blood Group A, 1412.6 were expected. This difference is of no significance.

Analyses were made of the patients in the present series subdivided in various ways. Subdivision into men with operable and inoperable tumours again showed no differences. Subdivision of the patients into those with proximal and those with distal lesions showed an excess of group A in the former and of group O in the latter; this was true both for operable and inoperable cases. Subdivision on histological grounds showed an excess of group O and a deficiency of group B in men with undifferentiated tumours whether these were proximal or distal, and a deficiency of group O in men with differentiated tumours. McConnell

and his colleagues (McConnell *et al.*, 1954) found an excess of group A at the expense of group O in men who had oat cell tumours but no differences in the other types. In this laboratory oat cell tumours are regarded as one of the forms of differentiation of neoplastic squamous cells (Ashley and Davies, 1967). McConnell's group of men with undifferentiated tumours showed 49% to be of group O compared with 48% of the control population. The different ABO blood group distribution in the proximal and distal lesions cannot be explained on the basis that there is a higher proportion of undifferentiated tumours in the distal group, as there is also a small excess of group O among the men with differentiated tumours which were distal in situation, and the proportion of patients with undifferentiated tumours is almost identical in those with proximal and those with distal lesions (Ashley and Davies, 1967). Rennie and Haber (1961) in a small series divided their patients on the basis of the histological appearance of the tumours. In their material there was a non-significant excess of patients of group O in those who had anaplastic tumours, and a non-significant excess of patients of group A in those who had differentiated tumours.

The strong association between cigarette smoking and lung cancer is well known (Doll, 1953), and it is possible that genetic factors affecting the formation of the smoking habit might in turn affect the frequency of lung cancer. Cohen and Thomas (1962) investigated the ABO and Rhesus groups of a series of 1398 men in Baltimore, and compared the blood group frequencies with the smoking habits of the men concerned. They found a deficiency of group B among the heavy smokers and an excess of group B among non-smokers and an excess of Rhesus negative individuals among those who smoked occasionally. These analyses were repeated on a survey of 1250 South Wales miners by Higgins and his colleagues (Higgins *et al.*, 1963) who were unable to find any significant differences in the various groups of smokers. When their series and that of Cohen and Thomas were combined the differences in the frequency of group B were highly significant.

The findings in smokers do not explain the differences in the frequency of the blood group O seen in the different forms of lung cancer. A deficit of blood group B was seen in men with undifferentiated tumours, while a deficiency of group B was also observed in the heavy smokers. Smoking as an aetiological factor is most strongly associated with lung cancer of squamous and undifferentiated type (Kreyberg, 1962), though it is at least possible

that there may be some association with adenocarcinoma of the lung (Ashley and Davies, 1967). In this series the correspondence of the blood group distribution supports the suggestion that smoking and undifferentiated carcinomata are causally related. There was a non-significant deficiency of individuals of group B among the men with squamous cell carcinoma, and the frequency of group B among these men did not differ significantly from that in the men with undifferentiated tumours though it did differ from that in the men with glandular lung cancer.

The mechanism connecting these two associations is less easy to understand. It is tempting to suggest that the development of the smoking habit may be genetically determined by some metabolic peculiarity which is less likely to be present if the mechanisms concerned in the production of the blood group B polysaccharide are active, and that the higher frequency of lung cancer in such men is a consequence of their increased tendency to use tobacco.

The significant excess of blood group O in men with undifferentiated tumours compared with those in whom the lesions showed either squamous or glandular differentiation suggests that there may be some intrinsic difference, at the genetic level, and separate from the effect of cigarette smoking, between men who develop undifferentiated carcinomata of the lung and those who develop differentiated carcinomata, and that the risk of the former type of tumour is greater in men who are group O Rh negative than in the general population. This may only be a liability to develop this type of tumour in response to whatever environmental carcinogens may be active, or an increased tendency for tumours to progress through increasing degrees of dedifferentiation after they have been initiated in differentiated cells.

A similar argument may be used in respect of proximal tumours, those accessible to bronchoscopy *vis a vis* those which are situated more distally in the lung. The proximal tumour is less likely to be operable and more likely to be of squamous cell type than its deeper counterpart (Ashley and Davies, 1967), and the patient with such a tumour is more likely to be of blood group A and to have a low haemoglobin concentration and a high erythrocyte sedimentation rate. Some of these differences are no doubt anatomical in nature, a proximal lesion encroaching on the carina is *ipso facto* inoperable, and squamous metaplasia, which is commoner in the proximal air passages than in the distal ones, is more likely to lead to squamous cell carcinoma.

Summary

Data are presented on the frequencies of the ABO and Rhesus blood groups in a series of 1257 men suffering from bronchial carcinoma.

There was no over-all difference in blood group frequencies when the whole series was compared with a control group collected in the same hospital.

When subgroups of the total series were compared, significant differences were observed. The frequency of blood group O was significantly lower and that of blood group A was significantly higher in men with proximal lesions than in men who had tumours which were too distal to be seen at bronchoscopy.

Three subgroups were separated according to the histological type of tumour. The frequency of blood group O was higher in men with undifferentiated tumours than in those with glandular or squamous tumours. The frequency of blood group B was greater in men with glandular tumours than in those with squamous or undifferentiated tumours.

It is suggested that these findings indicate the presence of genetic factors which may determine the site and type of lung cancer in men exposed to environmental carcinogens. In the case of the deficiency of blood group B in men with squamous and undifferentiated tumours this effect may be mediated by differences in smoking habit.

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REFERENCES

- Aird, I., Bentall, H. H., Mehigan, J. A., and Fraser Roberts, J. A. (1954). The blood groups in relation to peptic ulceration and carcinoma of colon, rectum, breast, and bronchus. An association between the ABO groups and peptic ulceration. *Brit. med. J.*, **2**, 315.
- Ashley, D. J. B., and Davies, H. D. (1966a). The use of the surname as a genetic marker in Wales. *J. med. Genet.*, **3**, 203.
- , and — (1966b). Lung cancer and chronic bronchitis in Wales. *Brit. J. prev. soc. Med.*, **20**, 148.
- , and — (1967). Cancer of the lung. Histology and biological behavior. *Cancer (Philad.)*, **20**, 165.
- Cohen, B. H., and Thomas, C. B. (1962). Comparison of smokers and non-smokers. II The distribution of ABO and Rh. (D) blood groups. *Bull. Johns Hopk. Hosp.*, **110**, 1.
- Doll, R. (1953). Bronchial carcinoma: Incidence and aetiology. *Brit. med. J.*, **2**, 521 and 585.
- Higgins, I. T. T., Oldham, P. D., Drummond, R. J., and Bevan, B. (1963). Tobacco smoking and blood group. *ibid.*, **2**, 1167.
- Jakoubková, J., and Májský, A. (1965). Blood groups and neoplastic disease. *Neoplasma (Bratisl.)*, **12**, 611.
- Kreyberg, L. (1962). *Histological Lung Cancer Types. A Morphological and Biological Correlation*. Norwegian Universities Press, Oslo.
- McConnell, R. B., Clarke, C. A., and Downton, F. (1954). Blood groups in carcinoma of the lung. *Brit. med. J.*, **2**, 323.
- , —, and — (1955). Blood groups in carcinoma of lung. *ibid.*, **2**, 674.
- Parker, G., and Walsh, R. J. (1958). Blood groups and disease: carcinoma of various organs. *Med. J. Aust.*, **2**, 835.
- Rennie, H. M., and Haber, R. W. (1961). Blood groups and carcinoma of the lung. *ibid.*, **2**, 61.
- Roberts, J. A. F. (1956/7). Associations between blood groups and disease. *Acta genet. (Basel)*, **6**, 549.