# EMPHYSEMA II: THE ROLE OF ALPHA-1-ANTITRYPSIN DEFICIENCY IN MALAYSIAN PATIENTS

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## INTRODUCTION

FOLLOWING THE work of Laurell and Eriksson (1963, 1964 and 1965) it is known that individuals with severe alpha-1-antitrypsin deficiency (A-1-ATD) are more susceptible to emphysema. While the majority of others develop the disease in their fifth to seventh decades of life (Thurlbeck, 1963 and Talamo *et al.*, 1966) these individuals do so in their forties (Eriksson, 1965), often earlier and with less exposure to tobacco smoke (Hutchison *et al.*, 1972). The role in emphysema of the heterozygous deficiency state with its resultant intermediate deficiency of A-1-AT however remains unsettled. Present knowledge of its epidemiology suggests A-1-ATD is more common in populations of northern European origin and less so in other ethnic groups (Mittman & Lieberman, 1970). Eriksson (1964) reported finding a frequency of 0.06% for the homozygous (phenotype ZZ) and 4.7% for the heterozygous (MZ) deficiency state in Sweden. Subsequent reports have shown comparable incidences in Norway (Fagerhol, 1967) and the United States (Schwartz *et al.*, 1973), while two studies, one in American blacks (Kellerman and Walter, 1970) and the other in Japanese (Harada and Omoto, 1970), failed to detect any individuals with the deficiency genes in the groups studied. Janus *et al.*, (1965) compared the frequency of A-1-ATD in New Zealand whites with that in the Maoris and found however a higher incidence of both the ZZ and MZ phenotypes in the latter. In a group of 430 Indians, Kellerman and Walter (1970) found 0.23% and 0.69% incidence of the ZZ and MZ phenotypes respectively, and there are reports of the occurrence of A-1-ATD emphysema in Indians (Hobbs, 1971 and Viswanathan *et al.*, 1976). The incidence of A-1-ATD and related emphysema in South East Asia is unknown and we have been unable to fnd any documented evidence of its occurrence from this part of the world. We report the result of a study to assess the role of A-1-ATD in a selected multiracial group of Malaysian patients with emphysema seen at our Chest clinic.

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## MATERIALS AND METHODS

Eighty five patients with radiological emphysema seen at the University Hospital, Kuala Lumpur between 1974 and 1978 were selected for this study. Patients with a history and clinical features suggestive of emphysema were screened, and the presence or otherwise of emphysema was assessed as in the previous paper.

For purposes of this study, patients selected had two additional investigations. Serum electrophoresis was performed on cellulose acetate paper and the strip examined for the presence of the alpha globulin band. A-1-AT levels were measured using a commercialy available kit (M Partigen, Hoechst). Venous blood was drawn from patients while in a basal state free of any detectable infection, allowed to clot, the serum separated and stored at -24°C. Alpha-1-antitrypsin was estimated by radial immunodiffusion on agarose plates containing antibody to A-1-AT. The values were expressed as milligrams per cent (normal value = 200-400 mg per 100 ml).

Controls: In order to obtain an indication of the normal levels in our population, A-1-AT levels were estimated in one hundred random blood specimens obtained from patients of comparable age free of lung or liver disease, and from detectable inflammatory or malignant conditions seen in the medical and surgical divisions of the hospital service.

## RESULTS

The clinical characteristics of the group studied have been described in paper I.

*Serum Electrophoresis.* Severe flattening or absence of the alpha globulin band was not seen in any of the patients in the group.

*A-1-AT levels* in the groups studied are shown in Table I. There was no significant difference in the A-1-AT values in the two groups ($p => 0.1$).

**Table I**

**A-1-AT values in the study group and in the controls**

| A-1-AT | Patients | Controls |
|---|---|---|
| Range of values (mg/100 ml) | 190 — 396 | 172-380 |
| Mean (mg/100 ml) | 266 | 261 |
| + Standard Deviation | 46 | 43 |

**Table II**

**Frequency of Homozygous A-1-ATD in Emphysema**

| Author | | % of patients |
|---|---|---|
| Kueppers *et al.* | 1964 | 1 |
| Lieberman | 1969 | 10 |
| Jones, Thomas | 1971 | 18 |
| Hutchison *et al.* | 1972 | 28 |

## DISCUSSION

Alpha-Antitrypsin deficiency has been quoted to account for 2-6% of all emphysema (Hobbs, 1971 and Litwin & Bearn, 1969). The estimated frequency of A-1-ATD in emphysema in some of the reported studies (all from American and British groups) is shown in Table II. Lieberman (1973) found that 26% of all patients with emphysema had either severe or intermediate deficiency of A-1-AT; the prevalence was 30% in patients aged 60 years of younger and it rose to almost 50% in patients aged 50 or less years. Hutchison (1973) states "nearly all of a narrowly defined group in whom severe lower zone emphysema has developed between the ages of 30 and 45 years are likely to have alpha-1-antitrypsin deficiency". It is apparent that successive reports have found a higher prevalence of A-1-ATD and given more prominence to its role in emphysema. The differences in the estimates of the frequency have been explained by different criteria for the selection of patients and the true frequency of the homozygous deficiency state amont patients with emphysema is uncertain even in western populations.

The criterion for selection and the functional data of the patients make it likely that only those with moderate to severe emphysema were included in our study. Despite this, we have not detected any patient over a five year period with severe deficiency wherein A-1-AT levels are reduced to around 10-15% of the normal, though we are unable to exclude the presence in our group of individuals with intermediate deficiency. In the group of patients with emphysema studied by Lieberman (1973) the age of individuals homozygous for the A-1-ATD gene averaged $45 \pm 8$ years and that of those with heterozygous deficiency $57 \pm 8$ years (Lieberman, 1969). Most of our patients were elderly, only 15% being below 50 years of age, and 27% had radiological changes preferentially affecting the lower zones. Only one male Chinese patient aged 37 had both of these features, in the presence of which the likelihood of A-1-ATD is high; however he had an A-1-AT level of 278 mg per 100 ml. It is known that the ZZ phenotype is uncommon, even in a group of emphysematous patients composed mainly of elderly males, and this may be taken to be the reason for the absence of cases with A-1-ATD in the group. However, considering the size of the hospital attendances per year (around 27,000), the fact that patients with clinical obstructive lung disease are referred to the Chest clinic, and that the criteria for selection were purely clinical, radiological and physiological without age limits, this is unlikely to be the case. Over this period we have not seen patients likely to have A-1-ATD on clinical and radiological grounds and we feel that it is very unlikely that such patients have been missed out from this study. We conclude that severe A-1-ATD is not likely to be a significant aetiological factor in emphysema in our Asian patients. Considering the commonness of the smoking habit and the fact that emphysema also occurs in non smokers and even children with the deficiency (Talamo *et al.*, 1971 and Kueppers and Black, 1974), the significance of this finding is obvious.

## SUMMARY

Over a five year period, eighty five Malaysians of Chinese, Malay and Indian origin with emphysema seen at our Chest clinic were investigated for alpha-1-antitrypsin deficiency, using the radial immunodiffusion method. None of the patients studied had evidence of severe alpha-1-antitrypsin deficiency, and only one presented with lower zone emphysema of early onset. We conclude that severe alpha-1-antitrypsin deficiency is unlikely to be an etiological factor in emphysema among Malaysians of Asian origin.

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