No response could be induced in 50% of the patients in the present series despite the use of steroids and cyclophosphamide alone or in combination. Failure to respond to steroids in mercury-induced nephrotic syndrome has been recorded previously (Cameron and Trounce, 1965). Certainly in consideration of world-wide experience of the adult nephrotic syndrome the prognosis for most patients is poor (Miller *et al.*, 1969). Lack of response to therapy is believed by McIntosh *et al.* (1971) to relate to immune complex deposition in the glomeruli. In view of the known prevalence of this phenomenon in adult nephrotics (British Medical Journal, 1970), the poor prognosis in a significant proportion of patients can thereby be explained.

The group of patients presented are considered to represent a different spectrum of the adult nephrotic syndrome from that of common previous experience, in that most of them are thought to have developed as a result of exposure to self-administered mercury. This situation is believed to be entirely avoidable. We subscribe to the view expressed by Turk and Baker (1968) that "there remains no reason for ever prescribing mercury for topical use."

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Veno-arterial Difference in α_1 -Antitrypsin Levels

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Summary

α_1 -Antitrypsin levels, determined by radial immunodiffusion, were found to be higher in the venous than in the arterial blood of patients with pulmonary infections and in patients with obstructive airflow diseases. Large differences occurred in patients with both abnormalities. No difference was found in patients with other kinds of lung disease or in patients without lung disease. The veno-arterial difference probably occurs as blood passes through the lungs and probably results from alteration of the immunological properties of the α_1 -antitrypsin, perhaps by attachment to proteases, rather than absorption into the lung tissue. Further studies are needed

to define the diseases in which this antienzyme plays an active part and to determine the mechanisms causing the difference.

Introduction

Laurell and Eriksson (1963) and Eriksson (1964) first described an association between low levels of serum α_1 -antitrypsin and pulmonary emphysema. Eriksson pointed out that there are several sources of protease in the lung, including bacteria, leucocytes, and alveolar and peribronchiolar macrophages, and he postulated that α_1 -antitrypsin protects the normal lung against the destructive action of proteolytic enzymes. Since then it has been shown that α_1 -antitrypsin forms firm proteolytically inactive complexes with proteases and elastase from leucocytes (Ohlsson, 1971).

Alternatively, it has been proposed (Hunter *et al.*, 1968) that in normal ageing there is a metabolic turnover of connective tissue with a gradual enlargement of alveolar spaces and this is accelerated in the absence of α_1 -antitrypsin. Both of these

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Details of Patients with Lung Disease

Case No.	Sex	Age	Diagnosis	Lung Infection	α_1 -Antitrypsin			Percentage Predicted		
					Venous mg/100 ml	Arterial mg/100 ml	$\frac{V-A}{V}\%$	VC	FEV ₁	FRC
1	M	62	Chronic airflow obstruction + asthma	Yes	423	353	16.6	64	33	147
2	M	76	Chronic airflow obstruction + scleroderma	Yes	391	331	15.4	81	24	161
3	M	65	Chronic airflow obstruction + scleroderma	Yes	522	333	36.0	99	66	110
4	M	54	Chronic airflow obstruction	No	346	301	13.0	40	10	169
5	M	50	Asthma + tuberculosis	No	318	300	5.7	94	44	143
6	M	45	Chronic airflow obstruction + tuberculosis	Yes	522	500	10	72	65	131
7	M	42	Chronic airflow obstruction + tuberculosis	No	424	381	10	102	50	120
			Emphysema + pneumonia	Yes	660	414	37	68	60	120
8	M	62	Emphysema	No	431	379	12	86	—	—
			Lobectomy + pneumonia	Yes	479	303	37	70	55	170
9	M	57	Chronic airflow obstruction	No	447	393	12	77	61	121
10	M	48	Asthma	No	331	288	13.0	78	35	116
11	F	26	Asthma	No	305	305	0	—	—	—
12	M	43	Asthma	No	381	321	15.7	79	32	128
13	M	52	Chronic airflow obstruction	No	322	303	5.9	129	58	138
14	M	54	Chronic airflow obstruction	No	318	299	6.0	52	27	139
					431	405	6.0	—	—	—
15	M	62	Diffuse interstitial fibrosis (inactive)	No	372	390	-4.8	73	59	117
16	M	45	Sarcoidosis	No	282	282	0	66	33	85
17	M	38	Sarcoidosis	No	241	233	3.3	70	45	82
18	M	63	Asbestosis	No	342	342	0	99	51	104
19	M	45	Pigeon breeder's lung	Yes	348	340	2.3	70	23	142
20	M	57	Inactive tuberculosis	No	318	318	0	94	65	106
21	M	48	Scleroderma	No	221	221	0	70	63	81
22	F	57	Carcinoma lung	No	312	317	-1.6	90	89	80
23	M	54	Carcinoma lung	No	403	403	0	98	57	109
24	F	54	Lobar pneumonia	Yes	492	470	4.5	—	—	—
25	F	41	No lung disease	No	383	383	0	88	84	120
			Lobar pneumonia	Yes	440	420	5.3	—	—	—

hypotheses suggest that α_1 -antitrypsin has a direct function in lung tissue though its concentration there is not known.

If α_1 -antitrypsin has a protective role in the lung, then, in diseases in which proteases are excessive or metabolic turnover of connective tissue is increased, not only may increased serum levels of α_1 -antitrypsin occur but larger than normal amounts of α_1 -antitrypsin may be removed from or altered by the blood in the lungs. This would result in lower levels in the systemic arterial than in the systemic venous blood. We present the preliminary results of a study of the venous and arterial levels of immunodiffusion determined α_1 -antitrypsin in patients with different lung diseases.

Present Investigation

Blood was obtained from 25 patients with lung disease undergoing routine lung function assessment and from nine patients without lung disease undergoing cardiac catheterization. Measurements were made on two occasions in four of the patients with lung disease. The physical characteristics and clinical diagnoses of the patients with lung disease are shown in the Table. The cardiac patients were judged free from lung disease if they had no cough and the lung fields were clear on chest radiography.

The arterial and venous blood samples were collected in glass tubes, allowed to clot, and the serum was separated by centrifugation. The two samples were collected within five minutes of each other from opposite arms and tourniquets were not used. Immunologically active α_1 -antitrypsin was measured by radial immunodiffusion as described by Mancini *et al.* (1964) using partigen plates. The standard deviation of this measurement, tested by putting the same serum into 18 wells on two plates, was shown to be 4.7 mg/100 ml, for a mean value of 277 mg/100 ml. Vital capacity (VC) and forced expiratory volume in one second (FEV₁) were recorded on a Godart spirometer and functional residual capacity (FRC) was measured by the closed-circuit helium dilution method.

Results

The immunodiffusion values for α_1 -antitrypsin in the venous and arterial bloods of the patients with lung disease together with the difference between the two values, expressed as a

percentage of the venous level, and the lung function results are given in the Table. All but two of the patients with infection had venous levels of α_1 -antitrypsin above the normal limit of 400 mg/100 ml. Four of those without infection had raised levels. The veno-arterial differences were largest in patients with infection but not all patients with infection had significant differences.

Fig. 1 shows the veno-arterial α_1 -antitrypsin difference expressed as a percentage of the venous level in patients with

FIG. 1—Veno-arterial difference in α_1 -antitrypsin expressed as a percentage of the venous level in three groups of patients without lung infection. The mean values for each group are shown.

obstructive airflow disease and other lung diseases without lung infection. The difference in the patients without lung disease is also shown. The venous level of α_1 -antitrypsin in all these patients was normal.

The mean percentage difference in the group with obstructive airflow disease without infection was 9.9 (range 0 to 15.7). This was significantly different from the group with non-

obstructive lung disease where the mean difference was 0.4% ($P < 0.001$) and the control group where the mean difference was -1.0% ($P < 0.001$).

In Fig. 2 the veno-arterial difference is plotted against FRC, expressed as a percentage of the predicted value in the patients with lung disease without pulmonary infection. There is a significant relation between the degree of overinflation and the veno-arterial difference ($r = 0.676$, $P < 0.01$).

FIG. 2—Veno-arterial difference in α_1 -antitrypsin expressed as a percentage of the venous level, related to functional residual capacity in patients without lung infection. The dots indicate patients with airflow obstruction, the open circles indicate patients with other lung diseases.

In patients without lung infection the mean venous level of α_1 -antitrypsin in the group with airflow obstruction was 369 mg/100 ml, which is significantly greater than in those with other lung diseases (mean 319 mg/100 ml) or those without lung disease (mean 303 mg/100 ml).

Discussion

The radial immunodiffusion method of quantitating α_1 -antitrypsin has proved valuable but the method has fallacies. A reading which is less than expected indicates that less α_1 -antitrypsin has been detected and may mean that there is less present, that its antigenic properties have been altered, or that its molecular weight has changed, for example by polymerization or absorption, to a protein molecule such as a protease.

Although at the present time we have no direct evidence that the veno-arterial difference is in fact a difference across the lung, this seems the most likely explanation for our findings. Lieberman (1971) has some evidence that the α_1 -antitrypsin is cleared from the blood by the lungs.

If the veno-arterial difference does occur across the lung, it seems unlikely that as much as 100 mg/100 ml or more of the antienzyme is removed and more likely that its antigenic

properties or molecular weight are altered in the lungs. If this occurs, however, the α_1 -antitrypsin must be immunologically or molecularly reconstituted during the passage of blood through the peripheral limb tissues.

If, as Eriksson (1964) postulated, α_1 -antitrypsin is needed to inhibit protease activity in macrophages and leucocytes, patients with lung infections might have higher venous than arterial levels of α_1 -antitrypsin. Initially this study was undertaken to see if differences could be detected in patients with lung infections. Somewhat surprisingly some of the patients studied had very large differences and after the infection was resolved a small veno-arterial difference persisted. Since these patients also had underlying chronic airflow obstruction, patients with obstructive airflow disease without evidence of infection were studied and they too proved to have differences. The investigation was then extended to include patients with other kinds of lung disease and it soon became apparent that patients without evidence of airways obstruction had little or no difference.

In the present study two patients had lung infection without underlying obstructive airflow disease and although their venous levels were raised, the veno-arterial difference was not great in either patient. Most of the patients with airflow obstruction but no infection had only moderate differences. However, a combination of chronic airflow obstruction and lung infection was associated with very large differences, which decreased as the infection was treated in the three patients whose studies were repeated.

Hunter *et al.* (1968) proposed that α_1 -antitrypsin is active in the normal turnover of connective tissue in the lung and that there is a gradual increase in the size of alveolar spaces with age which is greatly accelerated in patients with reduced amounts of the inhibitory enzyme. It could be postulated that overinflation accelerates metabolic turnover, so that in diseases leading to overinflation more α_1 -antitrypsin is required to inhibit the excessive breakdown of connective tissue. The correlation between the veno-arterial α_1 -antitrypsin difference and FRC shown in Fig. 2 supports such a theory as does the fact that the mean venous level was higher in patients with obstructive airflow disease.

The present observations suggest that α_1 -antitrypsin may be important in protecting the lung not only in pulmonary infections but also in diseases causing overinflation of the lungs. It is possible that it acts as a transport system, renewing potentially destructive proteases from the lung. Further studies of the α_1 -antitrypsin levels in pulmonary arterial and venous blood and of the molecular and immunological properties of α_1 -antitrypsin in patients with different lung diseases are needed to define the meaning of the difference.

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