Angiotensin-converting enzyme and its clinical significance – a review

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SUMMARY There have been considerable advances in understanding the metabolic role of the endothelial lining cells of the blood vessels. Angiotensin-converting enzyme activity is concentrated in these cells, especially those lining the pulmonary circulation. The enzyme exerts control over systemic vascular tone indirectly through the powerful pressor effect of angiotensin II. A number of therapeutic agents are now available which directly inhibit converting enzyme activity and thereby effect a reduction in blood pressure.

Macrophages are the source of increased angiotensin-converting enzyme activity commonly found in association with active sarcoidosis. A better understanding of this phenomenon may give fresh insight into this puzzling condition. Pulmonary endothelial metabolism is affected by lung injury and it is likely that in this situation changing activities of serum angiotensin converting enzyme may indicate the extent of damage and the response to therapy. The full clinical significance of serum ACE measurements has yet to be established. However, raised activities have been reported in a number of other conditions and diabetes mellitus and hyperthyroidism are of particular current interest.

The numerous methods and reference ranges described in the literature for the measurement of serum ACE activity require further assessment, and there is a clear need for an accepted reference method.

Angiotensin I, a decapetide generated by action of the enzyme renin on a glycoprotein substrate angiotensinogen II, is converted to the pressor octapeptide angiotensin II. The exopeptidase responsible for this conversion was first identified and isolated in plasma by Skeggs et al., who named it angiotensin-converting enzyme. This enzyme is a halide-activated, EDTA-sensitive, peptidase that catalyses the cleavage of dipeptidyl residues from the COOH terminus of peptide substrates, and releases His-Leu from the COOH terminus of the decapetide angiotensin I.

The ready conversion of angiotensin I to angiotensin II was assumed to take place in the circulation until Ng and Vane* recognised that the enzyme activity present in plasma was insufficient to account for the rapidity of "in vivo" conversion, and demonstrated most conversion of circulating angiotensin I to angiotensin II occurred during passage through the lungs. Stanley and Biron confirmed the importance of lung as a site of angiotensin-converting enzyme activity by demonstrating reduced angiotensin I conversion in dogs on cardiopulmonary bypass; the lowered rate of conversion, however, was still higher than that in blood alone.

The pulmonary vascular bed is uniquely placed to modify levels of circulating vasoactive substances, being immediately up stream of the high pressure systemic circulation and receiving virtually the whole cardiac output. However, the fact that blood pressure control is maintained, albeit at a lower level, during cardiopulmonary bypass indicates that angiotensin-converting enzyme is present in vascular beds other than the lungs. Cushman and Cheung measured angiotensin-converting enzyme activity in a large number of rat tissue homogenates and found high specific activities in lung and in segments of the digestive tract but the highest activities in mature animals were in the testes and epididymis associated with tubular fluids, but not in sperm cells.

Other sites in which conversion of angiotensin I to II has been reported to occur include the renal vasculature of humans and dogs, the vascular bed of the intestine, the hind limb of the dog forearm
arteries and hand veins in man. In 1977 Lanzillo isolated angiotensin-converting enzyme from human serum and as expected, found high concentrations in the vascular bed of the lungs.

Electron microscope studies with microperoxidase labelled antibody against angiotensin-converting enzyme localise the enzyme activity to the luminal surface of the capillary endothelium and associated caveolae in the aorta, lungs, and in other vascular beds and this work provided visual confirmation of the many reports linking angiotensin-converting enzyme to the vascular endothelium. Therefore, angiotensin-converting enzyme is a membrane-bound glycoprotein located predominantly in endothelial pinocytic vesicles. Circulating angiotensin-converting enzyme almost certainly derives from sloughing of, or secretion from, the endothelium. The unique feature of the pulmonary circulation in terms of the renin-angiotensin system is that it is the only vascular bed through which angiotensin II passes without inactivation. Ferreira and Vane investigated bradykinin, another vasoactive substance, and found its activity disappeared during circulation through the lungs, leading Ng and Vane to suggest that the same pulmonary enzyme responsible for conversion of angiotensin I may also inactivate bradykinin. Supporting evidence for this hypothesis includes finding that bradykinin is a competitive inhibitor of angiotensin I conversion and that bradykinin potentiating factors (peptides from the venom of a Brazilian pit-viper Bothrops jararaca) not only inhibit the destruction of bradykinin by plasma, but also inhibit the conversion of angiotensin I by lung extracts. The isolation of snake venom inhibitors (Bothrops jararaca) of angiotensin-converting enzyme enabled studies to be made showing the importance of the renin-angiotensin system in the maintenance of blood pressure. A number of other inhibitors have been characterised and synthesised and shown to possess similar pharmacological properties with inhibition of the vasopressor response to angiotensin and enhancement of the vaso depressor effect of bradykinin. It was later established that pure converting enzyme from rabbit, and pig lung catalysed sequential release of Phe-Arg and Ser-Pro from the COOH-terminus of bradykinin.

The details of the two protease pathways that share angiotensin-converting enzyme are summarised in Fig. 1. The one enzyme acting upon its two currently recognised substrates has been classified as a peptidyl dipeptide hydrolase and named "peptidyl dipeptidase" by the IUPAC-IUB Commission on Biochemical nomenclature. Since large amounts of angiotensin I converting enzyme are found in plasma and in a number of organs and since angiotensin I infused in supraphysiological concentration is rapidly converted into angiotensin II in vivo, the conversion step has not generally been regarded as rate-limiting for angiotensin II production. Relatively little attention has been given to the regulation of converting enzyme activity in vivo.

However, several reports have suggested that alterations in angiotensin I conversion occur in pulmonary disease or when abnormalities in pulmonary function are experimentally induced. Manipulation of pulmonary vascular surface area and mean transit time through the pulmonary capillary bed, by changing pulmonary venous pressure, altered conversion of infused angiotensin I in the isolated perfused dog lung. Molteni studied changes in both serum and pulmonary angiotensin-converting enzyme activity and renal renin content in mice exposed to hypoxia in a hypobaric chamber at 0.5 atmospheres. A small fall in the activity of both enzymes was demonstrated at two days followed by a progressive rise reaching significance (p < 0.005) by nine days. The finding in dogs that acute hypoxia inhibited the activity of angiotensin-converting enzyme suggested a possible explanation for the low plasma aldosterone and raised plasma renin activity found at altitude. Milledge and Catley studied the effect of moderate exercise continued for 120 min upon renin, aldosterone and angiotensin-converting enzyme. After 60 min exercise while breathing room air plasma renin activity and plasma aldosterone rose while angiotensin-converting enzyme activity remained unchanged. The same subjects continued exercise for another 60 min while breathing 12.8% oxygen and further blood samples showed a 30% fall in angiotensin-converting enzyme activity and a further rise in renin and aldosterone. These findings may have implications for humans who suffer from mountain sickness on exercise at altitude. Therefore, alterations in pulmonary function may have a regulatory effect on the renin-angiotensin system through the activity of angiotensin I converting enzyme.

This led to studies of the enzyme's activity in patients with pulmonary disease. Depressed converting enzyme activity has been reported in patients with several kinds of pulmonary disease, including chronic bronchitis and emphysema, carcinoma of the bronchus, bronchial asthma and cystic fibrosis. This raised the possibility that the reduction in converting enzyme activity may relate to a loss of vascular endothelial surface area; but in fact no correlation was demonstrated between the severity of the pulmonary disease and reduction in converting enzyme activity.

In contrast, Lieberman in 1975 demonstrated that serum converting enzyme activity was raised in sarcoidosis and his finding has been confirmed by many, and is discussed further.
Properties of angiotensin-converting enzyme

Human angiotensin-converting enzyme (ACE) has been successfully purified by a combination of chromatographic and electrophoretic techniques. It is an acidic glycoprotein (isoelectric point 4.6) consisting of a single polypeptide chain of molecular weight about 140 000. The activity of the enzyme depends upon the presence of chloride ions, while chelating agents, sulphhydryl compounds, heavy metals and certain peptides are inhibitory. The presence of zinc has been demonstrated in rabbit and canine enzymes and is thought to be closely associated with human angiotensin-converting enzyme. In phosphate-saline buffer, serum ACE is most stable at pH 8.0–8.8 with an optimum pH of 8.3. The most extensively characterised of the pure enzyme preparations is an extract from rabbit pulmonary membranes separated with DEAE-cellulose ion exchange, Sephadex G-200 gel, and lectin affinity chromatography. Apart from variations in the glycoprotein content the human enzyme appears to be very similar if not identical to rabbit and canine enzymes.

There does not appear to be any significant difference in behaviour between raised serum angiotensin-converting enzyme from sarcoid patients and serum angiotensin-converting enzyme from normal subjects, with respect to temperature and pH properties. At the present time isoenzyme forms have not been identified. Serum samples may be stored prior to assay, for we have found that the enzyme's activity is stable for at least 20 days at 25°C, 1 month at 4°C and 6 months at -20°C.

Methods of measuring serum angiotensin-converting enzyme activity

A number of different methods for determining angiotensin-converting enzyme (ACE) are available. Cushman and Cheung described a method for assaying the enzyme's activity in rabbit lung extracts and measured the activity in terms of the rate of release of hippurate from a substrate analogue hippuryl-L-histidyl-L-leucine, which substitutes for angiotensin I. Cushman and Cheung's method as modified by Lieberman is simple to perform and is now widely used to measure serum ACE activity. The test serum and substrate are incubated under controlled conditions. The reaction is terminated by acidification, and after separating the unhydrolysed substrate by extraction with ethyl acetate, hippurate is measured spectrophotometrically by determining its absorbance at 228 nm. In the authors' experience the method is relatively insensitive and difficult to control when used for the routine assay of serum ACE. All traces of ethyl acetate must be removed by evaporation for this substance absorbs strongly at 228 nm and therefore interferes with the assay. Lipaemic or haemolysed serum samples may cause interference in the extraction step. Chiknas described a modification of Cushman and Cheung's method in which high pressure liquid chromatography is used to measure the hippuric acid end product. This procedure overcomes a number of problems encountered with the spectrophotometric assay.

An alternative spectrophotometric method uses cyanuric chloride/dioxan as reagent which reacts with liberated hippurate in the presence of phosphate buffer to yield a chromogen that is quantified by its absorbance at 382 nm. Recently, a two-point kinetic assay based on this reaction has been described, which is said to be unaffected by jaundiced or lipaemic specimens.

Friedland and Silverstein described a sensitive and reproducible fluorimetric assay using hippuryl-L-histidyl-L-leucine as substrate in which the rate of production of L-histidyl-L-leucine is quantified spectrofluorometrically by the formation of a fluores-
cent adduct with o-phthaldialdehyde. This method is highly sensitive, reproducible and unaffected by haemolysed, jaundiced or lipaemic sera. An inherent criticism in measuring the production of L-histidyl-L-leucine is that L-histidyl-L-leucine itself is susceptible to hydrolysis by serum peptidase enzymes. However, under the conditions of the assay, hydrolysis of L-histidyl-L-leucine is minimal and no correction need be made. In a similar assay Friedland and Silverstein used the physiological substrate angiotensin I instead of the synthetic analogue. This is converted by serum ACE to angiotensin II and L-histidyl-L-leucine and the latter substance was quantified fluorimetrically as in the previous method. There was a highly significant correlation between measured serum ACE activity determined with angiotensin I compared with the analogue substrate hippuryl-L-histidyl-L-leucine, \( r = 0.903 \).

In an alternative method described by Dorer, hippurylglycylglycine is used as the substrate and serum ACE activity measured in terms of release of glycylglycine. The glycylglycine is quantified by a ninhydrin method. Glycylglycine is less susceptible to hydrolysis by peptidases in serum than histidyl-L-leucine but the method is complicated by the need for prior dialysis. Other fluorogenic substrates have been used.

A rapid two-step colorimetric assay has recently been described by Kasahara and Ashihara, based upon the formation of the quinoneimine dye formed from the substrate 4-hydroxyhippuryl-L-histidyl-L-leucine, and the results are said to correlate closely with Cushman and Cheung's method \( r = 0.98 \). This method is to be made available as a test kit (ACE color, Fujizoki Pharmaceutical Co Ltd, Tokyo, Japan). (Agent: Diamed Diagnostics LTD, England.)

Radioassays, using radiolabelled substrates have recently been developed for the determination of serum angiotensin-converting enzyme activity. The method described by Rohrbach used (Glycine-1-\(^{14}\)C) hippuryl-histidyl-leucine as a substrate, whereas the method described by Ryan now commercially available (Ventrex Laboratories Inc, Portland, Miami), uses (P-\(^{3}\)H benzyloxy) hippuryl-glycylglycine. Both methods measure enzyme activity in terms of release of radiolabelled hippuric acid from the substrate, and in both methods haemolysed and lipaemic samples can be processed. As in the method of Cushman and Cheung, hippurate is separated from unhydrolysed substrate by extraction with ethyl acetate. However, ethyl acetate need not be removed by evaporation as the hippurate content of the ethyl acetate extract can be quantified directly by liquid-scintillation counting, thus eliminating a potential source of error. Ryan compared their assay with that of Cushman and Cheung (as modified by Lieberman)

and obtained a highly significant linear correlation \( r = 0.891 \). McGregor, Roulston and Bird (unpublished data) compared the assay of Friedland and Silverstein with that of Ryan et al and also obtained a highly significant linear correlation \( r = 0.98 \).

### Clinical applications of serum ACE measurements

#### SARCOIDOSIS

**Introduction**

Sarcoidosis is an enigmatic multisystem granulomatous disorder of unknown aetiology. The clinical features and chest radiograph appearance are often very characteristic but confident diagnosis requires histological confirmation. Problems in managing sarcoidosis include diagnosis in atypical cases, for treatment of patients sarcoidosis is unsuspected until sarcoid granulomas are found at biopsy, and the assessment of activity in chronic disease.

A number of biochemical abnormalities are common in sarcoidosis, including hypercalcaemia and hypercalcuria, hydroxyprolinuria, hyperglobulinaemia, changes in individual immunoglobulin concentrations, increased levels of lysozyme, collagenase or elastin, but none of these abnormalities is specific or sensitive enough to discriminate sarcoidosis from a number of other conditions.

Angiotensin-converting enzyme (ACE) activity is frequently raised in the serum and virtually always in granulomatous lymph node tissue of patients with sarcoidosis. This association between serum ACE and sarcoidosis was reported by Lieberman, who suggested serum ACE may be a useful diagnostic test and that serial measurements of activity may help in clinical management.

Lieberman's observation has been confirmed by many. All demonstrated significantly raised serum ACE activity in sarcoidosis, and most showed falling enzyme activities with corticosteroid or spontaneous remission. Rising activities were associated with relapsing sarcoidosis.

**Origin of increased serum ACE in sarcoidosis**

The origin of the increased ACE activity in sarcoidosis is debated, but is thought to reflect stimulation of the monocyte macrophage system. The high turnover sarcoïd granulomas are sites of considerable macrophage activity and receive massive reinforcements of monocytes to sustain their activity. The epithelioid cells are derived from macrophages, appear biosynthetically active and are the most likely source of the increased serum and tissue ACE activity as well as
other biologically active molecules, including lysozyme, glucuronidase and elastase. This hypothesis is supported by the following evidence. Human and rabbit monocytes, the precursors of macrophages, can be induced on culture to secrete ACE in concentrations up to 700 times that obtained before induction.\textsuperscript{62, 63} Immunofluorescence studies localise angiotensin II specified fluorescence to epithelioid cells, indirectly locating abundant ACE activity\textsuperscript{44} to specific cells in sarcoid granulomas.

**Diagnostic sensitivity**

The reported diagnostic sensitivity of serum ACE varies; but overall some two-thirds of patients with active sarcoidosis have raised enzyme activity. An even higher proportion will show increased ACE activity in fluid aspirated from the lungs at bronchoalveolar lavage and virtually all will show increased ACE activity in biopsied granulomatous lymph nodes.\textsuperscript{59--61}

Serum ACE activity is independent of sex, race and diurnal variation in normal adult subjects (> 18 y of age) and shows no significant fluctuation throughout adult life. In normal healthy infants, children and early adolescents serum ACE activity is substantially higher and more variable than in adults\textsuperscript{32 67 76 77 85} and then declines to adult values as growth ceases. Because of this variability, a normal range of serum ACE activity for patients under 18 y remains to be generally established.

In our series,\textsuperscript{67} serum ACE activity was measured in normal adult subjects (> 18 y), in adult patients with sarcoidosis and other granulomatous or respiratory diseases using the spectrofluorimetric method of Friedland and Silverstein. The normal range was from 16 to 52 nmol/min/ml with a mean of 34 nmol/min/ml (mean ± SD = 34 ± 18), obtained from 80 age and sex matched healthy adult subjects, (mean age 42 y, range 18–60 y).

Compared to normal subjects serum ACE activity in 146 sarcoid patients was significantly raised (p < 0.001) with a mean activity of 54 ± 27 nmol/min/ml (mean ± SD), (Fig. 2). Serum ACE was raised in about half with active untreated sarcoidosis and in one-fifth after corticosteroid treatment. The highest individual enzyme activities are found in those patients with extensive pulmonary and hepatic involvement. Serum ACE activity appears to be most influenced by the extent of sarcoidosis, for most investigators demonstrate a clear trend for activity to increase in parallel with the degree of radiographic or clinical abnormality. In our series this trend was very apparent, for raised serum ACE was found in 27% of sarcoidosis patients with a normal chest radiograph, in 56% with hilar gland enlargement but clear lung fields (stage 1) in 72% with pulmonary infiltration in association with hilar gland enlargement (stage 2) and in 80% with active sarcoidosis and pulmonary infiltration alone (stage 3).

**Serum ACE in other granulomatous conditions**

Serum ACE activity was increased in 6% of a group of patients with other granulomatous conditions and so is not absolutely specific for sarcoidosis. Four per cent of untreated Hodgkin's patients, 16% of untreated primary biliary cirrhosis and 10% of untreated pulmonary tuberculosis patients had raised serum ACE activity. In this personal series no

<table>
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<th>Condition</th>
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<th>Serum ACE raised</th>
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<tr>
<td></td>
<td>No</td>
<td>False positive %</td>
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<tr>
<td>Tuberculosis</td>
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<td>3 14</td>
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<td>Coccidioidomycosis (86)</td>
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<td>1 7</td>
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<tr>
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<td>19 27</td>
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<tr>
<td>Hodgkin's</td>
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<td>3 3</td>
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<td>Beryllium disease (89)</td>
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<td>3 75</td>
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<tr>
<td>Asbestosis</td>
<td>26</td>
<td>3 11</td>
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<td>Silicosis</td>
<td>19</td>
<td>8 42</td>
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<tr>
<td>Primary lung cancer</td>
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<tr>
<td>COPD</td>
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<td>1 0 5</td>
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<tr>
<td>Asthma</td>
<td>86</td>
<td>1 1 5</td>
</tr>
<tr>
<td>Diabetes mellitus (87)</td>
<td>265</td>
<td>48 18</td>
</tr>
<tr>
<td>Alcoholic liver disease (88)</td>
<td>151</td>
<td>43 28 5</td>
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<tr>
<td>Hyperthyroidism (90)</td>
<td>21</td>
<td>17 81</td>
</tr>
<tr>
<td>Total</td>
<td>1527</td>
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Provided due caution is taken in interpreting the result, a demonstration of raised serum ACE in patients with strongly suspected acute sarcoidosis can be diagnostic, or at least provide supporting evidence that will supplement other diagnostic procedures. Serum ACE measurements are especially helpful in two other situations. Firstly, in patients with suspected chronic sarcoidosis the Kveim-Siltzbach test is positive in only a minority of cases and in this situation a raised serum ACE supports the diagnosis and suggests that the disease is active. Secondly, in patients whose clinical presentation and chest radiograph fail to suggest any particular diagnosis a raised serum ACE will provide a lead for additional investigations.

The diagnostic usefulness of serum ACE as a test in sarcoidosis was confirmed at the IXth International Conference on Sarcoidosis (Paris 1981). The combined experience for 12 centres of "false positive"
values in conditions apart from sarcoidosis is summarised in the Table. The raised values seen in other conditions reduce the specificity. It is therefore appropriate to consider how often a raised serum ACE will accurately predict a diagnosis of sarcoidosis. The combined data showed that sarcoidosis was present in 90% of subjects with raised serum ACE (the positive predictive value). However, some 40% of patients with active sarcoidosis have normal serum ACE, indicating that normal enzyme activity does not exclude the diagnosis.

Serial serum ACE measurements in sarcoidosis
While a raised serum ACE is diagnostically useful, of even more importance are serial measurements to give advance warning of changing activity. Relatively few longitudinal studies of converting enzyme activities in sarcoidosis have been reported, but it is clear that raised activities fall to normal should the disease spontaneously remit or when corticosteroids suppress activity. Rising activities may herald a relapse. The course of one patient is summarised in Fig. 3. Converting enzyme activities closely parallel clinical and radiographic changes and are helpful in determining the adequacy of glucocorticoid therapy.

Apart from the clinical and radiographic features does serum ACE correlate with other findings in sarcoidosis? No significant correlation has yet been demonstrated linking the enzyme with characteristic haematological or biochemical findings, and even hypercalcaemia may be found with normal activity. The findings obtained by Gallium 67 Lung Scanning or bronchoalveolar lavage correlate well with the intensity of pulmonary sarcoidosis, but poorly with measurements of serum ACE activity.

THERAPEUTIC AGENTS INHIBITING ANGIOTENSIN CONVERTING ENZYME
Current attention focuses on the renin angiotensin system in relation to mechanisms controlling blood pressure and renal function. ACE inhibitors have clinical antihypertensive properties. The role of renin in essential hypertension has been the subject of a review by Atlas and Case. They provide convincing evidence that ACE inhibitors can be used as phar-
macological probes for assessing the renin system in hypertension. A synthetic nonapeptide SQ 20881,97 was the first converting enzyme inhibitor to be tested in man and early clinical studies provided evidence that inhibition of the renin angiotensin system might be beneficial in hypertension.98 This has led to the development of SQ 14225 (Captopril) the first orally effective and apparently specific inhibitor of the converting enzyme.99 100 Captopril causes long-term inhibition of angiotensin II formation and it has been shown to be effective in lowering blood pressure.101–103 The use of orally active ACE inhibitors has enabled the role of renin in long-term blood pressure control in essential hypertension to be investigated. The degree of inhibition of ACE by Captopril can provide an indirect method of assessing the activity of the drug. However, Roulston104 found that although Captopril is a potent inhibitor of serum ACE, the serum had to be assayed within a few hours. In samples stored at −20°C progressively less inhibition was observed as the time of storage was increased. Kamoun105 using lower temperatures, −80°C or −196°C found the binding of Captopril to ACE stable for 12 days.

OTHER CONDITIONS AND SERUM ACE ACTIVITY

The brush border of kidney tubules is rich in ACE activity and the measurement of urinary ACE has been used by Baggio106 to provide an index of renal tubular damage. Lieberman found that raised serum ACE values correlated strongly with the presence of severe retinopathy in diabetes mellitus and considered that vascular damage may release the enzyme into the blood. Microangiopathy has been noted to accompany retinal choroidopathy in sarcoidosis and he suggests that raised serum ACE activity in sarcoidosis may have a dual origin; from the sarcoid granuloma and sites of microangiopathy.

Mention must also be made of one rare chronic familial disorder. Very high enzyme activities are found in the serum of most patients with Gaucher's disease.107 The common denominator between Gaucher's disease and those granulomatous diseases, including sarcoidosis, in which serum ACE is raised is the macrophage which is transformed into either storage or secretory cell respectively.

Finally, a number of studies in animals have demonstrated fluctuations in ACE activity after experimentally induced lung damage and recently Dobular et al.,108 working with rabbits, have reported reduced in vivo ACE after hypoxic lung injury even before light or electron microscopy histological change could be detected.

Further work will need to consider the influence of diffuse vascular or pulmonary injury on enzyme activities and its measurement may provide an indirect guide to the extent of damaged endothelial surfaces.

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