Renal enlargement in chronic cor pulmonale

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SYNOPSIS
Examination of the post-mortem records of 1,391 unselected cases showed that the commonest condition associated with excessive diffuse enlargement of the kidneys was chronic cor pulmonale. A less striking enlargement was found in some cases of chronic rheumatic heart disease.

A hypothesis is put forward in which the renal enlargement is regarded as a work hypertrophy brought about by the kidneys' efforts to compensate for a chronic respiratory acidosis.

Very little is to be found in the literature on the subject of structural kidney changes in chronic cor pulmonale. Black and Stanbury (1958) comment on this lack of information and describe two patients with cor pulmonale in both of whom the last illness was associated with renal failure. Simpson (1957) also described renal failure as occurring, along with liver damage, in patients suffering from severe anoxia. Anatomical changes were present in one of Black and Stanbury's cases and were interpreted as being the earliest changes of tubular necrosis. Their other case also showed some enlargement of the kidney as a whole (combined weight 420 g.) and a small tuberculous focus was present. Simpson states that no anatomical lesions were present to account for the renal failure associated with anoxia.

The present investigations were undertaken as the result of an impression gained while performing routine post-mortem examinations that very large kidneys are often found in cases of chronic cor pulmonale.

MATERIAL
The records of 1,391 necropsies were examined. This total was made up of all the necropsies performed at Newcastle General Hospital in 1956 and 1957 (1,197) and 194 personal cases examined in 1958 and 1959.

Cases were admitted to the series when chronic lung disease was present along with enlargement of the right ventricle. All those with left ventricular enlargement or valvular disease were excluded.

RESULTS
Thirty-seven cases satisfied these criteria and Fig. 1

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Correlation of Heart and Kidney Weights In Fig. 2 kidney weights are plotted against heart weights. Any increase in heart weights in these cases is, because of the criteria for inclusion in the series, the result of right ventricular hypertrophy. The correlation which is shown between heart and kidney weights, therefore, suggests a correlation between right ventricular weight and kidney weight, and consequently between kidney weight and the degree and duration of pulmonary disease.

The first mechanism that suggests itself as responsible for the renal enlargement is back pressure due to chronic congestive cardiac failure. If this were the only mechanism, one would expect to find a similar degree of renal enlargement in cases of chronic cardiac failure from other causes. Mitral stenosis was chosen for comparison because this condition commonly produces pure right ventricular hypertrophy associated with repeated episodes of congestive cardiac failure as does cor pulmonale.

In Fig. 3, 16 cases of pure mitral stenosis, all with enlargement of the right but with normal left ventricles, are similarly plotted. While there is some correlation between heart and kidney weight in Fig. 3 it appears that cases of mitral stenosis with hearts of a given weight have smaller kidneys than cases of cor pulmonale; and though the kidneys of one case reach 500 g. none exceed it. The numbers, of course, are smaller.

A large number of cases of rheumatic heart disease were excluded from the graph because the

left ventricle was enlarged, due as a rule to aortic valve disease or to mitral incompetence. Figure 1b shows the distribution of kidney weights in all cases of rheumatic heart disease in which the right ventricle was enlarged, irrespective of other lesions. A single case of congenital heart disease with right ventricular enlargement was also included. Comparison of the two histograms clearly shows that there is a greater tendency to diffuse renal enlargement in chronic cor pulmonale.

A significant but less extreme degree of renal enlargement sometimes occurs in rheumatic heart disease (three cases with kidneys weighing between 475 and 500 g.).

Morbid Anatomy of the Enlarged Kidneys To the naked eye, except for their size, the intact kidneys appeared normal. They were firm to the touch in common with kidneys of chronic congestive failure.
Figs. 4 and 5 show cortex from two cases of cor pulmonale, Fig. 6 is a normal control, and Fig. 7 shows the cortex of a kidney hypertrophied (weight 320 g.) because of removal of its fellow many years before the patient's death. All × 75.
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in general. On cross section the cortex appeared broad (up to 1 cm. in thickness) and there was, as a rule, some degree of congestion.

Histological material was available from six cases in which the kidneys had weighed more than 500 g. and examination showed a striking and consistent increase in the diameter of the glomeruli (Figs. 4 to 7). In all six the diameters of 50 glomeruli were measured and the mean diameter and standard deviation calculated. Similar measurements were also taken from six normal kidneys and from the remaining kidney from a patient who died many years after a nephrectomy (see Table 1). Detailed histological assessment of the tubules was not possible because of post-mortem autolysis which was advanced in some cases and present to some extent in all.

In none of the six cases was there a significant degree of nephron loss, though in all of them occasional glomeruli were hyalinized or fibrosed. Measurement of tubular diameters was not attempted as it appeared that a very large number of measurements would have to be taken to make the figure representative of the whole kidney and it was felt that the increase in tubular diameter could best be appreciated by means of photomicrographs (Figs. 4, 5, 6, and 7).

**TABLE I**

<table>
<thead>
<tr>
<th>Name</th>
<th>Mean (μ)</th>
<th>Standard Deviation (μ)</th>
<th>Diagnosis</th>
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</thead>
<tbody>
<tr>
<td>WAD</td>
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<td>32</td>
<td>Cor pulmonale</td>
</tr>
<tr>
<td>AIR</td>
<td>244</td>
<td>30</td>
<td>Cor pulmonale</td>
</tr>
<tr>
<td>REY</td>
<td>224</td>
<td>33</td>
<td>Cor pulmonale</td>
</tr>
<tr>
<td>HOD</td>
<td>218</td>
<td>24</td>
<td>Cor pulmonale</td>
</tr>
<tr>
<td>MGU</td>
<td>232</td>
<td>30</td>
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</tr>
<tr>
<td>BAR</td>
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<td>Cor pulmonale</td>
</tr>
<tr>
<td>MEL</td>
<td>181</td>
<td>29</td>
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</tr>
<tr>
<td>DOD</td>
<td>184</td>
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</tr>
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<td>ESM</td>
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<tr>
<td>MAC</td>
<td>205</td>
<td>28</td>
<td>After nephrectomy</td>
</tr>
</tbody>
</table>

Incidental findings. In the present 37 cases of cor pulmonale active chronic peptic ulcers occurred in no fewer than 10 and a healed chronic ulcer in one. Three patients had given a past history of gastrointestinal haemorrhage. The ulcers were multiple in three of the ten.

**DISCUSSION**

It might be argued that this increase in renal weight is entirely the result of congestion from chronic right ventricular failure. If this were so, the degree of renal enlargement should be approximately the same in cases with equal degrees of right ventricular enlargement, whether due to mitral stenosis or to primary lung disease. Figs. 2 and 3 were constructed in an attempt to refute this argument.

Kidney weights were available in only two patients dying of constrictive pericarditis, a condition in which passive venous congestion is prolonged and intense. The first, a man aged 51 years, had kidneys weighing 290 g., and in the second, a woman aged 62 years, the kidneys weighed 300 g. These figures argue against chronic congestion as the operative factor in the renal enlargement of cor pulmonale.

The following hypothesis is put forward as a possible mechanism. It is well known that when the total bulk of renal tissue is reduced, for instance by nephrectomy or by widespread nephron loss in chronic nephritis, the remaining nephrons become hypertrophied. That such hypertrophy is advantageous to the body's economy is obvious but the mechanism whereby it is brought about is obscure. Presumably it results from the accumulation of some substance or substances excreted or detoxicated by the kidney.

In chronic pulmonary disease associated with carbon dioxide retention the kidney is required to excrete an increased amount of acid; this it does by means of two mechanisms:—

1. An increase in hydrogen ion output results in an increase in the titratable acidity of the urine. The hydrogen ion is produced in the reaction 
\[ \text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{H}^+ + \text{HCO}_3^- \], the first part of which is accelerated by the carbonic anhydrase of the renal tubular cells (Pitts and Alexander 1945: Pitts, Lotspeich, Schiess, and Ayer, 1948). One might expect this reaction to be pushed to the right by an increase in carbon dioxide tension in accord with the law of mass action. 2. An increase in ammonia excretion, ammonia being formed in the tubule cells from glutamine and certain amino-acids by the action of specific enzymes. By accepting a hydrogen ion each molecule of ammonia becomes an ammonium ion (\( \text{NH}_4^+ \)). Once formed, the ammonium and hydrogen ions within the tubular cells change places with filtered sodium in the tubular lumen (Van Slyke Philips, Hamilton, Archibald, Futcher, and Hiller, 1943). The net result is a loss of hydrogen ion, either free, or in combination with ammonia as ammonium ion; an increase in the concentration of plasma bicarbonate ion \( \text{HCO}_3^- \) (formed in the above reaction); and sodium reabsorption to balance the increase in bicarbonate.

An increase in the plasma bicarbonate raises the pH according to the Henderson-Hasselbalch equation...
\[ \text{pH} = 6.1 + \log \left[ \frac{\text{BHCO}_3}{\text{H}_2\text{CO}_3} \right] \]

Stated in another way, an increase in concentration of the bicarbonate ion causes a decrease in hydrogen ion concentration by pushing the reaction \( \text{H}^+ + \text{HCO}_3^- \rightarrow \text{H}_2\text{CO}_3 \) to the right, i.e., it retards the ionization of carbonic acid (law of mass action).

It is known that in subjects made acidic by the administration of \( \text{NH}_4\text{Cl} \) by mouth, \( \text{NH}_4^+ \) output in the urine rises rapidly in the first few hours as the urine becomes more acidic (Ferguson, 1951), after which it rises more gradually over several days. Davies and Yudkin (1952) rendered rats acidic for periods of up to 30 weeks by giving \( \text{N}/20 \text{ HCl} \) as drinking water. By means of studies on kidney slices they were able to demonstrate an increase in renal glutaminase, glycine oxidase and L. amino-acid oxidase, enzymes responsible for the formation of ammonia from glutamine, glycine, and L. leucine respectively. The gradual rise in ammonia output in chronic acidosis is thought to be due to this enzyme increase.

These observations indicate that the kidney tubule is able to respond to the stimulus of acidosis by increasing its content of those enzymes whereby the acidosis may be reduced, and, while in none of the experiments quoted above was renal hypertrophy mentioned, it is perhaps not entirely unjustifiable to suggest that it might occur, provided that the stimulus of an increased acid load were sufficiently prolonged.

The mechanism whereby glomerular enlargement is brought about cannot so easily be explained. Presumably it results in an enhanced rate of glomerular filtration in the presence of a falling cardiac output. In this connexion Davies and Kilpatrick (1951) have shown that in cor pulmonale with congestive failure, and in congestive failure from other causes, the effective renal plasma flow is reduced. The glomerular filtration rate is also decreased but not to the same extent, the filtration fraction (glomerular filtration rate/effective renal plasma flow) being raised.

It is possible that the above hypothesis may explain not only the renal enlargement of cor pulmonale but also the less striking enlargement seen in some of the cases of rheumatic heart disease. Gaseous exchange in the rigid lung of severe, long-standing mitral stenosis is known to be inefficient with regard to oxygen: however, the handling of the more diffusible carbon dioxide is said to be unaffected (Wood, 1956).

Several writers have commented on the association between chronic chest disease and peptic ulceration, the latter being present in about 20% of cases (Green and Dundee, 1952; Latts, Cummins, and Zieve, 1956). Flint and Warrack (1958) have shown that acute peptic ulceration can be found in a higher proportion of necropsies on cases of cor pulmonale if the lesions are looked for carefully. This is in agreement with the findings in the three cases described above.

The incidence of multiple chronic ulcer is remarkably high (four out of 10) but in so small a series this might be due to chance. The frequency of ulceration is probably related to a high acid output by the stomach. The hydrogen ions secreted by the parietal cells are believed to be produced in the reaction \( \text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{H}^+ + \text{HCO}_3^- \), the first part of which is catalysed by gastric carbonic anhydride. As postulated above, for the same reaction occurring in the kidneys a high carbon dioxide tension would push this reaction to the right and increase acid production (Latts et al., 1956). Though the exact relationship between hyper-secretion of gastric hydrochloric acid and peptic ulceration is not yet clear, it is widely recognized that an association exists.

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REFERENCES
