basis of a comparative study of human and animal thyroid carcinomas, I have suggested that medullary carcinoma is a parafollicular cell tumour of the thyroid (Williams 1966). The parafollicular cell is a second type of thyroid epithelial cell which lies between the follicular epithelium and the basement membrane – in a situation analogous to that of the Kulchitsky cell. The parafollicular cell in the sheep has been shown by Falck *et al.* (1964) to contain 5-hydroxytryptamine. Thirdly, a single case report of a patient with a 'solid' carcinoma of the thyroid and the carcinoid syndrome has been recorded (Moertel *et al.* 1965); the 5-HIAA excretion was raised. Finally, we have been estimating 5-HIAA excretion in patients with medullary carcinoma. So far one of the 3 patients tested showed an elevated level, 25 mg/24 hours. This patient did not have any diarrhœa.

It has been known for some years that serotonin is not the sole explanation of the carcinoid syndrome, and recent work from Sjoerdsma's laboratory provides evidence that carcinoid tumours contain kallikrein, an enzyme which acts on a globulin substrate to produce bradykinin or other similar vasoactive polypeptides (Oates *et al.* 1964). The exact roles played by kinins and by serotonin in the causation of the carcinoid syndrome are not clear, but it is likely that the kinins play a major role. Kinins and serotonin are found together in a number of situations in nature, so that as parafollicular cells can make serotonin, it is likely that they and their tumours are also capable of producing kinins.

In conclusion, I suggest that medullary carcinoma of the thyroid is a tumour allied to the carcinoid group of tumours, and that it may on occasions produce 5-hydroxytryptamine or its precursor, 5-hydroxytryptophan. Patients with widespread medullary carcinoma not infrequently have severe unexplained diarrhœa, and sometimes facial flushing. The most likely explanation for this is the production by the tumour of a kinin polypeptide acting on smooth muscle. Preliminary experiments on an extract of one tumour support this conclusion.

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The Conversion of Cortisone to Cortisol and Prednisone to Prednisolone in Man
[Abridged]

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In the history of steroid therapy, cortisone occupies the place of first importance but there is now considerable evidence that cortisone itself is biologically inactive. Several investigators (Hollander *et al.* 1951) have reported that the injection of cortisone locally into inflamed joints is ineffective when compared with cortisol. Jenkins *et al.* (1964), studying the effects of steroids on lipid metabolism, showed that the local infusion of cortisol intra-arterially into the forearm was followed by release of free fatty acids into the venous blood but the infusion of cortisone was without effect. Even more striking is the difference in behaviour of the 2-methyl derivatives of cortisol and cortisone when given systemically. 2-methyl cortisol is several times more active than the parent cortisol, whereas 2-methyl cortisone is almost devoid of activity. Bush & Mahesh (1959) showed that this difference was due to the 2-methyl group hindering the reduction of the 11-ketone group. It is this reduction of the 11-ketone to 11β-hydroxyl by the enzyme 11β-dehydrogenase which renders the 11-ketosteroids biologically active when they are administered systemically. Jenkins (1966) has shown from experiments carried out *in vitro* using human tissues, that the liver was the most important site for this conversion. Other tissues, such as the kidney, which were very active in oxidizing cortisol to cortisone, could not carry out the reduction of the 11-ketone. Since steroids having the 11-ketone configuration such as cortisone and prednisone are widely used therapeutically it was considered important to study the extent to which they became converted to the biologically active 11β-hydroxy compounds.

The Conversion of Cortisone to Cortisol

This was determined by estimating plasma cortisol levels at hourly intervals after the oral administration of single doses of cortisone; 25 mg was given to each of 3 patients with Addison's disease, and 100 mg or 200 mg to 9 normal subjects. Plasma cortisol was measured specifically in the presence of cortisone by a fluorimetric technique. On separate occasions a similar dose of cortisol was administered to each of the same subjects and the plasma cortisol levels were compared. The peak value in the plasma

usually occurred two hours after the administration of cortisone and one hour after cortisol. The plasma cortisol after cortisone was always much less than after cortisol itself and at the 200 mg dosage of cortisone the peak was only about a third to a half that obtained after 200 mg cortisol. This difference was not due to differences in absorption from the intestine since measurement of the urinary metabolites showed that the values were substantially the same for both steroids. In order to obtain further information as to the fate of cortisone the various unconjugated steroids present in the plasma two hours after 200 mg of cortisone and cortisol were examined more specifically by a chromatographic technique. The cortisol level after cortisone in this particular normal subject was about half that after cortisol but this difference was not wholly accounted for by unreduced cortisone. A large amount of tetrahydrocortisone was also found and it appeared that much of the cortisone was wasted by reduction of the ring A and not converted to the biologically active 11-hydroxy form.

Conversion of Prednisone to Prednisolone

At the present time, when large doses of steroids are required therapeutically, cortisone has been largely superseded by the synthetic 1–2 dehydro compounds prednisone and prednisolone. Many physicians do not distinguish between these two steroids, and prescribe them indiscriminately. It is, however, necessary to know the extent to which prednisone is converted to the active prednisolone. One hundred milligrams of prednisone and, on a subsequent occasion, 100 mg of prednisolone were administered in single oral doses to 3 normal subjects, and the plasma prednisolone levels were estimated at hourly intervals. These same subjects had all previously received 100 mg each of cortisone and cortisol, and the very large dose of prednisone was used so that a direct comparison could be made on a weight basis with cortisone in the same subject. Plasma prednisolone was estimated by a paper chromatographic technique.

Prednisone was converted to prednisolone with a much higher degree of efficiency than that of cortisone to cortisol, the peak plasma prednisolone values after prednisone varying from 85% to 95% of those after prednisolone itself.

The Conversion of 11-keto to 11-hydroxy Steroids in Liver Disease

Since there is evidence that the liver is the chief site for reduction of the 11-ketone group, it was obviously relevant to determine the effect of liver disease.

A patient suffering from acute infective hepatitis with considerably impaired liver function tests was given 100 mg of cortisone and subsequently 100 mg of cortisol. The values for plasma cortisol after cortisone fell within the normal range, although the values after cortisol rose above normal, in keeping with the known impairment of cortisol metabolism in liver disease.

Another patient, suffering from hepatic cirrhosis, was given 200 mg of cortisone and subsequently 200 mg of cortisol, and the various plasma unconjugated steroids were studied chromatographically at the two-hour period. A normal subject given 200 mg of the steroids was compared. In the patient suffering from cirrhosis the cortisol level after cortisone was greater than in the normal subject although much more cortisone remained unmetabolized. This seemed to be due to a relative failure to form tetrahydro compounds, thereby also accounting for the persistence of the cortisol which was formed. The conversion of prednisone to prednisolone was also studied in one patient with hepatic cirrhosis and another with infective hepatitis. In one case the conversion to the 11-hydroxy steroid was complete and in the other it was substantial.

All 4 cases of liver disease, therefore, showed preservation of 11-dehydrogenase activity to a considerable degree, and this was in contrast with the impairment of ring A reductase activity which occurred. It is of course possible that more severe cases of liver failure than those studied here would have shown more definite impairment of 11-ketone reduction.

Summary

There is much wastage of cortisone when large doses are administered orally, mainly due to reduction of ring A. Since cortisone is a relatively inefficient source of cortisol, there seems to be a good case for always using cortisol itself rather than cortisone when this steroid is required orally. On the other hand, prednisone is virtually interchangeable with prednisolone, in view of its high degree of conversion to that steroid, probably because reduction of ring A can occur only to a limited degree with the 1–2 dehydro steroids.

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(*Meeting to be continued*)