SOME METABOLIC EFFECTS OF THE ENDOCRINE TREATMENT OF RECURRENT AND METASTATIC CARCINOMA OF THE BREAST

By

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That the growth of neoplastic tissue need no longer be regarded as entirely autonomous has become more and more evident in recent years. This applies particularly to carcinoma of the prostate and breast, where the purely destructive effects of surgery and treatment by irradiation are being supplemented by methods of management involving the administration of hormones, or removal of the sources of certain hormones.

There are now several procedures available which may be used to modify the growth of tumours of the breast. However, it is frequently difficult to recognise early changes in the behaviour of the tumour when endocrine treatment is employed. The simple clinical methods of photography, radiography and measurement of tumours are often inadequate for this purpose. In view of the relatively wide choice of therapeutic procedures, and because some of these may sometimes be harmful rather than helpful, it has become all the more important that an early decision should be reached regarding the nature of the response to any form of treatment used.

Any investigation which provided a consistent objective and quantitative estimate of the response of a tumour to treatment would be of great value. The importance of studying the excretion of calcium in the urine for this purpose was shown by Pearson, West, Hollander & Treves (1954), and further observations on these lines were described by Emerson & Jessiman (1956). This method, although most useful, is of limited scope, since it will only be expected to apply to those patients with metastases in bone. In view of this, and the need for further information about metabolism in carcinoma of the breast as well as other forms of cancer, a study has been made of a number of patients under treatment for metastatic and recurrent mammary cancer.
Observations have been made on nitrogen balance as an indication of protein metabolism. Calcium balance was studied as a measure of the activity of cancerous tissue involving bone, and sodium, chloride and potassium balances were also examined, since their metabolism is known to be affected by many of the measures used in the hormonal treatment of carcinoma of the breast. Only examples to illustrate certain aspects of the problem will be presented in this paper.

METHODS

All food was weighed and the intake of nitrogen, calcium, sodium, potassium and chloride was calculated from the tables prepared by McCance & Widdowson (1946). Nitrogen was estimated by a micro-Kjeldahl technique, calcium by precipitation as calcium oxalate and titration with potassium permanganate (King, 1951), chloride by the method of Schales & Schales (1941), and sodium and potassium by flame photometry, using a lithium internal standard.

Checks on the validity of using tables to calculate intakes were made by analysing samples of diet. These were found to agree reasonably well, usually better than ±10%, and the longer the period of observation the closer was the agreement. In any event the conclusions to be offered do not depend directly on the accuracy of measurement of the intake, but rather on the changes in excretion, which will only be partly dependent on intake.

In most cases only the urinary excretion of nitrogen, calcium, sodium potassium and chloride has been measured, as it was felt that in the absence of diarrhoea the amounts excreted in the stool would not affect the conclusions reached.

RESULTS

Fig. 1 represents the findings in a male aged 70 who had developed widespread metastatic disease in bone from a carcinoma of the breast removed two years earlier. He was admitted to hospital for orchidectomy and at the same time the opportunity was taken of investigating nitrogen and mineral metabolism in relation to this operation. Simultaneously, a study was being made of the excretion of injected steroids, but with the exception of some transient changes in sodium and chloride metabolism, it is considered unlikely that these had any effect on the metabolic study.

Nitrogen. It is apparent that whereas before orchidectomy this patient had been in constant negative balance, 10 days after operation he was in nitrogen equilibrium, and assuming a faecal nitrogen of 1 g. daily, he remained in equilibrium for the further 10 days during which observations were continued.
Fig. 1.
Metabolic study in a male aged 70 with widespread metastases in bone from a mammary carcinoma removed 2 years earlier. In this and other diagrams intake is plotted downwards from the base line (0), and excretion upwards from the lowest point indicating intake. Thus a clear space below the base line indicates that intake exceeds excretion and the balance is positive, and if the block representing excretion crosses the base line the balance is negative.

Calcium. During the 13 days before orchidectomy, calcium excretion in the urine had varied between 200 and 500 mg. daily, but after the fourth post-operative day the amount in the urine fell below 200 mg. and remained very low thereafter.

It became apparent later that the clinical response was as satisfactory as the metabolic studies had suggested it should be, and it is striking that the reduced
amount of calcium in the urine should have indicated this within five days of operation. The change in nitrogen balance occurred more slowly and steadily over the course of the 10 days after orchidectomy. As the patient remained active throughout the period of the study, the changes are not likely to have been due to alterations in the amount of physical exertion. Apart from the bony metastases the patient probably had soft tissue metastases as well, which would affect the N balance, and in any case the external balance of intake and excretion of N as measured is complicated by the internal balance of N between the normal tissues and the cancerous tissue. For this reason the external balance would not necessarily represent accurately changes in the behaviour of tumour tissue.

About nine months later it was apparent clinically and radiologically that the patient's condition was again deteriorating, and he was admitted to hospital so that the effect of stilboestrol on his disease might be studied. The results are illustrated in Fig. 2. Before treatment with stilboestrol was initiated the nitrogen balance was consistently negative. Twenty four hours after starting treatment with stilboestrol the balance became much more negative, only to improve slowly over the next two weeks while treatment with stilboestrol continued. The calcium content of the urine had been about 500 mg. daily for 6 days before stilboestrol, but although the negative nitrogen balance was very rapidly aggravated when treatment with stilboestrol was initiated, the excretion of calcium only increased in a striking manner after 7 days.

It became clear on clinical and radiological grounds that the patient was deteriorating rapidly, and treatment with stilboestrol was therefore withdrawn.

There was some discrepancy between the changes in nitrogen and calcium excretion after withdrawal of stilboestrol. Excretion of nitrogen had almost reached equilibrium when stilboestrol was withdrawn: calcium excretion had been diminishing but fell very rapidly at this stage.

In the earlier part of the course of treatment with stilboestrol there was a transitory but marked retention of sodium and chloride, with some «rebound» after 7 days.

In view of the deterioration during treatment with stilboestrol, it was decided to proceed with bilateral adrenalectomy. This procedure was performed in two stages with an interval of 12 days between the operations (see Fig. 3). At the time of the first operation no hormone replacement was given, but throughout and after the second stage both deoxycortone acetate and cortisone were given in large doses. The metabolic response to the two operations is illustrated in Fig. 3, and is shown to be similar in kind and to a considerable extent in degree. Two weeks after the second operation nitrogen balance became positive and remained so. Calcium excretion in the urine had diminished after withdrawal of stilboestrol, and was further reduced after the first stage of the adrenalectomy.
Fig. 2.
The metabolic response to the administration of stilboestrol. The data refers to the same patient as in Fig. 1.

In the subsequent 4 months the condition of this patient improved in a most remarkable way. The bones recalcified until their radiographic density appeared normal. His weight increased from 82.5 kg. to 97.5 kg. The effect of substituting $9\alpha$ fluorohydrocortisone ($9\alpha$ FF) for his maintenance dose of corti-
Cortisol was then studied, and is shown in Fig. 4. On a dose of 1.5 mg. daily of 9α FF his weight increased by 3 kg. in 4 days. At the same time he was clearly retaining much sodium and chloride, and because of the appearance of oedema he was given an injection of mersaly1 B. P. 2 ml. intramuscularly. This was followed by a diuresis of water and sodium chloride. (The corticotrophin infusion was given as part of a test for residual or accessory adrenocortical tissue, and is not relevant to this paper).

On 13th June it was noted that the serum potassium concentration had fallen to 3.3 mEq./l., and he was given extra potassium by mouth as potassium citrate. This additional potassium was all retained, and at the same time an approximately equivalent amount of sodium was excreted along with similar amounts of chloride.

Fig. 3.

The metabolic response to adrenalectomy performed in two stages.

Data refer to the same patient as described in Figs. 1 & 2.
Nitrogen and electrolyte balance in the same patient as described in Figs. 1, 2 and 3, four months after bilateral adrenalectomy. (The broken lines in the histogram for 6th June indicate incomplete collection, but the amounts shown are as measured).
The study confirms that calcium excretion in the urine is a useful indicator of the activity of metastases in bone. To a considerable extent this evidence of tumour activity was matched by a negative N balance. In some circumstances, for example when the patient was given stilboestrol, the nitrogen balance became markedly negative within 48 hours, whereas a week elapsed before the calcium in the urine showed any striking change.

Fig. 5 illustrates the metabolic response to bilateral adrenalectomy and oophorectomy performed in two stages. The patient, a female aged 51, had widespread soft tissue and bone metastases. Although the N balance was negative before operation, the urinary calcium was very low and remained so throughout the period of observation. Indeed as the N balance became positive

Fig. 5.
Metabolic response to adrenalectomy performed in two stages in a woman, aged 51, with widespread metastases in bone and soft tissue.
after operation the excretion of calcium increased slightly. In this patient urine calcium would have been misleading as an indicator of bone disease, and the N balance gave some indication that the condition of the patient was later improving. In part this may have been due only to increased N intake, which before the first operation was only about 5 g. daily.

In Fig. 6 the converse is shown in a patient immediately after completing a course of treatment with testosterone phenyl propionate. Although the N balance was positive for one week after observations were begun, throughout this time calcium excretion remained between 400 and 500 mg. daily.

The sequence of metabolic events in a patient aged 57 with soft tissue and bone metastases is illustrated in Figs. 7, 8 and 9. Before treatment she was in slightly negative N balance, and was excreting less than 200 mg. of calcium daily in the urine. When treatment with stilboestrol was begun the N balance became positive, though Ca excretion was apparently unaffected. After 8½

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**Fig. 6.**

Nitrogen balance and calcium excretion in the urine in a patient (H), aged 55, with extensive metastases in bone. The patient received the last of six weekly injections of testosterone phenyl propionate each of 100 mg. on 30. 12. 55.
Fig. 7.
Nitrogen balance and calcium excretion in urine in a patient of 57 years commencing treatment with stilboestrol.

Fig. 8.

weeks treatment with stilboestrol, the drug was withdrawn (day 75), and it will be seen in Fig. 8 that although N balance was positive at the initiation of treatment with stilboestrol, it remained slightly negative until several days after treatment with testosterone had begun on day 90. Calcium excretion was not obviously increased at the time when stilboestrol was withdrawn, but the amount in the urine declined over the next few days.
Clinically the patient's condition had certainly deteriorated while being treated with stilboestrol, and she developed a spontaneous fracture through the left humerus which was treated by the insertion of an intramedullary pin on day 87.

Fig. 9 represents the period commencing two days after the last of six weekly injections of 100 mg. of testosterone phenyl propionate. Although N balance remained definitely positive, calcium excretion had increased appreciably since the period before treatment with testosterone began (Fig. 8). It would therefore appear that while the evidence based on the N balance is satisfactory and suggests control of tumour growth, the increase in calcium excretion would indicate an increase in the activity of the metastases in bone. The alternative explanation of a change in the patient’s physical activities to account for these
Nitrogen balance and calcium excretion in urine of the same patient (H) as described in Fig. 6, before and at the time of commencing treatment with stilboestrol.

The delay in metabolic response to stilboestrol in one patient is shown in Fig. 10. It is apparent that the response appeared to be favourable for the first four days, but thereafter it suddenly deteriorated. This deterioration was abundantly confirmed on clinical and radiological grounds six weeks later.

**DISCUSSION**

These studies have shown that the excretion of calcium in the urine is frequently a useful indicator of the activity of metastases in bone from carcinoma of the breast. The technique of nitrogen balance also provides a measure of activity of the disease, and because it may be expected to show changes in patients with tumours in other sites as well as in the bones, it is potentially a more useful method than the estimation of urinary calcium. Furthermore, a difference in the excretion of calcium in the urine may not be apparent for as long as seven days after a change in the method of treatment, whereas alterations in nitrogen balance were generally found to occur much more rapidly.

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Neither of these two methods, however, or even a combination of the two, will provide a consistent and reliable indication of the activity of metastatic disease. Both nitrogen and calcium metabolism may be altered by factors other than the activity of the disease. For example, immobilisation in bed, infection and a low caloric intake, all of which are liable to complicate the management of malignant disease, can each lead to a negative N balance, and excessive loss of calcium is always liable to accompany confinement to bed for any reason. Such factors as these cannot be eliminated, though their effect will be small in the less ill patient.

The metabolic response to the second stage of adrenalectomy when hormone replacement therapy is used, is so similar to the first stage when no replacement treatment is given, that it seems possible these metabolic changes are due to some factor other than adrenal cortical hormones or their analogues. An alternative explanation would be that the response is due to these hormones, whether endogenous or exogenous, but that the degree of response is unrelated to the amount of hormones secreted or administered.

SUMMARY AND CONCLUSIONS

1. Nitrogen balance and calcium excretion in the urine are useful measures of the activity of advanced malignant disease.
2. Either or both may provide an early indication of the response to treatment.
3. Metabolic response to adrenalectomy is remarkably consistent. The changes with one adrenal remaining are reproduced by substitution therapy after removal of the second gland.
4. A reliable objective measure of response to the treatment of malignant disease is urgently required.

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REFERENCES