Summary

Conditions are described in which pituitary growth hormone consistently produces an "insulin-like" effect on the glucose uptake of diaphragm from normal rats.

The effect is shown to be absent when the rats have been made diabetic, and to return when diabetic rats are injected with insulin. It is postulated that the effect is due to the liberation by growth hormone of insulin held in an inactive state in the blood or tissue.

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STRUCTURAL CHANGES IN PROSTATIC CANCER AFTER BILATERAL ADRENALECTOMY REPORT OF A CASE

BY

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[WITH SPECIAL PLATE]

Bilateral adrenalectomy and orchidectomy is claimed by Huggins (Huggins and Scott, 1945; Huggins and Bergenstal, 1952; West *et al.*, 1952) to have induced substantial clinical improvement in some cases of advanced prostatic carcinoma. It is also claimed that post-operative substitution therapy enables the patient to enjoy a fair measure of health and activity. The operation is still in the stage of therapeutic trial, but is being carried out on an increasing number of patients in this country. Most of the published evidence in its support is clinical in character, and remarkably little has been written on the effects of deprivation of adrenal cortical hormones on the structure of the growth and its metastases.

This report concerns a man of 63 with an oestrogen-resistant prostatic carcinoma, who was subjected to orchidectomy with no clinical improvement and finally to bilateral adrenalectomy. He died from an acute pulmonary infection 40 days after this operation. Massive necrosis was found in the primary growth and in its metastases in the regional lymph nodes, liver, and lung. The changes in all these situations had occurred simultaneously a few weeks before death, and, although incapable of rigid scientific proof, it is reasonable to suppose that this widely scattered necrosis was the direct consequence of total deprivation of adrenal hormones.

Case Report

A man aged 63 was admitted to hospital on August 14, 1952, complaining of rectal pain and urinary frequency for six weeks. The prostate was hard, craggy, and fixed. Serum acid phosphatase was 3.3 units (King-Armstrong).

An x-ray film of the spine and pelvis showed osteoarthritis; no metastases. An endoscopic resection on August 19 relieved the urinary symptoms, but the rectal pain persisted, and on September 16 a bilateral subcapsular orchidectomy was done. Severe rectal pain and dysuria increased in spite of this, and was not relieved by large doses of stilboestrol (30–60 mg. daily). He was then transferred to St. Philip's Hospital, where an enlarged liver and palpable enlarged lymph nodes in the groin were found. Bilateral adrenalectomy was advised, and he was transferred to the Central Middlesex Hospital for operation. A pre-operative blood-sugar curve revealed moderately severe diabetes mellitus, but the patient's general condition remained fair.

Substitution therapy with cortisone acetate (200 mg. decreasing to 66.5 mg. daily), deoxycortone (5 mg. daily, decreasing to 5 mg. on alternate days), and sodium chloride (5 g. decreasing to 3 g. daily), as described by Huggins and Bergenstal (1951), was begun on December 4 and continued post-operatively. Both adrenals were removed on December 5 by Mr. J. D. Fergusson. The left kidney was absent. There was no immediate clinical improvement, and stilboestrol, 100 mg. daily, was given from December 22 onwards. The diabetes mellitus remained unchanged and was controlled by diet and insulin, but in spite of this there were a number of hypoglycaemic episodes. On January 14, 1953, he collapsed, complaining of dyspnoea, and died the next day, apparently from a pulmonary embolus.

Post-mortem Examination

Necropsy was performed eight and half hours after death. The lungs showed basal congestion, scattered bronchopneumonic areas, many small tumour nodules, and a large wedge-shaped area at the periphery of the right upper lobe showing central degeneration and haemorrhage—apparently an infarct, but the pulmonary arteries, which showed nodular atheroma in the large branches, contained no embolus. There were many large and small tumour deposits in the liver, some with a zone of congestion around them. The right kidney was large (weight 13½ oz.; 383 g.). The left kidney and ureter were absent, and the renal vessels on this side were of normal size but ended blindly in a dense mass of fibrous tissue. The adrenals were absent. The bladder was dilated and there were several small diverticula. The left ureteric orifice could not be found. The prostate was largely replaced by a firm nodular tumour mass spreading into the seminal vesicles, periprostatic tissues, and the base of the bladder. The rectum was compressed but not obviously infiltrated. There were large tumour deposits in left and right internal, external, and common iliac, left inguinal, para-aortic, and mediastinal lymph nodes, some of which showed central degeneration. The breasts were normal. Bones (8–12 thoracic, 1–5 lumbar vertebrae, and sacrum) were normal. The pituitary was small. All other organs were normal. The immediate cause of death was thought to be the lesions in the lung.

Histology

Tissues were examined by a "big section" technique which has been in routine use in these laboratories for the past two years. By this method histological sections (5–8 μ) of whole organs are cut and examined microscopically. The pathological changes in this case might have been overlooked had smaller sections been cut, because the extent and distribution of the degenerative changes was much greater than was apparent to the naked eye. In all sections from the primary tumour and metastatic deposits in lymph nodes, liver, and lung there was a massive central necrosis involving both neoplastic tissue and stroma. The necrotic central mass was surrounded by a narrow zone of granulation tissue and, beyond this, a rim of surviving tumour cells (Plate, Figs. 1, 2, and 3). The change involved both large and small deposits, and the zone of granulation tissue was apparently about the same age (2–3 weeks) in all. The ratio between the amount of necrotic and surviving tumour tissue was approximately the same in the primary growth as in its

metastases. No comparable lesions were found in any tissue other than the tumour and its secondaries. In the larger necrotic areas there was some haemorrhage, and occasional blood vessels around the margin were filled with hyaline thrombus and their walls were necrotic. However, in the smaller lesions clumps or even single tumour cells had undergone a hyaline eosinophil necrosis without obvious change in the blood vessels.

In some of these smaller lesions and at the margins of the larger ones a series of degenerative changes were noticed. The outer zone of surviving tumour with cells arranged in solid cords surrounded an inner zone where the cells were separated, the nuclei smaller and more deeply staining, and the cytoplasm more eosinophilic. Towards the centre of the nodule the nuclei had become pyknotic and finally disappeared, leaving clumps of degenerate eosinophil cytoplasm which fused to form a central necrotic mass in which the "ghost" outline of the cells could be seen. This succession of changes suggested that cell degeneration might still have been going on at the periphery, although much more slowly than at first. It would seem that the first change had been necrosis of central tumour cells with secondary necrotic change in the stroma, where large numbers of cells had been destroyed. This stromal change is perhaps due to the release of enzymes from the damaged tumour cells. The surviving tumour is pleomorphic, with solid trabecular, small acinar, and anaplastic areas.

The lung showed bronchopneumonia and some haemorrhage into the wedge-shaped area in the right lower lobe. There were tumour emboli in the subpleural lymphatics. All secondary nodules showed central necrosis.

Discussion

There seems to be no doubt that degenerative changes in the tumour occurred shortly after bilateral adrenalectomy. Necrotic areas in rapidly growing tumours are of course commonly seen, but not as a rule involving both primary and secondary tumours simultaneously. No similar change has been seen in 29 other cases of prostatic carcinoma examined by the "big section" method using post-mortem material. Other possible causes are oestrogens, cortisone, insulin, or some other unknown agent. The first can probably be excluded because the cytotoxic changes it produces in prostatic cancer (Schenken *et al.*, 1942; Fergusson and Franks, 1953) differ from those seen in this case. There is little convincing evidence that cortisone affects the growth of human prostatic tumours (Huggins and Bergenstal, 1952), but a report on one case which showed clinical improvement after such treatment has recently appeared (Hayward, 1953).

It is also unlikely that insulin or the diabetic state could produce such massive necrotic lesions. On the whole the evidence suggested that the changes which occurred in this case were caused by the removal of both adrenals, but the possibility remains that the necrotic changes may be due to the interference with vascular supply so commonly seen in malignant tumours. The histological appearances, however, seem to show that the first degenerative changes took place in the tumour cells, and that these caused secondary changes in the stroma. If blood vessels are involved in this process an added ischaemic necrosis may occur in the area supplied by the vessel.

One further point of interest in this case is the absence of clinical evidence of regression in spite of the massive and widespread destruction of tumour cells.

Summary and Conclusions

Massive central necrosis apparently involving primary and secondary tumours simultaneously was seen in a patient dying six weeks after bilateral adrenalectomy for advanced prostatic cancer. A narrow zone of actively growing tumour cells surrounded these necrotic centres. It is highly probable (but not proved) that

these regressive changes were directly related to the removal of both adrenals. It is important that any similar material should be examined by methods which allow the extent and distribution of any degenerative changes to be appreciated.

The patient was operated on by Mr. J. D. Fergusson, and I am indebted to him and to the research department of the Institute of Urology for the clinical notes and post-mortem material: the case forms part of his series of advanced cancer cases treated by bilateral adrenalectomy, which will be described more fully later. My thanks are also due to Professor G. Hadfield for many helpful suggestions and to Dr. J. Craigie for the photographs.

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HAEMOLYTIC ANAEMIA IN TYPHOID FEVER

A REPORT OF SIX CASES, TOGETHER WITH THE EFFECT OF CHLORAMPHENICOL AND A.C.T.H.

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Acute haemolytic anaemia with haemoglobinuria has been reported as a rare complication of typhoid fever. Osler (1895) encountered one case in his series of 1,500. Curschmann (1898) reported two fatal cases. Musser and Kelly (1901) and Castellanos and Montero (1940) each described one case with recovery. Wright (1945) reported two fatal cases in East Africans. Batty Shaw (1951) described two cases with recovery, but one of these was subsequently thought to be a case of familial haemolytic anaemia. Gordon Smith (1951) reported one case to which chloramphenicol had been given before the onset of the haemoglobinuria.

Before 1945 the occurrence of haemolytic anaemia without haemoglobinuria was reported very infrequently. Under the guise of "acute pernicious anaemia" Mouisset, Mouriquand, and Thévenot (1906), Sicard and Gutmann (1911), Marcora (1919), and Stanzani (1924) reported, in all, five cases. There is no doubt that these were cases of severe haemolytic anaemia. According to Batty Shaw (1951), Kadrnka in 1928 described two cases of acute haemolytic anaemia complicating typhoid fever. Davidson and Fullerton (1938) reported haemolytic crises in a woman with *Salmonella dublin* infection, but she was thought to have a latent haemolytic anaemia.

Berman, Braun, and Rachmilewitz (1945) investigated 152 cases of typhoid fever and found nine cases of haemolytic anaemia of varying degrees of severity. The criteria employed were anaemia, increased reticulocyte count, retentive jaundice, and increased urobilinogen in the urine. In one case there was unequivocal evidence of haemolysis in that urobilinogen excretion in the urine and faeces was estimated quantitatively and found to be significantly raised.

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FIG. 1.—Prostate and rectum ($\times 2$). A dark peripheral zone of growth surrounds a large pale central area of massive necrosis. There is a similar change in tumour deposits in lymph nodes and periprostatic tissues included in the section.

FIG. 2

FIG. 3

FIGS. 2 and 3.—Liver ($\times 2$) and mediastinal lymph nodes ($\times 2$), showing areas of massive necrosis similar to that in Fig. 1.