1957, he said he was much better since taking the tablets, and that he was reminded by discomfort if he did not take them. He has worked regularly during treatment.

Case 14.—A man aged 53 had had symptoms for 30 years. In October, 1956, he had a straight rigid dorsal and lumbar spine and slight movement of his neck, which was projected forward. His ribs showed no appreciable movement during respiration. Lumbar spine and sacro-iliac joints were completely ankylosed. His E.S.R. was 25 mm. in 1 hour. He complained of considerable pain in his shoulders and neck. Prednisolone was started in October, and one month later he reported that he was "practically free of pain—more so than for six or seven years"; also that movement of his neck had improved and he felt fully active. His chest expansion was then 1 in. (2.5 cm.). In February, 1957, he reported that pain was negligible, and he thought that movement of his neck had further improved. His chest expansion was 1½ in. (3.8 cm.). He had worked continuously as a schoolmaster. His E.S.R. was 5 mm. in 1 hour.

Summary

The response of 14 consecutive patients with advanced and painful ankylosing spondylitis to treatment with corticotrophin, cortisone, and prednisolone is recorded. There has been an appreciable degree of relief of symptoms, which had not been obtained by other means. The relief of pain was rapid, and was accompanied by some increased freedom of movement. In some cases treatment was stopped, with continuing relief.

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REFERENCES

- Baird, J. P. (1955). *Proc. roy. Soc. Med.*, **48**, 201.
British Medical Journal, 1957, **1**, 215.
 Copeman, W. S. C. (1953). *Cortisone and ACTH in Clinical Practice*. Butterworth, London.
 Forestier, J., Jacqueline, F., and Rotes-Querol, J. (1956). *Ankylosing Spondylitis*, p. 321. Thomas, Springfield, Illinois, U.S.A.
 Hart, F. D. (1952). *British Medical Journal*, **1**, 188.
 — (1955). *Ann. rheum. Dis.*, **14**, 77.
 Morrison, R. J. G. (1955). *Proc. roy. Soc. Med.*, **48**, 204.
 West, H. F., and News, G. R. (1954). *Ann. rheum. Dis.*, **13**, 109.

ADRENOCORTICAL HYPERACTIVITY IN A PATIENT WITH BRONCHIAL CARCINOMA AND DIABETES MELLITUS

BY

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Adrenal hyperplasia has been reported to be present at necropsy in about 6% of all patients dying with malignant disease, and appears to be associated most commonly with carcinoma of the bladder, endometrium, kidney, and respiratory tract (Parker and Sommers, 1956). Dobriner (1952) showed that in cases of cancer the mean urinary corticosteroid excretion was higher than normal, and Voigt and Kny (1954) recorded a case of bronchial carcinoma with increased insulin tolerance. The interest in the present case lies in the occurrence of marked adrenocortical hyperactivity in association with bronchial carcinoma.

Case Report

A 48-year-old furnaceman was admitted to hospital on May 17, 1955. For many years he had suffered from a cough with some mucoid sputum which he attributed to smoking about 15 cigarettes a day. In March, 1955, he had a short

febrile illness, following which he failed to regain his strength. His mouth and tongue felt dry; he drank a great deal of fluid and passed large quantities of urine at frequent intervals. His appetite decreased, he lost weight, and for one week prior to admission took no solid food. Progressive pigmentation appeared on the face and arms. For two weeks his ankles had been swollen, and he noticed tingling in his fingers and toes. Throughout this period he was troubled by an unproductive cough.

Examination showed him to be a well-built muscular individual with evidence of recent weight loss. A bluish-brown pigmentation affecting the skin and buccal mucous membranes was most pronounced on the face and extensor surfaces of the arms. The skin and tongue were dry; the sputum was mucoid. At the right lung base the percussion note was decreased and air entry diminished. The liver was enlarged to 8 cm. below the right costal margin; it was firm and its surface irregular. The urine gave an orange colour with Benedict's solution, and Rothera's test for acetone was strongly positive. His blood pressure was 130/75 mm. Hg; temperature 99° F. (37.2° C.).

A radiograph of the chest showed an opacity in the right cardiophrenic angle due to collapse of the right lower lobe; the right paratracheal lymph nodes were enlarged. Tomography of the chest revealed a mass 4 cm. in diameter in the right cardiophrenic angle with narrowing of the right lower lobe bronchus. At bronchoscopy rigidity of the right main bronchus with narrowing of the right lower lobe bronchus was demonstrated, but no neoplasm was identified; biopsy showed normal bronchial mucosa. Liver needle biopsy contained metastatic carcinoma, and the bone marrow also contained carcinoma cells.

Liver-function tests showed serum bilirubin 0.4 mg. per 100 ml., thymol turbidity less than 1 unit, serum alkaline phosphatase 28 King-Armstrong units, serum proteins 5.4 g. per 100 ml. (albumin 3.7 g., globulin 1.7 g.), bromsulphthalein excretion normal, serum iron 115 µg. per 100 ml., and prothrombin efficiency 100%. The urine was free from bile and contained only traces of urobilinogen.

Other investigations performed were: fasting blood sugar 441 mg. per 100 ml. (following 50 g. of glucose by mouth the blood sugar rose to 483 mg. after 1½ hours, and was 378 mg. after 2½ hours); 24-hour urinary excretion of 17-ketosteroids 50.4 mg., of 17-ketogenic steroids 138 mg., and of pregnanediol 8.7 mg.; serum sodium 152 mEq/l., serum potassium 4.4 mEq/l., serum chloride 99 mEq/l., and plasma alkali reserve (four days after admission) 28 mEq/l.; blood urea 40 mg. per 100 ml.

The haemoglobin was 10 g. per 100 ml., W.B.C.s 4,000 per c.mm. (polymorphs 68%, lymphocytes 28%, monocytes 4%). The Wassermann reaction was negative and an electrocardiogram showed no abnormality.

Skin biopsy revealed atrophy of the Malpighian layer and some hyperkeratinization of the epidermis. The deeper layers of the epidermal cells were heavily pigmented with melanin.

Progress.—On a diet containing 160 g. of carbohydrate a day it was possible to control his diabetes with 88 units of insulin zinc suspension. The patient slowly deteriorated, however; he continued to lose flesh, his oedema increased, he developed ascites, and the liver became larger and more irregular. There was increasing evidence of peripheral neuritis with weakness of the arms and legs, loss of deep reflexes, and absence of sensation over the hands and feet. On June 16 he was noticed to be jaundiced and to have a petechial rash. He died on June 23.

Special Investigations.—The daily urinary 17-ketosteroid and 17-ketogenic steroid urinary excretion from June 10 until his death on June 23 is shown in the Chart. Cortisone, 50 mg. six-hourly by mouth, was administered for 48 hours on June 14 and 15, and corticotrophin of known potency, 25 mg., was given six-hourly intramuscularly for 48 hours on June 21 and 22. It will be seen that the 17-ketosteroid excretion showed no great variation, and that the 17-ketogenic steroid excretion remained between 106 and 159 mg.

Urinary excretion of 17-ketosteroids and 17-ketogenic steroids.

with the exception of the two days on cortisone, when the excretion was 163 and 176 mg. The raised pregnanediol excretion was confirmed on two occasions (6.7 and 8.2 mg.). Dehydroisoandrosterone was present in the urine in increased quantities, but considerably less in amount than has been found in cases of adrenocortical carcinoma.

Post-mortem Examination

Naked Eye.—There was deep brown pigmentation of the skin as described in life, and patches of brown pigmentation were present in the buccal mucous membranes. There were petechial haemorrhages in the skin of the trunk and legs; the legs were oedematous. A carcinoma of the right lower lobe bronchus with bronchopneumonia in the lung beyond the growth was found; the mediastinal lymph nodes were grossly enlarged, metastatic tumour was present in the right cardiophrenic angle, and the remaining lung tissue was oedematous. A small right pleural effusion and the ascites were blood-stained. The liver contained multiple secondary deposits and weighed 3,090 g. Tumour deposits were found in the retroperitoneal lymph nodes and the vertebral bodies. The adrenals both contained whitish growth; together they weighed 30 g.

Microscopy.—The tumour was a poorly differentiated adenocarcinoma of the bronchus showing extensive intra-alveolar spread; the deposits in the liver and lymph nodes had a similar histological appearance. The pituitary, thyroid, and pancreas showed no abnormality. There was marked adrenocortical hyperplasia with focal lipid depletion; both adrenals contained secondary growth in the cortex and medulla.

Discussion

The sustained hyperexcretion of adrenocortical hormones is the outstanding feature of the present case. Increased adrenocortical secretion has only occasionally been observed in cases of cancer. Hardy (1955), studying steroid excretion in advanced malignant disease, reported three cases in which corticoid excretion was raised. Moore *et al.* (1955) reported the case of a woman with cancer of the breast whose urinary hydroxycorticoids remained raised for 15 days following mastectomy. Jepson *et al.* (1956) described an unusually high 17-ketogenic steroid excretion following laparotomy in a patient with inoperable gastric cancer. These findings suggest that some cancer patients respond to their disease with adrenocortical overactivity, and that in such patients the adrenocortical response to trauma as measured by urinary corticoid excretion is greater than is usually found.

In view of the normal liver-function tests and the absence of reports of high urinary excretion of adrenocortical hormones in even advanced liver disease, it must be assumed that the high 17-ketogenic steroid and 17-ketosteroid ex-

cretion in the above case was due to adrenocortical overactivity. Norymberski *et al.* (1953) have shown that the normal daily urinary excretion of 15 mg. of 17-ketogenic steroid corresponds approximately to the production of 30 mg. of 17- α -hydroxycorticosterone by the adrenals. In the present case the daily output of between 106 and 159 mg. of 17-ketogenic steroids indicated a 17- α -hydroxycorticosterone production of between 215 and 320 mg. a day. This rate of production was unaffected by the administration of 200 mg. of cortisone a day, the administered cortisone accounting for a rise of about 60 mg. in daily 17-ketogenic steroid excretion (Jepson *et al.*, 1956) and the 17-ketosteroid excretion remaining essentially unchanged. Similar failure to suppress adrenocortical steroid production by means of cortisone has been reported in severe Cushing's syndrome due to adrenocortical hyperplasia resulting from increased production of corticotrophin (Segaloff *et al.*, 1955; Laidlaw *et al.*, 1955).

To hypersecretion of adrenocortical hormones must be attributed the diabetes, hypernatraemia, and oedema, but, although symptoms suggesting diabetes had been present for three months, most of the features of Cushing's syndrome such as obesity, cervical fat pad, moon-face, red striae, hypertension, polycythaemia, and osteoporosis were absent, and in spite of the high pregnanediol excretion there was no disturbance of sexual function. In Cushing's syndrome and in adrenal virilism due to adrenocortical hyperplasia the administration of corticotrophin leads to an increase in steroid excretion (Laidlaw *et al.*, 1955), but in the present case no such increase was obtained. In the absence of such features the possibility that the bronchial carcinoma arose in a patient with primary hypercorticism must be regarded as remote.

With hypersecretion of adrenocortical hormones in response to trauma or other forms of stress a decreased glucose tolerance and sodium retention are common findings, but other features of hypercorticism are absent (Ingle, 1952); this increased secretion is thought to be caused by increased production of corticotrophin by the pituitary (Munson and Briggs, 1955). In the present case the failure of the adrenal cortices to respond to exogenous corticotrophin suggests that the cortices were already maximally stimulated by the pituitary. The increased excretion of 17-ketogenic steroids and 17-ketosteroids may have been related to the presence of the bronchial carcinoma, being produced in a manner similar to that following trauma or other stress. The findings, however, differ from those following surgery, when commonly there is only a small rise in 17-ketosteroid excretion (Hardy, 1955).

The inability of exogenous corticotrophin or cortisone to influence steroid excretion might have been interpreted as suggesting the presence of a steroid-producing tumour, but this was excluded at necropsy and in life by the only moderately raised dehydroisoandrosterone excretion (Gardner and Migeon, 1952). The pigmentation of the skin and buccal mucous membranes, similar in distribution to that seen in Addison's disease, suggested excess production of corticotrophin by the apparently normal pituitary (Mellgren, 1945; Lerner, 1955).

In Cushing's syndrome and during the administration of corticotrophin or 11-17-oxysteroids decreased glucose tolerance is a common finding. Frank diabetes is, however, unusual, and when it occurs is insulin-resistant though mild (Conn, 1953; Frawley, 1955). Slight impairment of glucose tolerance due to increased secretion of adrenocortical hormones may be seen during the response to trauma and other forms of stress (Conn and Fajans, 1956). Acidosis in Cushing's syndrome is rare, and Plotz *et al.* (1952) were able to find only one published case (Petresco *et al.*, 1937). It might therefore be considered that the severe diabetes with ketonuria in the present case was only an incidental finding. This, however, would fail to account for the simultaneous onset of chest complaints, pigmentation, and symptoms suggesting diabetes, and the high 17-ketogenic steroid production would well explain the severity and insulin resistance of the diabetes.

High and prolonged steroid excretion in association with cancer has not previously been described, and it has been shown that their association is unlikely to have been coincidental. While the findings suggested that this was due to stimulation of the adrenals by pituitary corticotrophin, the present phenomenon differed from that seen following trauma or other stress in the degree and duration of the increased 17-ketogenic steroid and 17-ketosteroid excretion.

Summary

Marked hyperexcretion of adrenocortical hormones is reported in a patient with bronchial carcinoma and diabetes mellitus.

In spite of severe steroid diabetes only few of the features of Cushing's syndrome were observed.

The possibility that marked adrenocortical hyperactivity was due to stimulation of the pituitary in response to the presence of the bronchial carcinoma is discussed.

The present phenomenon differs from that observed following trauma and other forms of stress.

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REFERENCES

- Conn, J. W. (1953). *Ciba Foundation Colloquia on Endocrinology*, 6, 166. Churchill, London.
- and Fajans, S. S. (1956). *Metabolism*, 5, 114.
- Dobriner, K. (1952). *Ciba Foundation Colloquia on Endocrinology*, 1, 210. Churchill, London.
- Frawley, T. F. (1955). *Ann. N.Y. Acad. Sci.*, 61, 464.
- Gardner, L. L., and Migeon, C. J. (1952). *J. clin. Endocr.*, 12, 1117.
- Hardy, J. D. (1955). *Surgical Physiology of the Adrenal Cortex*. Blackwell's Scientific Publ., Oxford.
- Ingle, D. J. (1952). *J. Endocr.*, 8, xxiii.
- Jepson, R. P., Jordan, A., and Levell, M. J. (1956). *Brit. J. Surg.*, 43, 390.
- Laidlaw, J. C., Reddy, W. J., Jenkins, D., Haydar, N. A., Renold, A. E., and Thorn, G. W. (1955). *New Engl. J. Med.*, 253, 747.
- Lerner, A. B. (1955). *Amer. J. Med.*, 19, 904.
- Mellgren, J. (1945). *Acta path. microbiol. scand.*, Suppl. 60.
- Moore, F. D., Steenburg, R. W., Ball, M. R., Wilson, G. M., and Myrdren, J. A. (1955). *Ann. Surg.*, 141, 145.
- Munson, P. L., and Briggs, F. N. (1955). *Recent Progr. Hormone Res.*, 11, 83.
- Norymberski, J. K., Stubbs, R. D., and West, H. F. (1953). *Lancet*, 1, 1276.
- Parker, T. G., and Sommers, S. C. (1956). *A.M.A. Arch. Surg.*, 72, 495.
- Petresco, M., Sutienu, A., and Olaru, Z. (1937). *Bull. Acad. Méd. Roum.*, 2, 592. Quoted by Plotz *et al.* (1952).
- Plotz, C. M., Knowlton, A. I., and Ragan, C. (1952). *Amer. J. Med.*, 13, 597.
- Segaloff, A., Gordon, D., and Horwitt, B. N. (1955). *J. Lab. clin. Med.*, 45, 219.
- Voigt, K.-D., and Kny, W. (1954). *Arch. klin. Chir.*, 280, 74.

A memorandum entitled "In-patient Accommodation for Child and Adolescent Psychiatric Patients" has been prepared by the Child Psychiatry Section of the Royal Medico-Psychological Association. The recommendations are as follows: (1) That in-patient units for child psychiatric patients should be established in association with local child psychiatric or child guidance clinics. These units should be linked with mental hospitals, children's hospitals, or general hospitals. It is estimated that not less than 20 beds can serve a total population of 500,000. In addition to these local units, one unit of not less than 25 beds per regional hospital board area is necessary for a residual group of patients needing prolonged care. (2) That units for adolescent patients should be established in association with adult units. It is estimated that not less than 20 beds can serve a total population of 500,000. (3) That there should be increased provision of long-term substitute home care for disturbed children in the form of hostels or special boarding schools. (4) That there should be better provision of after-care hostels for adolescent patients.

TOXOPLASMOSIS SIMULATING GLANDULAR FEVER IN THE ADULT

BY

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Toxoplasmosis, or infection with the protozoon *Toxoplasma gondii*, may be congenital or acquired. The human disease was first recognized in infants, but later acquired acute infection in adults was also described. The source of infection is not known, but may be from animals, as the disease is common in both wild and domestic animals.

Three cases are described in which a diagnosis of glandular fever was made initially. Subsequently, the Paul-Bunnell test was found to be negative and serological tests for toxoplasmosis were positive. Poliomyelitis was considered as a possible diagnosis in Case 2, and Hodgkin's disease in Case 3.

Case 1

On December 14, 1955, a 16-year-old Irish spot welder, who had been in England for three weeks, was admitted to hospital with a history of sore throat for three weeks, and cough for five days. He had been sweating profusely and had had pain in the left wrist, knee, and ankle, and in the left side of the chest. He complained of frontal headache and had noticed a rash on his abdomen on the day of admission. He had a temperature of 102° F. (38.9° C.). The only abnormal signs were reddening of the throat, enlargement of the submental and anterior cervical glands and of the spleen, and a petechial rash on the abdomen.

The initial blood count suggested glandular fever. The white cells numbered 6,200 per c.mm., with 50% polymorphonuclears, 0.5% eosinophils, 21.5% lymphocytes, and 28% monocytes, many of which were atypical. The percentage of monocytes was reduced in subsequent counts. The Paul-Bunnell test was negative.

On January 14, 1956, the toxoplasmosis dye test showed a prozone to 1:64 and was then positive to 1:1024. The C.F.T. was positive in a titre of 1:8. A second specimen of blood examined three months later, on April 4, showed a dye test titre of 1:128 and a C.F.T. of 1:16. He was discharged from hospital symptom-free after three weeks and has remained well.

Case 2

On December 10, 1955, a 31-year-old housewife who was 16 weeks pregnant was admitted ten days after the onset of fever and backache. A week before admission she had had a sore throat and a rash, with blisters on her hands and feet and red blotches on her face, which faded after a few days. For five days her trunk and limbs felt sore, and her neck had been stiff for four days, during which she had vomited frequently.

On examination there was no rash, the cervical glands were enlarged, and neck stiffness was minimal. An apical systolic murmur was heard. The uterus was enlarged to a size consistent with a 16-weeks pregnancy. Her temperature was 100.4° F. (38° C.) and fell to normal after 24 hours. The haemoglobin was 84%, the E.S.R. 62 mm. in one hour (Westergren), and the total white-cell count 7,909, with 66% polymorphonuclears, 1.5% basophils, 22% lymphocytes, 10% monocytes, and 0.5% Türk cells. The Paul-Bunnell test was negative.

She was discharged home after a week, but when seen three weeks later she was tired and had pain in the back and legs. She had had a further attack of sore throat and the cervical glands were still enlarged. Lassitude persisted for a further four weeks.