cytopenia. He also pointed out that in arsenical agranulocytosis, in contradistinction to agranulocytosis produced by other heavy metals, there were a relatively high leucocyte count at the onset; a lower age incidence, and a higher incidence in males.

It has been established that heavy metals (including arsenic and gold) exert their toxic effects on a biological system by reacting with the sulphhydryl groups of the protein fraction of cellular enzymes to form mercaptides. The sulphhydryl groups in the dithiol B.A.L. (dimercaprol; 2:3-dimercapto-propanol) compete with the dithiol protein-metal complex in the tissues, thus combining with and eliminating the offending metal. This restores the enzyme system. The therapeutic efficacy of dimercaprol in some of the toxic manifestations of arsenical poisoning has been dramatic. Its effect on arsenical dermatitis has been good (Carlton *et al.*, 1948), and on gold thrombocytopenia and granulocytopenia encouraging (Lockie *et al.*, 1947; Cohen *et al.*, 1947; Ragan and Boots, 1947).

The results of dimercaprol therapy on the haematological disturbances occurring during arsenotherapy are variable. In 12 cases of agranulocytosis following intensive arsenic treatment for syphilis Fisher, Holley, and Fein (1947) reported good results with combined therapy including dimercaprol. Eagle (1946) treated 11 cases of arsenical agranulocytosis with dimercaprol, and 10 recovered; he found, however, that dimercaprol had no beneficial effect on three cases of aplastic anaemia caused by arsenic poisoning.

The first of our cases (Case 2) with agranulocytosis (and aplastic anaemia) did not receive dimercaprol, while the second (Case 3) was given a course of intramuscular injections of dimercaprol in oil to a total of 1.2 g. spread over six days. There was no essential difference in the clinical course of these two cases and no rise in the peripheral cellular counts of the blood, and both ended fatally. The fact that the associated arsenical dermatitis in Case 3 did not respond to dimercaprol suggests that the condition was of long standing (cf. Eagle, 1946). The damage to the bone marrow was severe, as it showed very few developing cells of either the myeloid or the erythroid series, and may have been irreversible.

Case 4 presented as a gross aplastic anaemia from the onset, and purpuric manifestations were not observed, although the platelet count was uniformly low. Despite blood transfusions, oral iron and ascorbic acid, and injections of vitamin B₁₂ and of dimercaprol she showed no clinical or haematological response and her condition proceeded inexorably to a fatal termination.

At the onset the clinical manifestations of a thrombocytopenic purpura of toxic origin are essentially similar to those encountered in the more severe cases of toxic pancytopenia in which all elements of the bone marrow are depressed. Yet the former has a good prognosis and the latter a uniformly poor one. As a case of toxic pancytopenia develops, the initial purpura becomes associated with a gradually increasing anaemia and a leucopenia which proceeds to agranulocytosis. If such severe bone-marrow damage occurs during anti-syphilitic therapy with heavy metals it appears that the prognosis is poor, despite treatment with dimercaprol. All cases of purpura developing during treatment for syphilis should be followed carefully, with repeated blood examinations, to distinguish between the benign and fatal forms which may arise during arsenotherapy.

Summary

Four cases of blood dyscrasia resulting from the toxic effects of organic arsenicals are presented.

One case of toxic thrombocytopenic purpura recovered spontaneously.

The three other cases showed a pancytopenia with marrow aplasia and ended fatally.

The administration of dimercaprol to two of the cases had no apparent effect on the severe toxic manifestations.

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CARCINOMA OF THE ADRENAL CORTEX WITH ENDOCRINE MANIFESTATIONS

REPORT OF A CASE

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Functioning adrenal cortical tumours can produce various clinical pictures. In women, a group of symptoms associated with virilism is referred to as the adrenogenital syndrome. When such abnormalities as obesity, decreased sugar tolerance, hypertension, amenorrhoea, and hirsuties appear without virilism the name Cushing's syndrome is employed. Considerable overlapping occurs, and cases of adrenocortical tumour may show features of both syndromes.

An unusual case is described below in which hirsuties, obesity, and cutaneous striae appeared in a girl before puberty, and in whom menstruation began normally and continued regularly until six months before her death from a metastasizing tumour of the right adrenal cortex. Virilism was absent and carbohydrate metabolism was normal.

Case Report

The patient, a social worker, was one of 12 children. Both parents were short and stout, and one grandmother was said to be exceedingly fat. She herself was plump from infancy, but not excessively so. At 8½ years she weighed 61 lb. (27.7 kg.). At 10 years pubic and axillary hair appeared. She was then sent to the London Hospital on account of obesity—weight 95 lb. (43 kg.), height 4 ft. 3 in. (129.5 cm.)—and was dieted. The following year increasing obesity made further schooling impossible. Striae appeared in the loins, and the pubic hair assumed the male distribution. She complained of occasional migrainous headaches.

A year later, aged 12, she entered hospital with pain in the left loin. Examination showed marked obesity; weight 104 lb. (47.2 kg.), height 4 ft. 4 in. (132 cm.), rubicund facies, pubic hair extending to umbilicus, with fine dark hair over shoulders and arms (Fig. 2a). Blood pressure was 135/95 to 150/80. Investigations showed: blood urea, 21 mg. per 100 ml.; normal intravenous pyelogram and urea-concentration test; cerebrospinal fluid normal; fundi, visual fields, and radiograph of pituitary fossa normal. Radiography showed no cardiac enlargement. In view of the

clinical appearances laparotomy was performed. The adrenals were poorly seen owing to fat, but nothing abnormal was observed except a small lump (? lymph node) on the right kidney: this lump does not appear to have been removed. After discharge she developed left-sided renal colic with haematuria, and subsequently passed a large calculus.

During the ensuing six months she gained 30 lb. (13.6 kg.). Striae were now present not only in the loins but vertically down the abdomen, around the breasts, and on shoulders

FIG. 1.—The patient's Weight Chart.

and thighs. The hirsuties increased, and she developed some coarse dark hairs on the chin and upper lip, and around the nipples and umbilicus. The breasts became moderately large and pendulous, but showed no evidence of functional activity. There were no signs of sexual precocity, and intellectual development was normal for her age, but she was emotionally immature. Blood pressure was 140/90 to 150/95. A blood count showed: red cells, 4,500,000; Hb, 80%; C.I., 0.88; white cells, 11,600 (polymorphs 75%, lymphocytes 15%, monocytes 9.5%, eosinophils 0.5%). Repeated glucose-tolerance tests

showed anomalous values, on one occasion being rather flat and on others normal. At this stage she was presented at the Royal Society of Medicine as a case of obesity and hirsuties of ? adrenal origin (Ellis, 1932). She then received deep x-ray therapy to the pituitary fossa (total pituitary dose 1,120 r). At this time she weighed 180 lb. (81.6 kg.), but rose to 193 lb. (87.5 kg.) two months later, and further x rays were administered (total pituitary dose 420 r). By the time she was 13 she weighed 225 lb. (102 kg.) and her blood pressure was 210/150. Renal-function tests were normal. Four pounds of abdominal fat was now removed at operation by Mr. Perry.

At the age of 15 (Weight Chart, Fig. 1) she weighed 263 lb. (119.3 kg.), her height was 4 ft. 5½ in. (135 cm.), and blood pressure 150/95. She was admitted to hospital for dieting, and lost 36 lb. (16.3 kg.). Following this her blood pressure was 120/70. A glucose-tolerance test was normal. Her photograph at this time (Fig. 2b) shows considerable hirsuties, with generalized obesity. Striae were not well marked, and the face was less moon-shaped than previously.

Her periods began at 16. During the first year she had three periods, each lasting three days, after which they became more frequent and occurred about every 30 days, with occasional intervals of up to two months. The loss at each period was scanty and lasted approximately three days. There was no dysmenorrhoea. She had no interest in the opposite sex.

She lost more weight subsequently, and for the next 14 years, under the dietary supervision of Miss R. Simmonds, she kept below 180 lb. (81.6 kg.). She remained well, active, and at work until three months before her final admission to hospital at the age of 30, when she developed progressive dyspnoea, and a cough with frothy sputum. The headaches became less severe. She began to lose weight (over 2 st.—12.7 kg.—altogether). The sputum became blood-streaked during the month before admission, and for three weeks she had noticed swelling of the ankles and palpitation. Amenorrhoea had been present for six months.

On examination she was afebrile, weight 143 lb. (64.9 kg.), height 4 ft. 6 in. (137 cm.), span 4 ft. 7 in. (139.7 cm.). She was breathless on moving about in bed. There was obesity, especially of buttocks, hips, and abdomen, and the tissues were very lax (Fig. 3). There were widespread pink-and-white striae, generalized hirsuties, and acne of the face and back. The facies was round and plethoric. The hands and feet were small and delicately formed, and the nipples rudimentary, with little underlying breast tissue. Over wrists and forearms were several ecchymoses, some probably spontaneous. The voice was feminine, and the larynx of female shape. External and internal genitalia appeared normal, apart from the male distribution of pubic hair, and in particular there was no gross enlargement of the clitoris. Respiratory system: early clubbing; impaired percussion note at both bases; generalized fine rales. Cardiovascular system: blood pressure 170/120, slight oedema of the legs, but none over the sacrum; jugular venous pressure normal; apex beat impalpable; no cardiac murmurs.

FIG. 2.—(a) Patient aged 12. From Harvey Cushing's *Pituitary Body, Hypothalamus, and Parasympathetic Nervous System*. By courtesy of Charles C. Thomas, Publisher, Springfield, Illinois. (b) Patient aged 15. From Raymond Greene's *The Practice of Endocrinology*. By courtesy of Eyre and Spottiswoode (Publishers) Ltd., London.

FIG. 3.—Patient aged 30 years, a few weeks before death.

Gastro-intestinal system: paramedian and horizontal abdominal scars; there was a large firm mass palpable in the right loin, dull to percussion, moving with respiration, slightly tender, and with a definable upper border. Central nervous system: normal. Urine: albumin, leucocytes, debris, and profuse growth of *Proteus vulgaris*; sugar absent; normal calcium concentration (Sulkowitch's test).

Investigations

Examination of the blood showed: Hb, 101% (14.9 g.); red cells, 5,100,000; marked anisocytosis and polychromasia; moderate poikilocytosis; E.S.R., 8 mm. (Westergren); white cells, 6,000; urea, 19 mg. per 100 ml.; cholesterol, 187 mg. per 100 ml.; chloride, 595 mg. per 100 ml.; sodium, 320 mg. per 100 ml.; potassium, 19 mg. per 100 ml.; calcium, 11.4 mg. per 100 ml.; phosphorus, 3.9 mg. per 100 ml.; alkaline phosphatase, 41.4 King-Armstrong units per 100 ml.; alkali reserve, 47.2 vols. per 100 ml. Total proteins, 7.2 g.% (albumin 3.9 g., globulin 3.3 g., A./G. ratio 1.2); glucose-tolerance test, 81 mg. per 100 ml. (fasting), 122 mg. (half an hour), 150 mg. (one hour), 136 mg. (one and a half hours), 150 mg. (two hours), 100 mg. (three hours); no glycosuria. X-ray examination:—Chest: multiple pulmonary metastases, with mediastinal adenopathy. Skull: normal sella turcica. Dorsolumbar spine: no evidence of secondary deposits. Hands: no osteoporosis. An intravenous pyelogram showed the right kidney to be displaced downward. An electrocardiogram was normal.

Endocrine assays gave the following results. 17-keto-steroids (see Table).

Specimen	Total (Normal 4–22 mg. per 24 hrs.)	β -fraction (Normal up to 10% of Total)	Colour Reaction for Dehydroandrosterone (Allen <i>et al.</i> , 1950)
1	221	34%	Strongly positive
2	256	34%	" "
3 (3 days before death)	150	19%	Positive

Reducing steroids (Dr. C. L. Cope): total neutral reducing steroids were 2.6 mg. a day, using deoxycortone acetate as standard, this being a low normal figure for the method used (Cope and Bain, 1951). Cortisone output, estimated by a biological method (Cope, 1951), was 250 μ g. daily, a high figure.

Clinical Course.—Progressive dyspnoea with cyanosis, terminating in sudden death on December 2, 1950, four weeks after admission.

Post-mortem Examination

Necropsy (Dr. C. V. Harrison) confirmed the clinical diagnosis of adrenal cortical carcinoma with metastases.

Cardiovascular System.—The heart weighed 266 g. The right ventricle was 6 to 7 mm. in thickness, the left 17 mm. The coronary arteries showed a little atheroma. The inferior vena cava was invaded by tumour from the right suprarenal, extending upwards into the right atrium.

Respiratory System.—The right lung weighed 1,135 g. and was largely replaced by innumerable metastases, averaging 2 cm. in diameter. The left lung weighed 532 g. Fine white spots averaging 1 mm. in diameter were scattered throughout, suggesting intravascular tumour. There were also a few metastases up to 1 cm. in diameter in the lower lobe posteriorly. The main left pulmonary artery at the entrance to the lung was occluded by tumour.

The **liver**, weighing 2,356 g., was directly invaded by tumour in the upper posterior part of the right lobe. Within the liver the mass of tumour measured 13 by 10 by 6 cm., but there were no other deposits, and the rest of the liver appeared normal.

Endocrines.—The thyroid weighed 24 g. and was of normal shape. One small 1-cm. fleshy nodule was present in the middle part of the right lobe posteriorly. The right

adrenal gland weighed 965 g. and measured 18 by 11.5 by 7 cm. It was nodular, had displaced the kidney downwards without involving it, and was adherent to and invading the liver. Most of the tumour was necrotic, but the surviving parts were pale pink and soft. Innumerable vessels were attached to it, and it had invaded the inferior vena cava. The left adrenal weighed 4.5 g., measured 5 by 1.3 by 1 cm., and was normal in position. On section a narrow (1 mm.) line of yellow cortex was visible. The parathyroids (two found) and pancreas appeared normal.

Reticulo-endothelial System.—The spleen weighed 286 g. and showed four metastases in the upper pole, the largest 2 cm. in diameter. Lymph nodes: two large malignant lymph nodes were found in the anterior mediastinum, just above the pericardium. Cervical, axillary, and supraclavicular nodes were normal. Spinal and sternal bone marrow were normal.

Genito-urinary System.—The right kidney weighed 220 g. and showed several recent infarcts. Two metastases, 1.5 and 1 cm. in diameter, were seen. The left kidney weighed 250 g., and also showed fresh infarcts and a 1.5-cm. metastasis near the outer border. Ureters, bladder, and vagina were normal. The uterus was 7.5 cm. long, 4.5 cm. wide, and 2.5 cm. thick at the fundus. The cervical canal constituted most of the uterus, being 4 cm. long. Both ovaries were of normal size, and contained numerous small yellow flecks, but no recognizable corpus luteum. Tubes were normal.

Central Nervous System.—The brain weighed 1,145 g. and appeared to be normal.

Skeleton.—The spine was straight and there was no osteoporosis macroscopically.

Histology

Adrenal Tumour (Fig. 4).—The tumour cells were arranged in solid alveoli and columns separated by fine fibrous strands containing wide vascular channels. The cells varied enormously in size from about 15 μ up to multinucleate syncytial masses. The nuclei were round, hyperchromatic, and vesicular, and the cytoplasm was homogeneous, ground-glass, and eosinophilic. Mitoses

FIG. 4.—Histological section of adrenal tumour, showing trabecular arrangement. H. and E. ($\times 90$.)

were uncommon. Vines's androgenic stain was negative. Gomori's alkaline phosphatase stain (Gomori, 1939) was strongly positive in the tumour cells as well as the endothelia of stromal vessels. The Ashbel-Seligman histochemical test (Ashbel and Seligman, 1949), reputedly specific for ketosteroids, was strongly positive. The Sudan IV stain for fat was positive, but this fat was not anisotropic.

The **left adrenal** was qualitatively normal, and contained rather less lipid than average, but this was anisotropic. Vines's stain was negative. Both **lungs** showed many metastases in arteries and invading the lung tissue. There was considerable interstitial fibrosis in the left lung, of uncertain origin. Some might have been a reaction to the tumour cells, and some a result of chronic infection. The **thyroid**

was normal, but appeared to have been a trifle inactive. In the ovary ripening follicles of various ages were present, but no corpus luteum; there were, however, plenty of corpora albicantia and several stomal foci of large, pale, foamy theca lutein cells. The endometrium was thick, and showed a proliferative reaction, but lacked mitoses. Both breasts showed gross atrophy and could be readily mistaken for male breasts. Bone: twelfth dorsal vertebra and first metacarpal were normal. There was no loss of trabeculae.

Pituitary (Dr. A. G. E. Pearse).—Macroscopically the gland appeared smaller than normal. Microscopically, three main changes were present. First, there was a large (3 mm. diameter) chromophobe adenoma containing a few acidophils, ghosts of hyaline basophils, and some mucoprotein secretion. Three smaller chromophobe adenomata were also noted. Secondly, the number of acidophils was considerably reduced, large degranulated forms and small deeply granulated types predominating. Thirdly, over 60% of the basophils were of Crooke's hyaline variety (Fig. 5)—a high proportion by comparison with other reported cases.

FIG. 5.—Histological section of anterior pituitary, showing hyaline changes in the basophils. Trichrome periodic-acid-Schiff stain. ($\times 1,150$.)

Discussion

The most striking feature of this case is the length of time during which symptoms suggestive of Cushing's syndrome were present before malignant changes supervened. A search of the literature reveals no comparable case.

The age of onset (8½ years) also appears to be unusual; most of the reported cases developed symptoms either before the age of 5 years or after puberty.

The diagnostic problem which our patient presented is evident from her history. In view of the absence of clitoral enlargement her case would presumably fall into the category of Cushing's syndrome rather than adrenal virilism (the adrenogenital syndrome). If this is so, the absence of amenorrhoea (except terminally) and of disturbed carbohydrate metabolism is atypical.

Cushing's syndrome has been observed in association with neoplasms and hyperplasia of the adrenal cortex, and with basophil adenomata of the pituitary. In the present case a carcinoma of the adrenal cortex was present, with four chromophobe adenomata of the pituitary; and, considering the long history, it seems highly probable that the initial adrenal lesion at the age of 8½ was either hyperplasia or adenoma. It is difficult to believe that pituitary adenomata can produce Cushing's syndrome except by stimulating the adrenal cortex—and such a belief would certainly complicate our present conception of adrenocortical hormone action. The administration of glucocorticoids produces many of the changes found in this condition (Sprague *et al.*, 1950), and adrenocorticotrophic hormone (A.C.T.H.) will produce such changes only if the adrenals are intact.

Indeed, pituitary basophil adenomata are sometimes found at necropsy in individuals not exhibiting endocrine abnormalities, and are often absent in florid cases of Cushing's syndrome. Admittedly, however, the incidence of such tumours is higher in these patients. The point will doubtless be settled when reliable methods are available for the determination of A.C.T.H. in blood and urine, as a normal blood level would exonerate the pituitary from aetiological responsibility. Such methods are now being developed (Bornstein and Trewella, 1950).

It is possible that in cases of Cushing's syndrome previously reported as being due to basophil adenoma of the pituitary the likelihood of anatomical or functional adrenal hyperplasia was not sufficiently considered; the histological criteria of hyperplasia are notoriously difficult to assess.

It has been thought from time to time that the regular occurrence in Cushing's syndrome of hyaline changes in the pituitary basophil cells (Crooke, 1935) indicated a causal relationship. However, Kepler (1945) was strongly of the opinion that these changes were secondary to adrenal hyperfunction—a view previously expressed by Bauer (1936) and supported by Albright (1942–3). Also, Laqueur (1950) has observed similar histological appearances in the pituitary following cortisone administration in man. This requires confirmation.

Crooke (1946) stated that hyaline cells do not occur in the hypophyses of patients with virilism alone, but Mellgren (1944) did find such cells in four cases of virilism. In no reported case of virilism, however, has the percentage of hyaline basophils exceeded 5, whereas much higher figures are recorded in Cushing's syndrome.

The results of hormone assays in our case conform to the usual 17-ketosteroid excretion pattern found in functioning adrenocortical tumours (Crooke and Callow, 1939)—namely, high total values, high β -fraction, and a strongly positive colour reaction for dehydroisoandrosterone.

The atypical corticoid excretion may possibly be correlated with the atypical clinical picture: it is usual for total reducing steroids to be raised in Cushing's syndrome.

Summary

A case is described in which obesity began in a girl aged 8 years 6 months, and was followed by hirsuties, cutaneous striae, and hypertension. The clitoris did not enlarge, carbohydrate metabolism was normal, and menstruation was unaffected until shortly before death at the age of 30 from a metastasizing carcinoma of the right adrenal cortex. The pathogenesis of Cushing's syndrome is discussed.

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