CANCER OF THE ADRENAL CORTEX

The natural history, prognosis and treatment in a study of fifty-five cases

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by
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INTRODUCTION AND HISTORICAL ASPECTS

KNOWING OF JOHN HUNTER'S abundant interest in human and animal experiments it is surprising that no reference appears in his works to a study of the adrenal gland. Although Bartholomew Eustachius is credited with the first description of these as specific organs in man in 1563 their function was not understood until many years after Hunter's death when the clinical observations of Thomas Addison in 1855 were confirmed by Oliver and Schafer in 1895 with the demonstration of a pressor substance in the medulla. Cortical function was more elusive and although Hartman's extract in 1927 and that of Pfiffner and Swingle in 1929 indicated the role of the cortex in maintaining life, it is only since the isolation of cortisone from such extracts in 1936 almost simultaneously by Kendall in the United States and Reichstein in Switzerland, followed by its clinical application by Hench and his colleagues at the Mayo Clinic in 1949 that surgical interest in the cortex has been stimulated.

Secondary carcinoma involving the adrenal glands is frequently seen but primary carcinoma is rare and as the majority of published works refer to isolated case reports it has been felt justifiable to discuss the experience with this disease which has been obtained from a study of the case reports of fifty-five patients who have been mainly from the London teaching hospitals. All are histologically proven cases and in many of them the sections have been reviewed with Professor Cunningham of the Department of Pathology of the Royal College of Surgeons of England.

Experimental production of tumours

Adrenocortical tumours can be produced experimentally in animals by an alteration in the hormonal environment. Although it has not yet been shown that such changes take place in man, a consideration of the principles in animal experiments is worthwhile and may later lead to a solution of the problem.

Woolley and Little in 1945 were able to produce adrenocortical carcinoma in all cases of one strain of female mice by simple castration within one to three days of birth. These tumours appeared from the age

of six months onwards and similar lesions but with a slightly lower frequency were seen in male mice from the seventh month who had been similarly castrated at birth. No such lesions appeared in non-castrated animals of the same strain. Growth on transplantation with evidence of metastases in liver and lungs has been obtained, and Mulay and Eyestone (1955) have shown it may be associated with atrophy of the contralateral adrenal gland.

Prevention of these tumours is possible by the implantation of oestrogens and in some instances androgens. There is evidence in animals of a relationship between pituitary and adrenal tumours and Woolley (1950) found that in all cases where pituitary tumours were present there were well-developed adrenocortical ones, although not all animals with adrenal tumours had hypophyseal ones. Further, hypophysectomy prevents the anticipated development of adrenocortical carcinoma in castrated mice.

The explanation of these changes is not clear and so far there has been no known carcinogenic action of ACTH but the close relationship in animal work may be similarly important in man.

Basic considerations

For an adequate understanding of malignant adrenal tumours a brief reference to the anatomy and physiology of the gland is essential, but will here be restricted to its cortical portion. Such division into cortex and medulla exists only in mammals, where three distinct layers are recognised —the outer or zona glomerulosa, the middle or zona fasciculata, and the inner or zona reticularis. In embryos and during the first year of life the last named is of considerable size and accounts for the largeness of the gland at this time. In the newly-born, accessary adrenal glands are common and although disappearing with advancing years they have been found in association with almost every structure below the diaphragm and are important as occasional sites of tumour formation.

To appreciate the physiological properties of the adrenocortical hormones, necessary because of their excess in certain forms of tumour, mention must be made of their chemistry. All are organic compounds possessing the reduced cyclopentanophenanthrene nucleus, a class of substances which also includes cholesterol.

They may be classified into three main groups, and are for the most part under the control of the anterior pituitary. First, the glucocorticoids also known as the 17-hydroxycorticoids because of the presence of a hydroxyl group at the C 17 position (Fig. 1). Hydrocortisone and cortisone are the main members of this group. Second, aldosterone, first isolated in 1952 by Tait, Simpson and Grundy is a powerful salt retaining hormone which is only doubtfully influenced by the anterior pituitary. The third group are the sex hormones both androgens and oestrogens. The former are produced in greater amounts and may be measured both biologically and

chemically. The results of both bear a close correlation but the chemical method is simpler. It depends on the presence of a ketonic group at the C 17 position giving the name of 17-ketosteroids. Not all 17-ketosteroids have the same biological activity—e.g., oestrone—and some are biologically inert. In the normal estimation the phenolic group, such as oestrone, are removed and the neutral ketosteroids like androsterone are measured. A further division of the non-phenolic 17-ketosteroids into α- and β-groups occurs, about 20 per cent. of the total 17-ketosteroids being excreted in the β form. Dehydroepiandrosterone is the main adrenal androgen of the β type and high concentrations are found in some adrenocortical carcinomas.

CHEMICAL STRUCTURE OF IMPORTANT ADRENAL STEROIDS

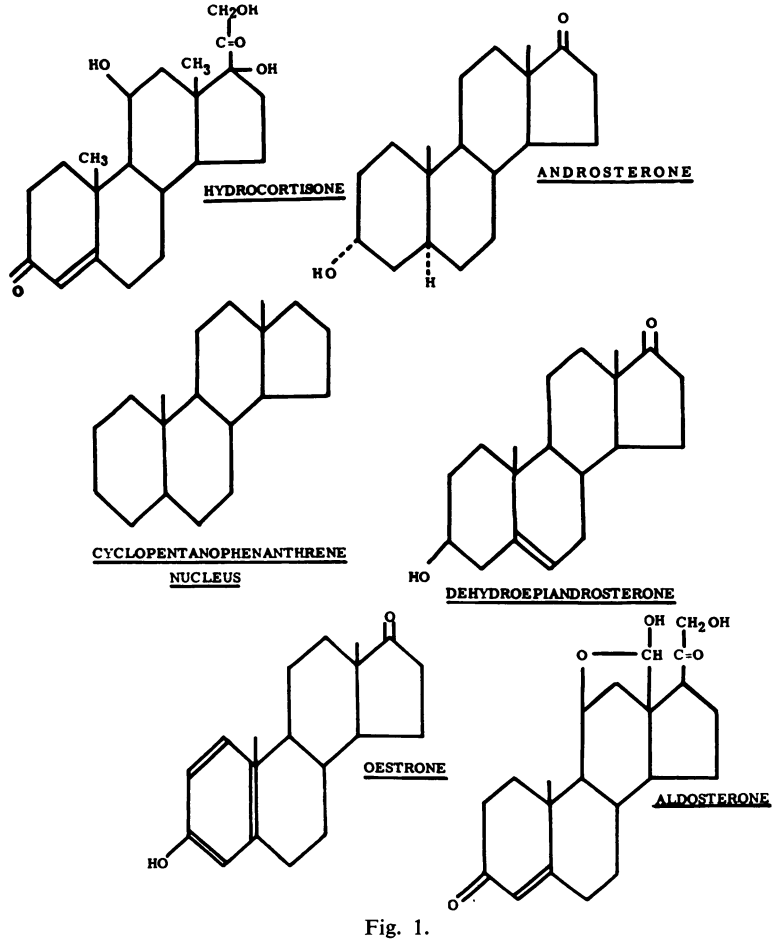


Fig. 1.

TUMOUR INCIDENCE

Types

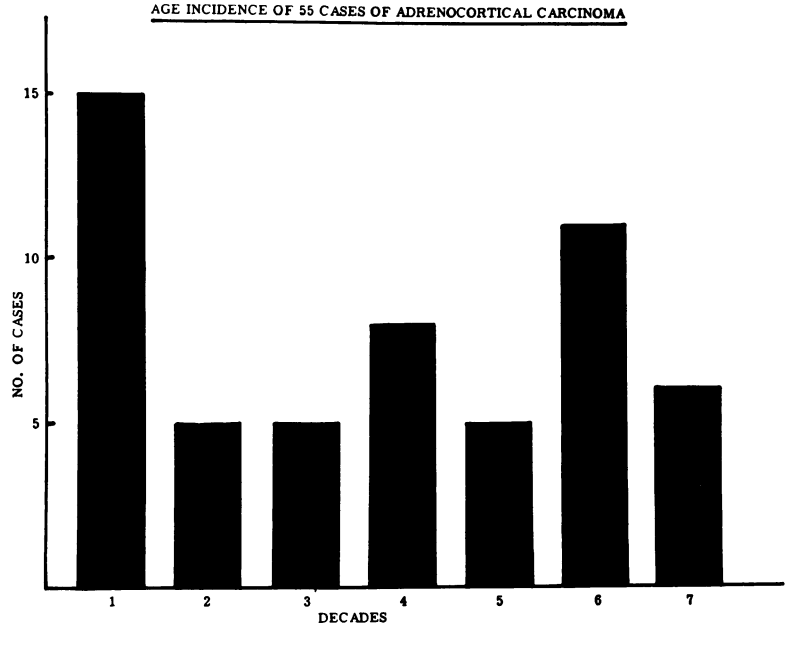
It is most convenient to divide cortical tumours into those which produce hormones and those which do not. In future, and for simplicity, these will be referred to as hormonal and non-hormonal.

Frequency

An appreciation of the rarity of these tumours may be gauged by reference to the literature. Steiner (1954) reviewed all the necropsies at the Los Angeles County Hospital during the period 1918 to 1947 and found it accounted for 0.2 per cent. of all tumours, a total of fifteen cases. Wu (1940) found only eighty-two cases in the literature up to 1940. More recent reviews have included those of Rapaport, *et al.* (1952), who collected 238 hormonal and thirty-four non-hormonal tumours over a twenty-year period from 1930 to 1949, and Heinbecker, *et al.* (1957), reporting ten of their own cases, three of which were non-hormonal, and who added a further eighty-three from the literature, but no clear distinction was possible in the reviewed reports between benign and malignant lesions. Wood *et al.* (1957), in a recent paper on eight non-hormonal tumours, were able to find only twenty-seven cases in the European and American literature since 1923. In the present series of fifty-five primary carcinomas thirty-five were hormonal and twenty non-hormonal.

TABLE I

AGE INCIDENCE OF 55 CASES OF ADRENOCORTICAL CARCINOMA



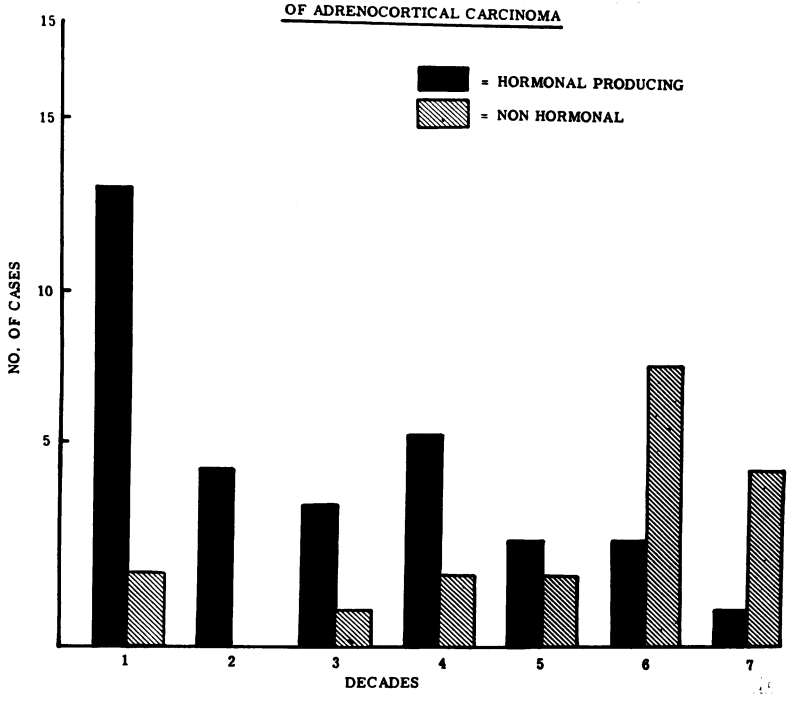
Age and sex

The age at diagnosis varied over the whole span of life; the youngest being four and a half months, the oldest sixty-eight years with an average age of thirty-two years. Table I shows the incidence in decades, the number in children being strikingly high.

Further analysis of these figures and division into hormonal and non-hormonal tumours (Table II) indicates that 80 per cent. of the former group occur before the age of forty years whereas 65 per cent. of the latter group occur after fifty years. Two non-hormonal tumours were encountered before puberty and one at twenty-nine years, the remainder being in patients of more than thirty-eight years, that is, more in keeping with the

TABLE II

AGE INCIDENCE RELATED TO HORMONAL EFFECT IN 55 CASES OF ADRENOCORTICAL CARCINOMA



general cancer age incidence. Further illustration of the earlier age incidence of hormonal tumours is indicated by nearly 50 per cent. occurring before the age of puberty, the ratio to the non-hormonal type at this period being 8.5 : 1. After puberty this ratio alters to one of equal numbers, but with the emphasis in the younger adult of the hormonal type—61 per cent. under the age of forty years—and in the older adult of the non-hormonal type—65 per cent. over the age of fifty years.

In Table III the endocrine effects have been related to the age and sex. It is noted that there are very few hormonal tumours in older patients, and only three are post-menopausal. In the female these tumours are fairly evenly spread over their earlier age spectrum and are not pronounced at puberty or menopause, but in the male a marked preponderance is seen in the young. The high incidence of the non-hormonal tumours in the older group is apparent so that the male seems to be largely affected at one or other end of the age spectrum by tumours differing widely in their clinical manifestations.

TABLE III

RELATION OF ENDOCRINE EFFECTS TO AGE AND SEX IN FIFTY-FIVE CASES OF ADRENOCORTICAL CARCINOMA

Age in decades	Hormonal tumours			Non-hormonal tumours		
	Male	Female	Total	Male	Female	Total
0–10	6	7	13	1	1	2
11–20	2	3	5	0	0	0
21–30	0	4	4	1	0	1
31–40	1	5	6	2	0	2
41–50	0	3	3	1	1	2
51–60	1	2	3	5	3	8
Over 60	0	1	1	4	1	5
TOTAL	10	25	35	14	6	20

The overall sex ratio shows a preponderance in favour of the female of 1.3 : 1, but when the hormonal and non-hormonal types are considered separately some variation is found. In the former group the ratio is 2.5 : 1, which corresponds closely to the accepted figure in favour of the female, but in the non-hormonal type this ratio is reversed in favour of the male.

The site of the tumours in all cases was unilateral with a slight preponderance of left over right in about the proportion of 1.25 : 1 ; thirty-one tumours being on the left side, twenty-four being on the right.

PATHOLOGY

Macroscopic

The gross appearance of adrenocortical tumours varies considerably. Small tumours of 2 to 3cms. were found but the majority were of a large size, some reaching 20 to 30cms. in diameter, and weighing several thousand grammes. Spherical in shape, often with a lobulated surface, many are soft in consistency with a cut surface showing areas of necrosis and haemorrhage intersected by bands of fibrous tissue.

Histology

The microscopic diagnosis of malignancy in adrenocortical tumours presents certain difficulties. Criteria such as giant and bizarre nuclei

which in tumours elsewhere might suggest malignancy are found in lesions which may appear clinically benign. The presence of numerous mitoses, a large nucleo-cytoplasmic ratio, and marked pleomorphism are suggestive

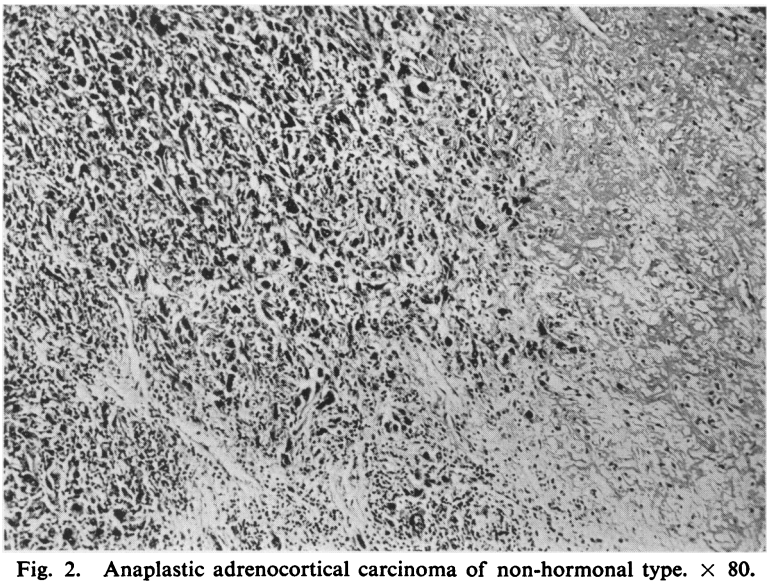


Fig. 2. Anaplastic adrenocortical carcinoma of non-hormonal type. × 80.

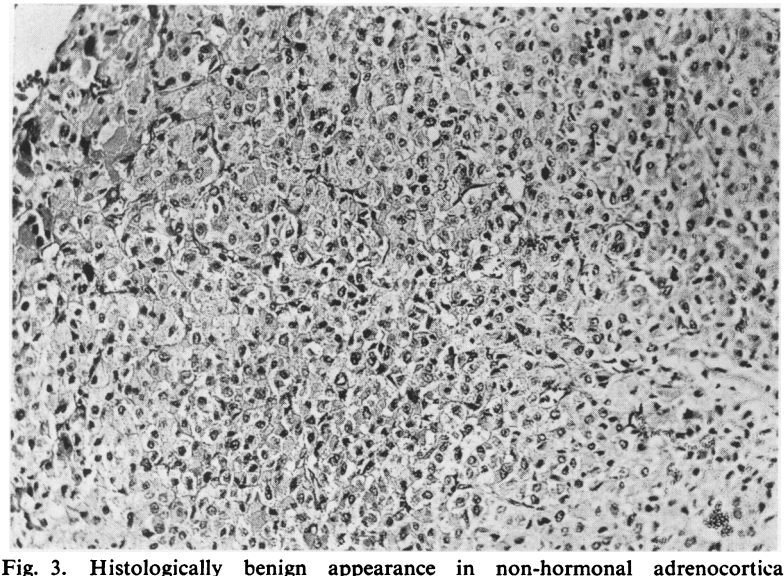


Fig. 3. Histologically benign appearance in non-hormonal adrenocortical carcinoma. × 80.

but not conclusive of malignancy. Whilst necrosis suggests malignancy much greater attention should be paid to mitoses which if frequent and abnormal should be regarded as diagnostic. Although these features

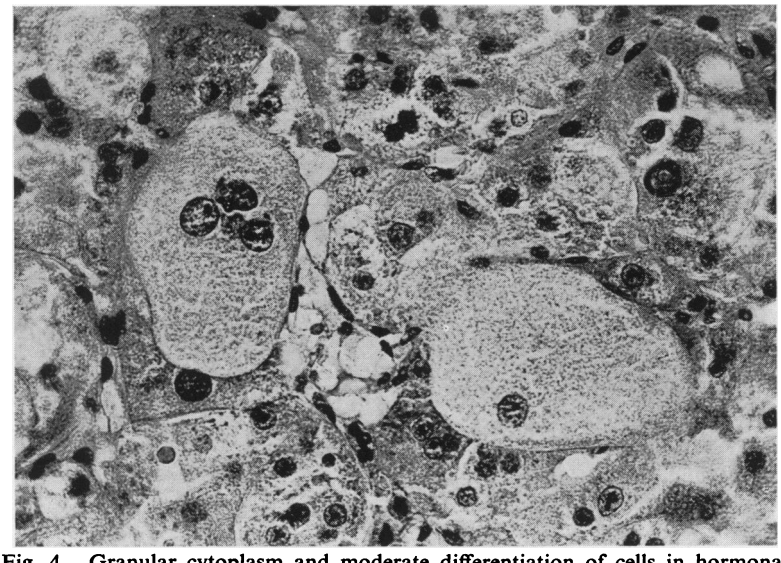


Fig. 4. Granular cytoplasm and moderate differentiation of cells in hormonal adrenocortical carcinoma. × 335.

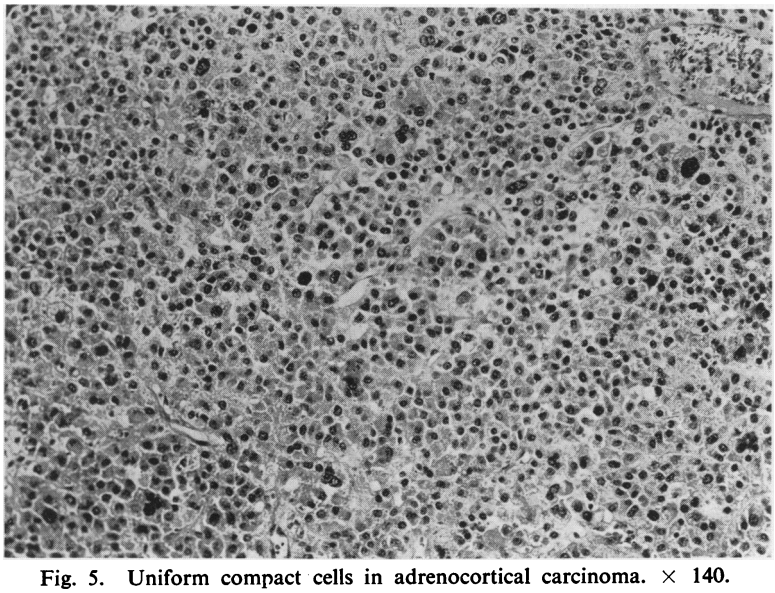


Fig. 5. Uniform compact cells in adrenocortical carcinoma. × 140.

suggest activity of the tumour, evidence of capsular infiltration or of invasion of venous or lymphatic channels are positive proof of the malignant potentialities of the growth.

Several types are noted. A very anaplastic form may be seen bearing little resemblance to the normal histology (Fig. 2). Others have a benign appearance, the cells closely resembling the normal (Fig. 3); that such a histological picture can be deceptive is shown by the fact that the tumour metastasized and the secondary growths had a histological structure in every way similar to that of the primary. Each of these cases was non-hormonal.

Although not always so, many tumours from hormonal cases contained cells which showed a moderate degree of differentiation and contained certain granules within their cytoplasm (Fig. 4). It would not seem unreasonable to assume that those cells were secreting hormones. A further difficulty arose in tumours composed of uniform compact cells seen in both hormonal and non-hormonal cases (Fig. 5). In such instances even special staining methods are of little use.

For a suggested explanation of this, the work of Symington *et al.* (1956) is important. Their experiments—based on the original concept by Yoffey and Baxter (1949)—have indicated that both glucocorticoids and the sex hormones may be produced in the zona reticularis. In stress, with ACTH stimulation, and more recently in Cushing's syndrome, they have shown an increase in the width of the zone of compact cells although the gland may appear macroscopically normal. Were this so in the present cases such proliferation of compact cells might be anticipated in a hormonally active gland but not in a non-hormonal one. It may well be that the compact cells from several tumours may appear identical when viewed by our present techniques but in fact a slight interference with the intermediate metabolism of the cell may result in hormone production in one case and failure in the other.

Whilst therefore the histological appearances are striking their interpretation is not possible in the present state of our knowledge. They must be taken in conjunction with the clinical picture and with the biochemical tests. The *in vitro* studies of Grant *et al.* (1957) following ACTH have borne close correlation with histology and might be applied in future to a study of tumours. It is only then that a reasonable and accurate diagnosis will be possible.

Spread

Extension of the tumour locally with involvement of the kidney, posterior abdominal wall, diaphragm, renal vein or inferior vena cava occurred in nearly one third of the cases (Table IV). Extirpation of the disease by radical dissection was contra-indicated in all but two of these because of metastases elsewhere, and in the two cases where still locally

TABLE IV
TUMOUR SPREAD IN FIFTY-FIVE CASES OF ADRENOCORTICAL CARCINOMA

	Number of patients	Percentage
Local invasion	17	30·9
Metastases	34	61·8

confined involvement of the aorta precluded resection. For surgical cure the diagnosis must be made early. Table V shows the sites and incidence of metastatic deposit. Blood and lymph borne spread occurred and the

TABLE V
METASTATIC SITES AND INCIDENCE IN THIRTY-FOUR CASES OF ADRENOCORTICAL CARCINOMA

	Number of patients	Percentage
Local Lymph Nodes	15	44·1
Liver	23	67·6
Lungs	16	47·1
Bones	6	17·6
Other sites	11	32·4

high proportion of metastases confirms the degree of malignancy. It is surprising that the liver is more frequently involved than the lungs and the latter more than the local lymph nodes.

Course in the untreated case

Twenty of the patients in the series, of whom six were children, fell into this category and provide the basis of study of the natural course of the disease. Eleven out of the twenty patients had non-hormonal tumours and all of these were male, emphasizing the preponderance of this type of tumour in the male sex.

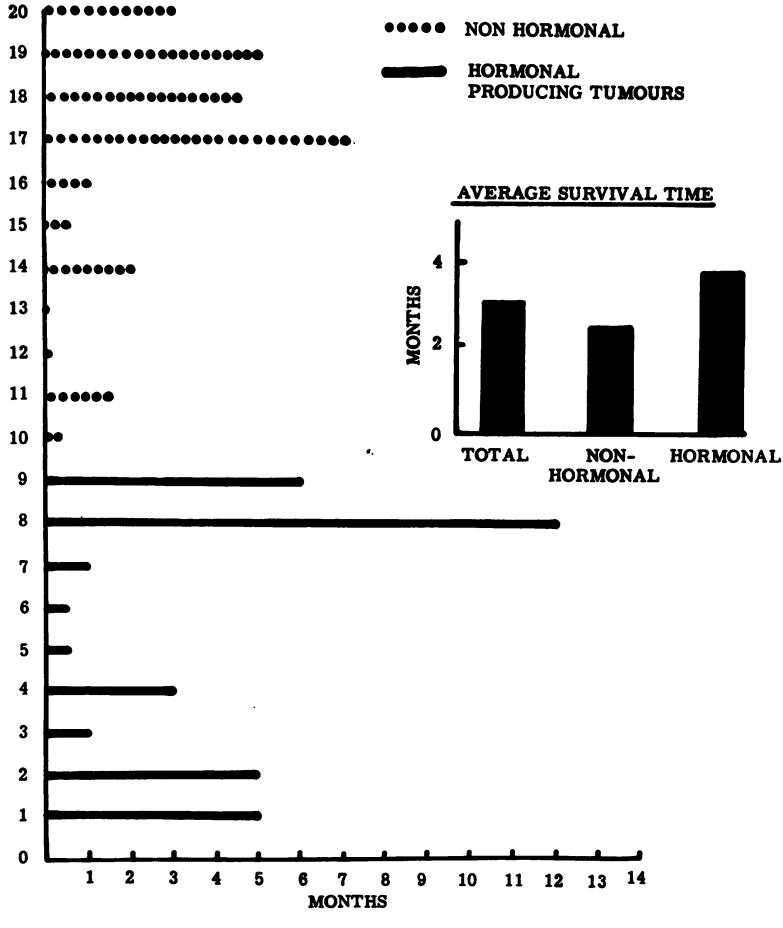
An appreciation of the malignancy of these tumours may be obtained from Table VI which shows the survival time after diagnosis. In almost all cases it is short, being on an average 2.9 months. It is more brief in the non-hormonal group where it is 2.2 months compared with 3.8 months in the hormonal type, suggesting that these tumours carry a more grave prognosis.

Table VII indicates the overall duration of the disease. In two cases this was thirteen years and twenty years but the vast difference from the remainder and the late alteration in symptoms which occurred in both are indicative of malignant change in a previously benign lesion. If these atypical cases are excluded the average overall duration of symptoms in the untreated cases is 13.2 months. The suggestion that the non-hormonal type may be more serious is supported by an overall duration of 10.8 months as compared with seventeen months in the hormonal group.

The apparently unfavourable prognosis may be considered in more detail. Eleven of the patients died within a year and the outlook with any

TABLE VI

SURVIVAL TIME AFTER DIAGNOSIS IN 20 UNTREATED CASES OF ADRENOCORTICAL CARCINOMA



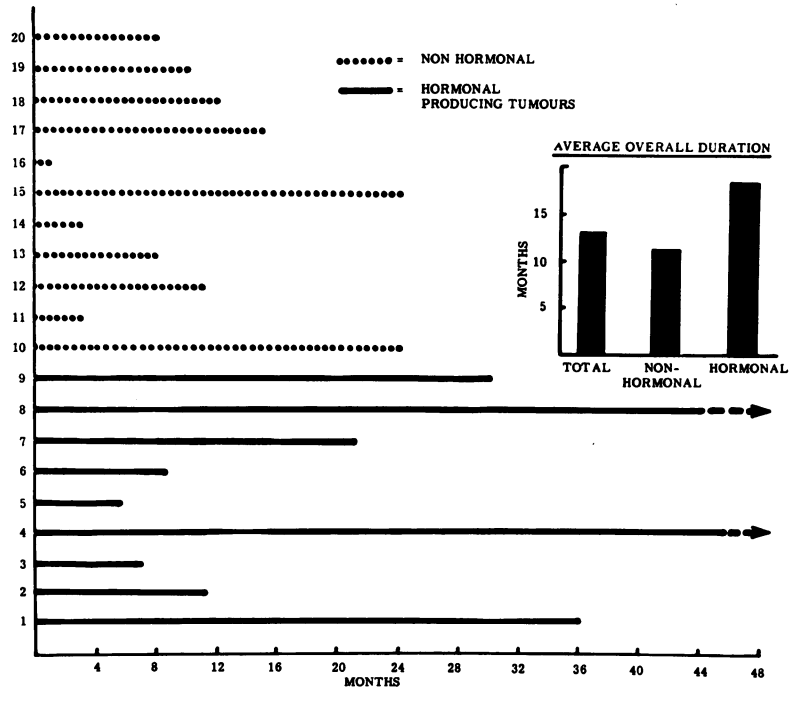
form of treatment might well be poor. Where the duration of the disease was more than a year and particularly in the two cases with a long history, salvage might have been possible. With earlier diagnosis in nearly half of the patients in this untreated series an improvement in the prognosis might have been obtained with surgical treatment.

Clinical

The non-hormonal tumours may present in a variety of ways, the majority being recognized by pain or a mass in the loin or abdomen, or by the presence of metastases. Haematuria where the kidney is invaded

TABLE VII

OVERALL DURATION IN 20 UNTREATED CASES OF ADRENOCORTICAL CARCINOMA



has suggested the diagnosis of carcinoma of this organ and one such mass in a child was thought to be a Wilms's tumour. The following histories are illustrative of this type of lesion.

(*a*) E.D. Female patient, aged fifty-seven years, gave a history of an increasing painless abdominal swelling for one year. A firm, smooth mass was present in the left hypochondrium which was not tender and did not move on respiration. A plain radiograph of the abdomen confirmed the presence of a mass and showed areas of scattered calcification. A barium meal (Fig. 6) showed the stomach was displaced to the right, and a barium enema that the splenic flexure was displaced towards the pelvis (Fig. 7). No excretion from the left kidney was visible on intravenous pyelography and a retrograde pyelogram was unsatisfactory because the ureteric catheter could only be introduced half way along the left ureter. An aortogram revealed a vascular mass above the left kidney, and although the appearance was in keeping with a large renal tumour, the absence of arterial pattern of the kidney was suspicious of an adrenal lesion. At operation through a left oblique incision with removal of the twelfth rib an encapsulated mass twelve inches in diameter displacing the left kidney was removed. Histology showed an adrenocortical carcinoma. The patient remained well for five and a half years and then later developed extensive hepatic metastases.

(*b*) H.C. was a male patient of thirty-eight years who was admitted to hospital with a two-month history of malaise and weakness together with an unproductive

cough which had been present since an attack of " influenza." He had lost two stone in weight in two months and for one week had experienced pain in the upper part of the right side of his chest. There were no abnormal physical signs but a radiograph of the chest showed a rounded opacity in the right upper pulmonary zone (Fig. 8). A barium swallow showed a rounded mass projecting into the right lung field from the mediastinum. There was no response from radiotherapy and the patient died three months later. Necropsy revealed an unexpected anaplastic carcinoma of the right adrenal gland with pulmonary metastases.

(*c*) E.D., a housewife of fifty years, demonstrated the slow recurrence of some of these tumours and the value of further radical surgery. The history of pain in the right side with lassitude and loss of weight for three months together with a large mass in the right loin, and an intravenous pyelogram showing the right

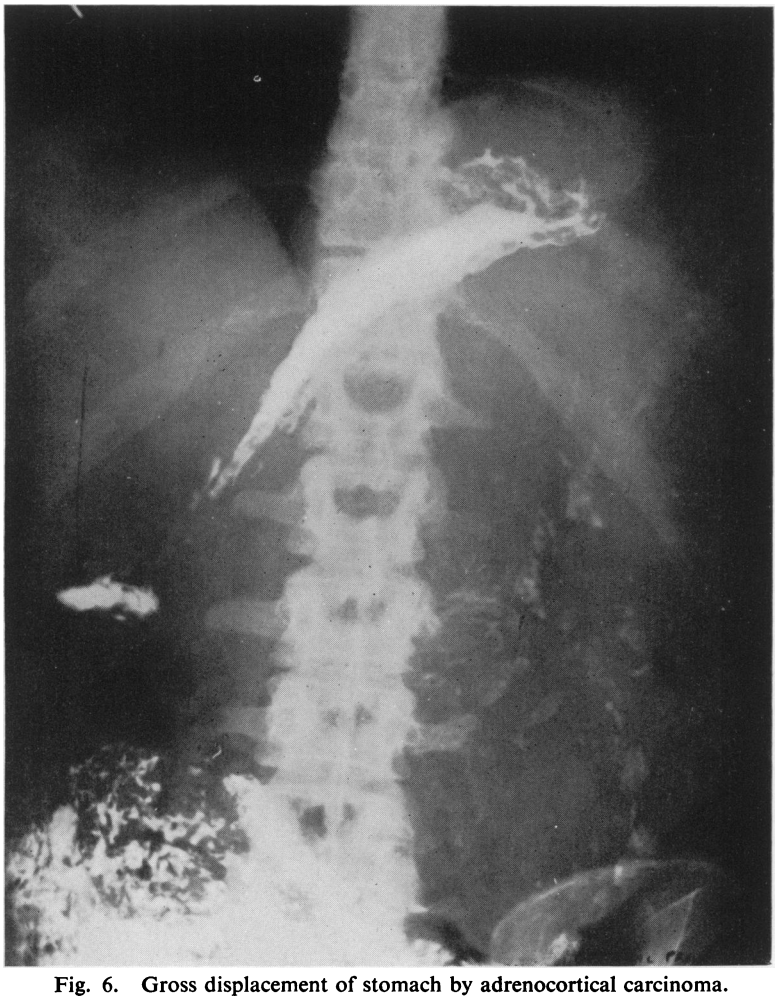


Fig. 6. Gross displacement of stomach by adrenocortical carcinoma.

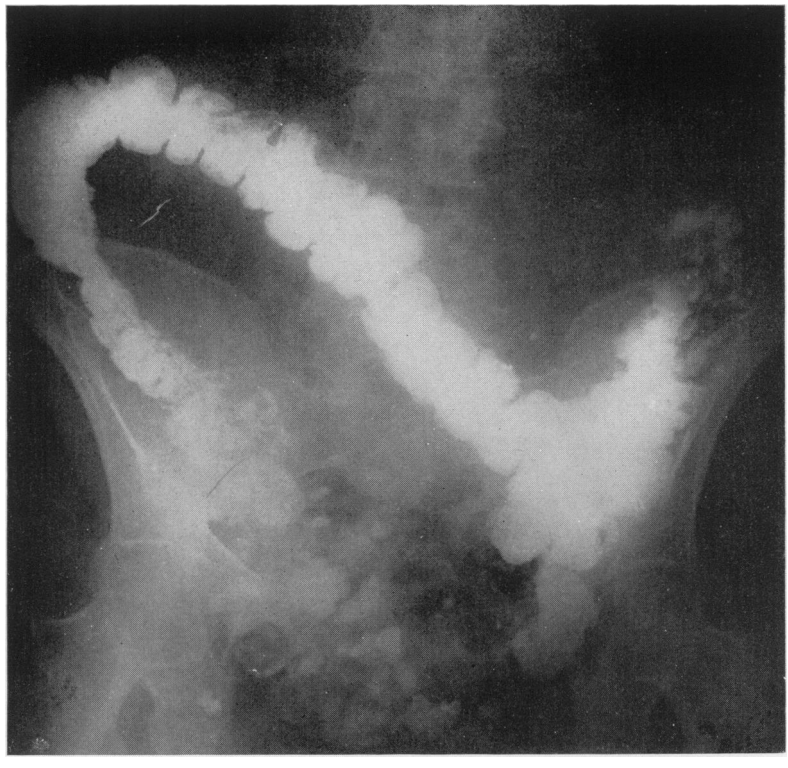


Fig. 7. Adrenocortical tumour causing marked colonic displacement.

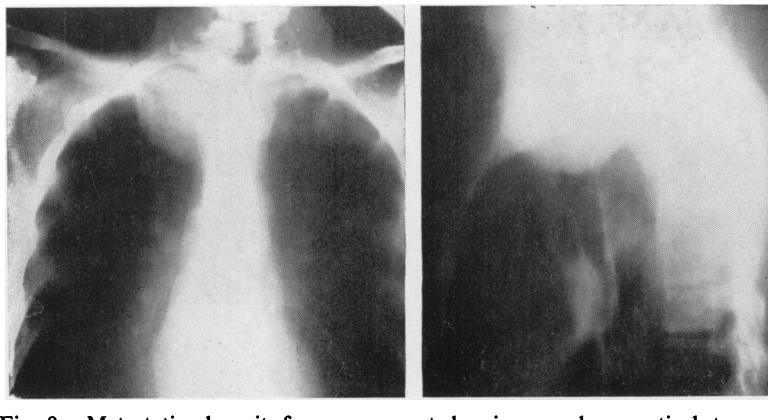


Fig. 8. Metastatic deposit from unsuspected primary adrenocortical tumour presenting as new growth of lung.

kidney being displaced to the pelvic brim all suggested a diagnosis of a renal neoplasm and the lesion was explored. A large tumour 32 × 30 × 12 cms. closely attached to the upper pole of the right kidney was removed together with the kidney. Histology did not reveal a highly malignant tumour. Two years later the patient was re-admitted with a large mobile mass in the right side of the abdomen and at laparotomy a tumour 19 × 12 × 11 cms. weighing 1,300 grammes was removed. Again the histology was not of high malignancy. Admission nine months later for another local recurrence which was this time invading the inferior vena cava allowed only partial removal of a growth of low malignancy. There was improvement for six months followed by further local recurrence, signs of anaemia, and inferior vena caval obstruction and death four years after the original treatment.

Wood *et al.* (1957), stress the importance of an intermittent low grade pyrexia associated with malaise and fatigue and when present this may be helpful in suggesting the diagnosis but it was not observed in more than two-thirds of the present series. In three cases it was thought to be a mild respiratory infection and not similar to a low grade renal infection.

An uncommon but important differential diagnosis is that of adrenal apoplexy. Although the majority of these occur soon after birth when hypoprothrombinaemia and increased vascular fragility are pronounced, they may occur later and be confused with a neoplasm. The following case is illustrative of the findings:

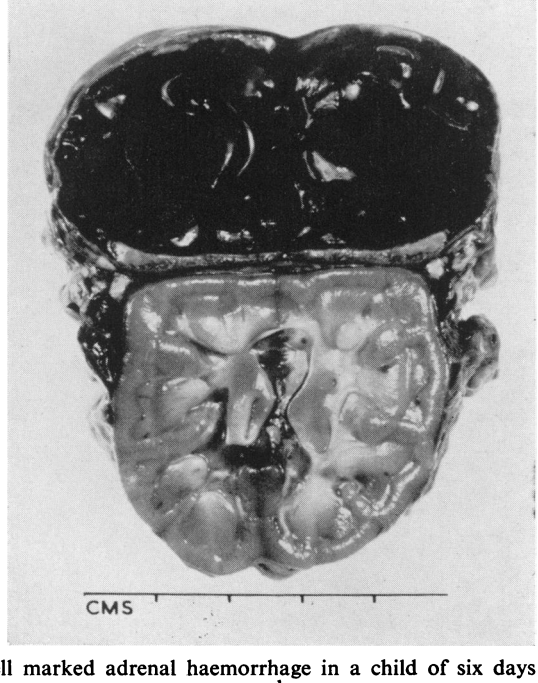


Fig. 9. Well marked adrenal haemorrhage in a child of six days with adrenal apoplexy.

R. D., a normal full-term male child weighing 11lbs. at birth made satisfactory progress until the sixth day when there was a sudden onset of pallor and vomiting necessitating blood transfusion. This was followed within twelve hours by a dull and non-shifting swelling in the right side of the abdomen. An intramuscular pyelogram revealed a distorted ureter on the right side. At laparotomy, adrenalectomy and nephrectomy were performed. The specimen (Fig. 9) showed histologically-marked adrenal haemorrhage with a surrounding zone of congested but otherwise normal adrenal cortex. A satisfactory recovery was made.

When the rapidity of the appearance of the mass associated with signs of adrenal insufficiency are considered, recognition that an adrenal or renal neoplasm is not present will result in the conservation of a healthy kidney.

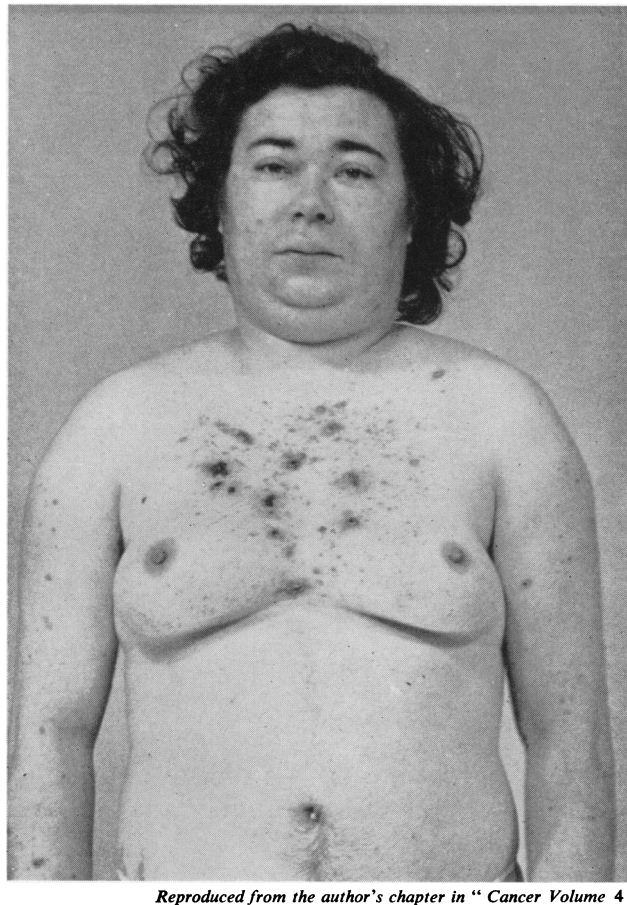


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Fig. 10. Hirsutism and acne in a patient of twenty-two years with adrenogenital syndrome.

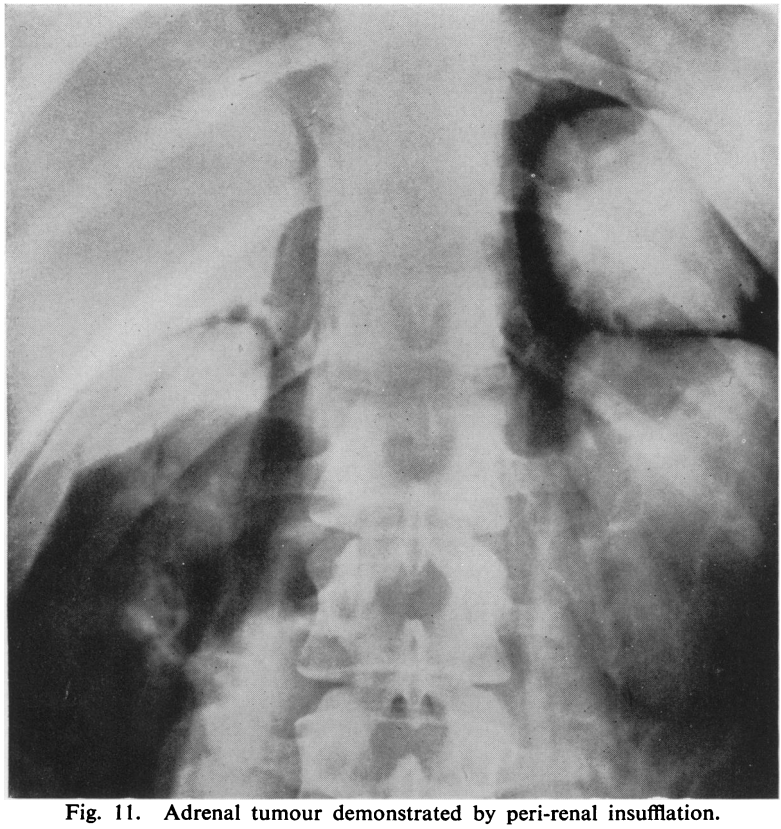

Fig. 11. Adrenal tumour demonstrated by peri-renal insufflation.

Hormonal tumours are recognized by the clinical effects of the hormones produced. The following are illustrative of the androgenic type :

(*a*) J. C., a young woman of twenty-two years, gave a history of four months hirsutism involving the upper lip and chin with male distribution on the abdomen. For the same period there had been an acneiform rash involving the front of the chest and an increase of two stone in weight. There was three months' amenorrhoea. On examination, she was a heavily built female of muscular type, with hirsutism and acne (Fig. 10), but no palpable abdominal mass. An intravenous pyelogram showed downward displacement of the left kidney, whilst peri-renal insufflation demonstrated a tumour (Fig. 11). The total urinary 17-ketosteroids were 110 mgms. per twenty-four hours. A large left adrenocortical carcinoma was found on exploration, not all of which could be removed, and death occurred six weeks later from pulmonary metastases.

(*b*) R. W. was a boy of eleven years who gave a history of eight months' left-sided abdominal swelling, increase in weight, the appearance of pubic hair and an acneiform rash on his forehead. In appearance he resembled a youth of eighteen years and there was a large tumour about the size of a football in the left side of his abdomen (Fig. 12). A left varicocele was also present. An intravenous pyelogram showed no excretion of the left kidney which

appeared replaced by a large mass. A radiograph of the epiphyses revealed a bone age of eighteen years, and in the chest pulmonary metastases were seen. No surgical treatment was of value and death occurred shortly afterwards.

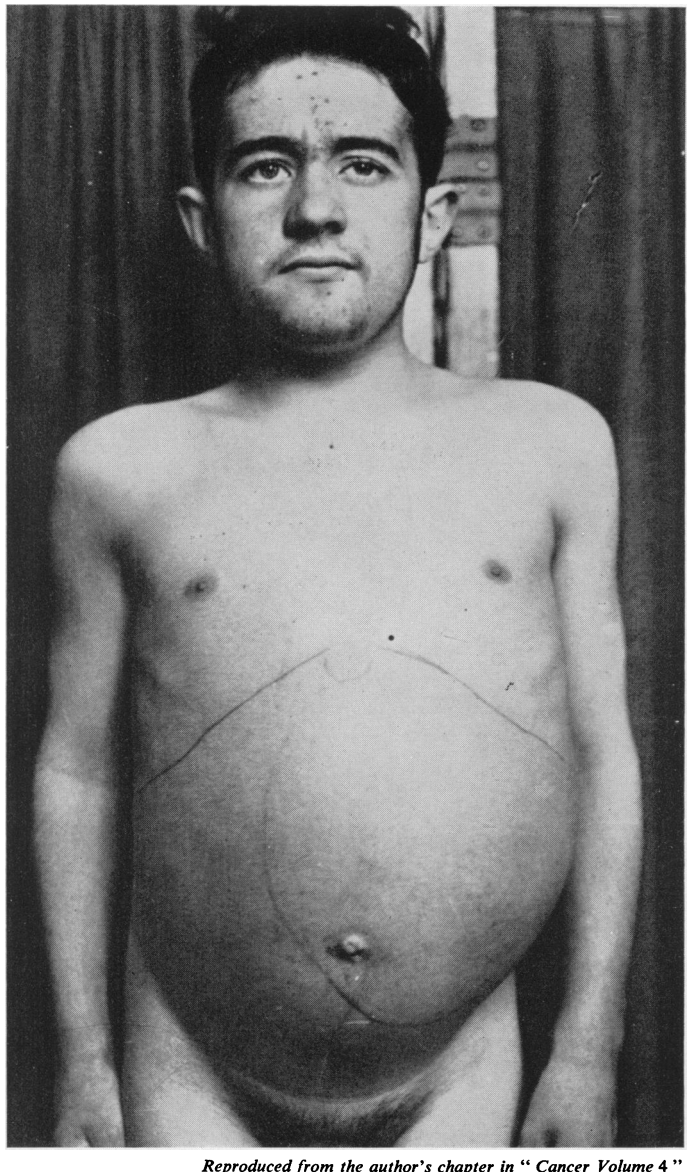

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Fig. 12. Gross abdominal swelling and secondary sex characteristics in a boy of eleven years with an adrenocortical tumour.

Necropsy showed an adrenocortical carcinoma of the left adrenal gland 10 × 11 × 8 inches invading and compressing the kidney with extension to the inferior vena cava, involvement of the para-aortic nodes and pulmonary and hepatic metastases.

(*c*) J. T., a six-year-old girl, was admitted with a two-year history of a growth of pubic hair, one year of deepened voice and six months of acne and hirsutism of face and axillae. She was a muscular child who appeared about nine years of age with a deep voice and marked hirsutism of face, arms and legs. In addition to the axillary and pubic hair there was marked enlargement of the clitoris (Fig. 13). Urinary 17-ketosteroids were 27.5 mgms. per twenty-four hours, and a radiograph of the hands revealed a bone age of ten to twelve years. Although an intravenous pyelogram was normal, peri-renal insufflation suggested a right-sided adrenal tumour. This was confirmed by exploration when a localized tumour 5 × 2 cms. was removed. An adrenocortical carcinoma with capsular invasion was found on histology. Four years later the patient was alive and well : the voice was less deep, the coarsened features and acne had disappeared although the pubic hair persisted : the urinary 17-ketosteroids were 3.0 mgms. per twenty-four hours.

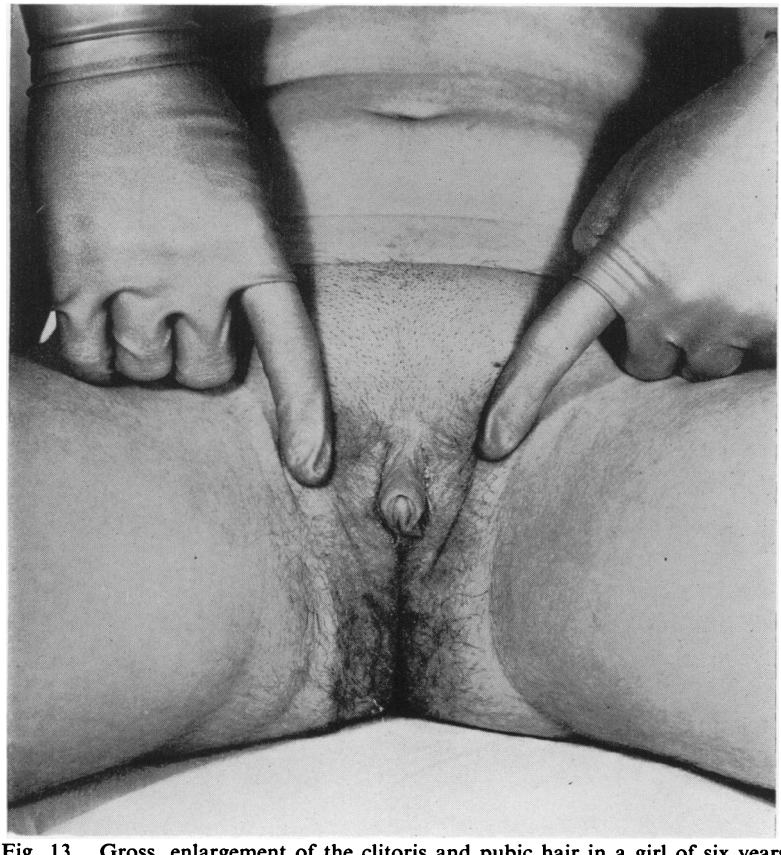


Fig. 13. Gross enlargement of the clitoris and pubic hair in a girl of six years with an adrenocortical carcinoma.

The following are representative of the Cushing's type of presentation :

(*a*) S. P., a housewife aged forty-seven years, noticed that fifteen months before admission to hospital her face had become florid and for the previous twelve months there had been an increase in weight, sub-sternal pain on exertion and amenorrhoea. On examination, she was obese with a rounded florid face and a blood pressure of 240/130 mms. Hg. The obesity mainly affected the face, neck and trunk, the limbs appearing thin. The glucose tolerance curve was 88, 157, 230, 229 and 157 mgms. per cent. ; the B.M.R. +43 per cent. ; and the urinary 17-ketosteroids 42.5 mgms. per twenty-four hours. Radiographs of the skull, spine and chest were normal but downward displacement of the right kidney on intravenous pyelography was noted and peri-renal insufflation showed a circular shadow 5 cms. in diameter in the region of the right adrenal gland. A well-encapsulated right adrenocortical carcinoma was removed with a post-operative reduction of weight and return of normal menses. The blood pressure fell to 160/90 mms. Hg. and the urinary ketosteroids to 6 mgms. per twenty-four hours. Two years later there was a recurrence of her obesity and a further rise of 17-ketosteroids to 110 mgms. per twenty-four hours. Laparotomy revealed an irremovable tumour mass surrounding the inferior vena cava and death occurred three days later.

(*b*) S. A., a taxi-driver of fifty-five years was admitted in a state of hypertensive cardiac failure with a year's history of irritability, depression, headaches, and impaired concentration. One month before admission fullness of the face (Fig. 14) and an increase in abdominal girth had been noted. The obesity was confined to the face and trunk ; there were no striae. The blood pressure was 210/125 mms. Hg. An electrocardiogram revealed left ventricular strain. A radiograph of the vertebral bodies showed general decalcification and an intravenous pyelogram downward displacement of the left kidney with poor filling of the calyces. Urinary 17-hydroxycorticoids were 88 mgms. per twenty-four

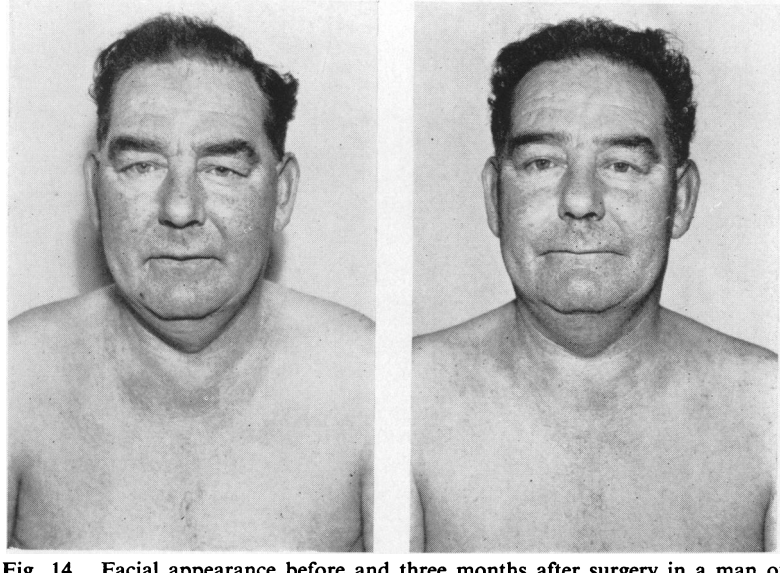


Fig. 14. Facial appearance before and three months after surgery in a man of fifty-five years with Cushing's syndrome due to tumour.

hours ; 17-ketosteroids 28 mgms. per twenty-four hours. There was no suppression with fluorohydrocortisone 25 mgms. per day for three days, or significant increase with ACTH 40 units b.d. for two days. At operation a large left-sided adrenocortical carcinoma was found adherent to aorta, diaphragm, pancreas and kidney. Tumour plus kidney were resected but a small portion adherent to the aorta could not be removed. Subsequently radiotherapy was given with slight improvement but hepatomegaly was noted four months later, and the patient died thirteen months post-operatively.

(*c*) R. P. was a boy of two years ten months admitted to hospital with increasing obesity and drowsiness for the previous five months. On examination a marked moon-shaped face and buffalo hump were present together with a blood pressure of 200/140 mms. Hg. Radiographs of skull and chest and an intravenous pyelogram were normal but urinary 17-ketosteroids and dehydroepiandrosterone were both raised. Cardiac failure developed and exploration of the adrenals performed. Both glands were normal but a primary adrenocortical carcinoma was found in a nodule near the left adrenal indicating carcinoma in an accessory gland. Death followed four days later and necropsy confirmed the findings.

No example of an oestrogen producing carcinoma was encountered, but thirty-four cases of this rare lesion have been collected from the world literature by Wallach *et al.* (1957), who report the most recent one. The main symptom is gynaecomastia which is present in more than half of the cases, but diminished libido, testicular atrophy and a thinning of the beard may occur. As in the present series a palpable mass has been found in 71 per cent. (Higgins *et al.*, 1956).

Foye and Feichtmeir (1955) report the only case of a malignant tumour producing aldosteronism. The clinical recognition is similar to Conn's syndrome with recurrent muscular weakness and transient paralysis, intermittent tetany and paraesthesiae, polyuria and polydypsia, accompanied by hypertension.

Distribution of clinical types

In the present series of hormonal tumours the androgenic type was most common, being three times as frequently seen as the Cushing's or mixed type (Table VIII). It is conceivable that the virilizing tumour is more easily recognized and that some of the other tumours masquerade as phaeochromocytomas or benign or malignant hypertension.

TABLE VIII

DISTRIBUTION OF SYNDROMES IN THIRTY-FIVE HORMONAL TUMOURS

Clinical Type	Number of Cases
Virilism	22
Cushing's	7
Mixed	6

Duration in relation to sex and endocrine function

Table IX indicates the duration of symptoms in the two sexes. Accepting an arbitrary period of six months it is striking that in 57 per cent. of the cases, symptoms have been present for longer than six months. In three exceptional instances a history of twelve years, twelve years and nineteen

TABLE IX

RELATIVE DURATION WITH REGARD TO SEX INCIDENCE IN TREATED AND UNTREATED CASES

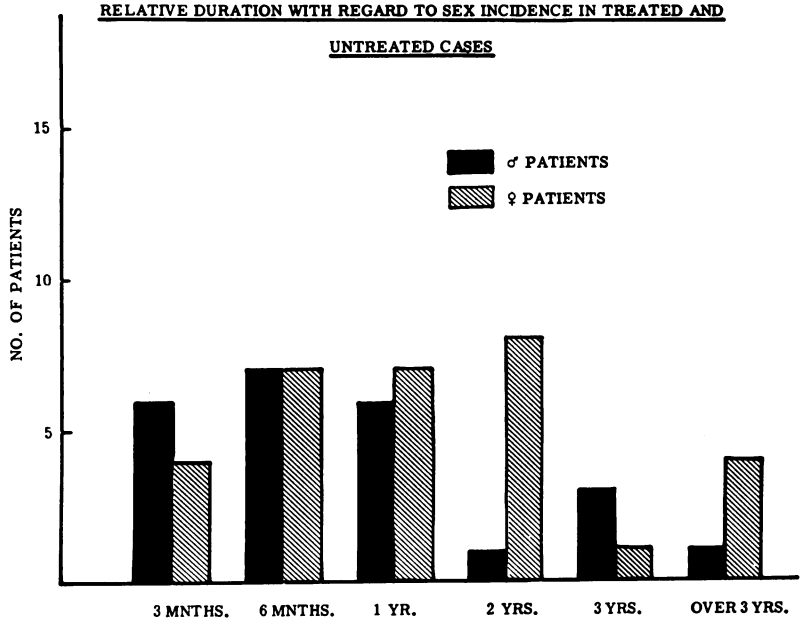
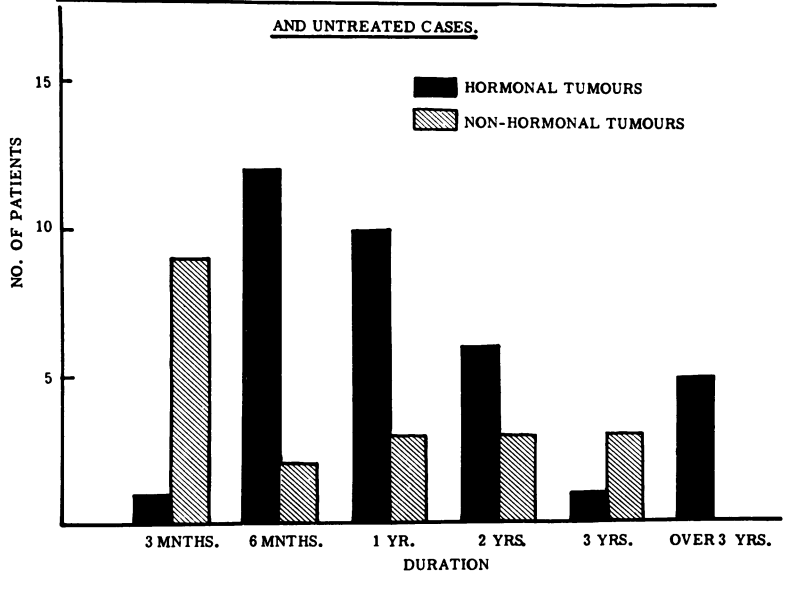


TABLE X

RELATIVE DURATION OF HORMONAL AND NON-HORMONAL TYPES IN TREATED AND UNTREATED CASES.



years respectively was noted and considerable variability exists so that many of the neoplasms are slowly growing, particularly in the case of the female patients.

Table X illustrates the influence of hormonal production on the duration of symptoms. In 45 per cent. of the non-hormonal group a very rapid history of less than three months is found and the combination of this with a male patient appears to indicate a bad prognosis. In 63 per cent. of the hormonal group a history of more than six months is found suggesting that with earlier diagnosis a more favourable prognosis may be obtained.

Relationship of a palpable mass to endocrine effect and duration

The presence of palpable mass in two-thirds of the patients indicates the importance of this sign of presentation (Table XI) more so in the non-hormonal group where there are no endocrine effects, and where it was found in 70 per cent. of cases. The size of the mass did not bear any relationship to the hormonal effects of the tumour either in their extent or their nature. The proportion of corticoid-producing tumours in which a mass was felt was lower than the other forms and the associated obesity of Cushing's syndrome might account for greater difficulty in palpation.

TABLE XI

RELATION OF A PALPABLE MASS TO ENDOCRINE EFFECTS

	Hormonal tumours	Non-hormonal tumours
Number of patients	35	20
Palpable mass	22 (62·8%)	14 (70%)
Androgen-producing with a mass ..	15 (68·0%)	Nil
Corticoid-producing with a mass ..	3 (40·8%)	Nil
Mixed type with a mass	6 (66·6%)	Nil

In 55 per cent. of the cases in which a mass was present there was a history of more than six months (Table XII) and the findings of a palpable mass does not necessarily indicate a very rapidly growing tumour. The close similarity of the curve representing those patients with a palpable lesion and the general trend of the disease denotes that the presence of such a mass does not indicate a worse prognosis.

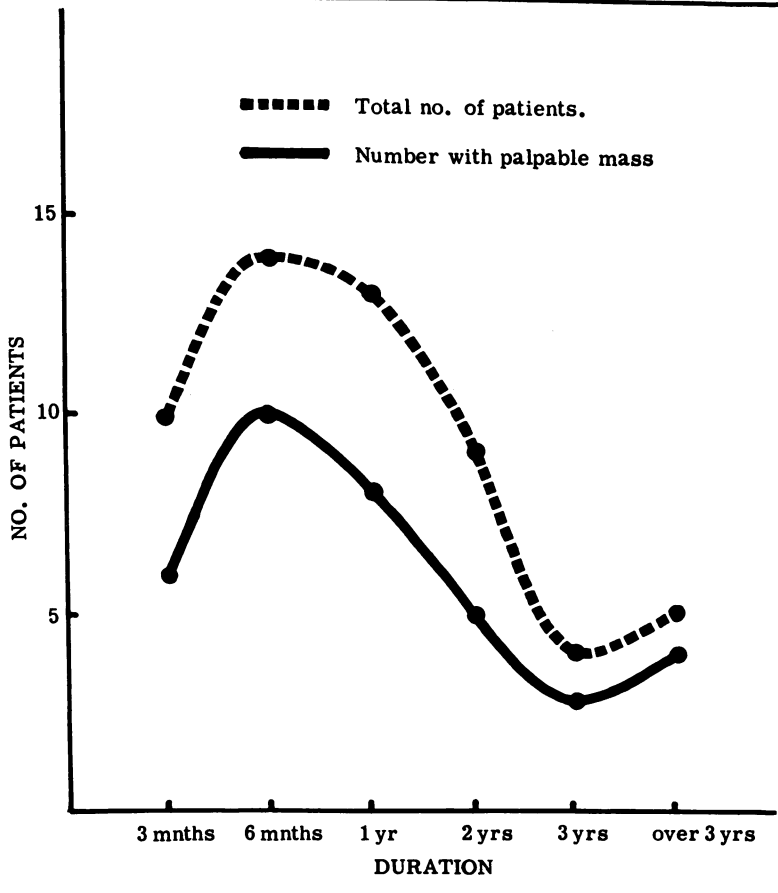
The type of hormone produced in the presence of a palpable mass did not appear to influence the duration of symptoms.

Accessory investigations

These are of two main types, the laboratory estimations of a steroidal nature, and radiological examinations. Table XIII shows the steroidal studies which may be undertaken in adrenocortical carcinoma. These include the total 17-ketosteroids and 17-hydroxycorticoids in urine or less commonly in peripheral blood, and the fractionation of those steroids—still largely a research procedure. The main β ketosteroid, dehydro-epiandrosterone must be estimated and where applicable the oestrogen and

TABLE XII

INFLUENCE OF PALPABLE MASS ON DURATION OF DISEASE



aldosterone levels. Blood obtained from the adrenal vein may contain 100 times the amount of hydrocortisone found in peripheral blood and cannulation of the main vein before excision of the tumour should be attempted. As the rate of flow may alter, e.g. with ACTH, the time must be noted and the measurement made in micrograms of steroid secreted per minute rather than per millilitre of blood. The steroidal studies should be completed by chromatographic estimations in the homogenized gland. Table XIV shows the radiological investigations which may aid the diagnosis. A plain radiograph of the abdomen may show a soft tissue mass or calcification in a tumour, whilst a radiograph of the spine may show decalcification in Cushing's syndrome. Radiography of the hands and wrists may indicate advanced bone age in a child with virilism and a film of the chest should be performed to exclude metastases. An

intravenous pyelogram must be done in all cases, and both a barium meal and enema may on occasions give valuable information. Peri-renal insufflation of air by the pre-sacral route aids in localizing the tumour and in doubtful cases recourse to aortography may be fruitful.

TABLE XIII

STEROIDAL ACCESSORY INVESTIGATIONS OF VALUE IN ADRENOCORTICAL CARCINOMA

Total Urinary 17-Ketosteroids
Total Urinary 17-Hydroxycorticoids
  Fractionated Steroidal Studies
Total Urinary Dehydroepiandrosterone
  Total Urinary Oestrogens
  Total Urinary Aldosterone
  Peripheral Blood Studies
Adrenal Vein Cannulation Studies
  Immediate Tumour Studies

TABLE XIV

RADIOLOGICAL ACCESSORY INVESTIGATIONS OF VALUE IN ADRENOCORTICAL CARCINOMA

Plain Radiograph of Abdomen
Plain Radiograph of Bones { Hands / Skull / Spine }
Plain Radiograph of Chest
Intravenous Pyelogram
  Barium Meal
  Barium Enema
Peri-Renal Insufflation
  Aortogram

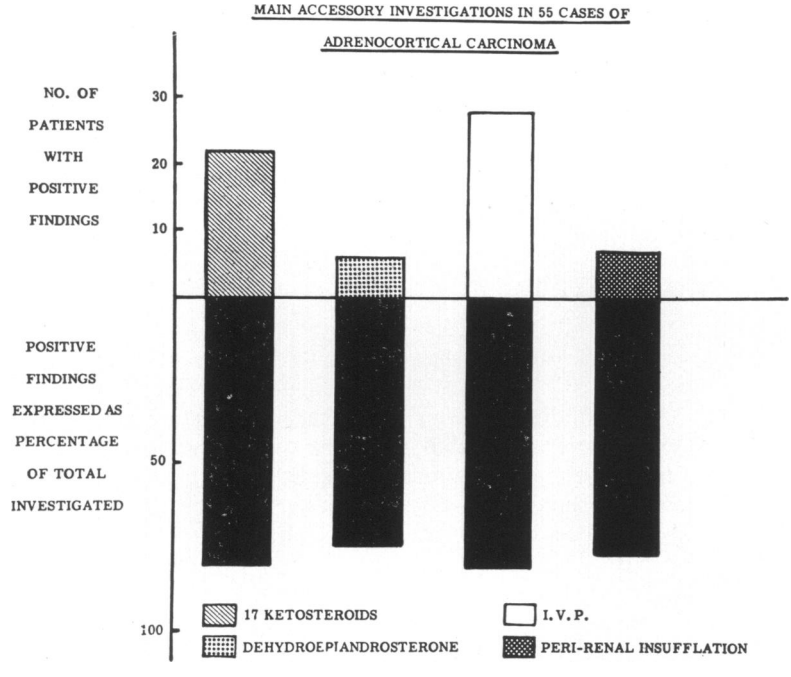
In Table XV the findings in four of the more important steroidal and radiological examinations are tabulated. The total urinary 17-ketosteroid estimation was the commonest laboratory investigation in the series. Were it not that some of the included cases were diagnosed nearly twenty years ago it would have been employed more often. A gross elevation was found in 81 per cent. of those investigated. Similarly, the Patterson test showing a rise in dehydroepiandrosterone was positive in 75 per cent. but the number in which it was estimated was not large (six) and its usefulness would be better ascertained if it were more frequently undertaken. An intravenous pyelogram gave a positive finding in 82 per cent. of the cases in which it was employed although the adrenal was not always correctly cited as the cause. Peri-renal insufflation justified its use in giving a 78 per cent. positive result. The remaining investigations were not performed in sufficient numbers to warrant their inclusion in this table but satisfactory information was obtained including the two cases in which aortography was used. The combination of the two simple tests of 17-ketosteroids and intravenous pyelography gives a high proportion of positive results in the androgen-producing tumour.

The degree of hormonal symptoms does not bear a constant relation to the urinary ketosteroid output and although in general the larger growths tend to produce the higher figures there are a number of exceptions. An increase above the normal level was noted in two clinically non-hormonal tumours—68 and 40mgms. per twenty-four hours respectively—further supporting the lack of correlation between the clinical

picture and the quantitative steroidal output. In general, the Patterson test was positive where there was a high level of alpha-ketosteroids. No correlation between the sex of the patient or the duration of symptoms and the steroidal output could be found and the highest figure recorded—324 mgms. per twenty-four hours—was in a patient in whom the first signs of hormonal activity were noted in hospital.

TABLE XV

MAIN ACCESSORY INVESTIGATIONS IN 55 CASES OF ADRENOCORTICAL CARCINOMA



Although no great emphasis should be placed on an individual quantitative steroid estimation, a series is of considerable qualitative value. A fall to normal levels occurred after extirpation of the lesion, including the non-hormonal type, and its subsequent rise was indicative of the presence of metastases. Urinary steroidal studies may help to differentiate between cases of adrenal hyperplasia and of tumour. Harrison and Laidlaw (1953) have shown that following an eight-hour infusion of ACTH a marked rise occurs in hyperplasia but not in carcinoma where the tumour appears autonomous. Venning *et al.* (1952), similarly demonstrated a fall in the steroid level after cortisone suppression in hyperplasia, but no alteration in carcinoma. This lack of response was frequently demonstrated, but such autonomy was not complete in one case in the series—of Cushing's syndrome—already reported by Prunty (1956) where a rise in 17-ketosteroids and 17-hydroxycorticoids took place with ACTH, but there was

no fall with cortisone suppression and both tests should therefore be performed.

Operative staging

Any satisfactory method of staging tumours is valuable in assessing prognosis, and, because of histological difficulties in interpretation, a clinical staging such as the T N M system attributed to Denoix and proposed at the International Congress of Radiology in Copenhagen in 1953 is more suitable. A modification of this classification so that an operative assessment may be made has been employed in this series. This allows the inclusion of a greater number of patients whose tumours were impalpable and an exact appreciation of the local spread. Table XVI illustrates such staging, which will be more accurate than clinical staging.

TABLE XVI

OPERATIVE STAGING OF ADRENAL TUMOUR

T	1.=Relatively Small Tumour—5cms. and under. 2.=Relatively Large Tumour—over 5cms. 3.=Infiltration locally reaching neighbouring organs. 4.=Invasion of neighbouring organs—Kidney, Veins, etc.
N	(*a*)=No Nodes (*b*)=Mobile Nodes (*c*)=Fixed Nodes
M	Distant Metastases
STAGE	I.=T1 Na II.=T2 Na III.=T3 Na, T1 Nb, T2 Nb IV.=T4, Nc or M contained in any combination

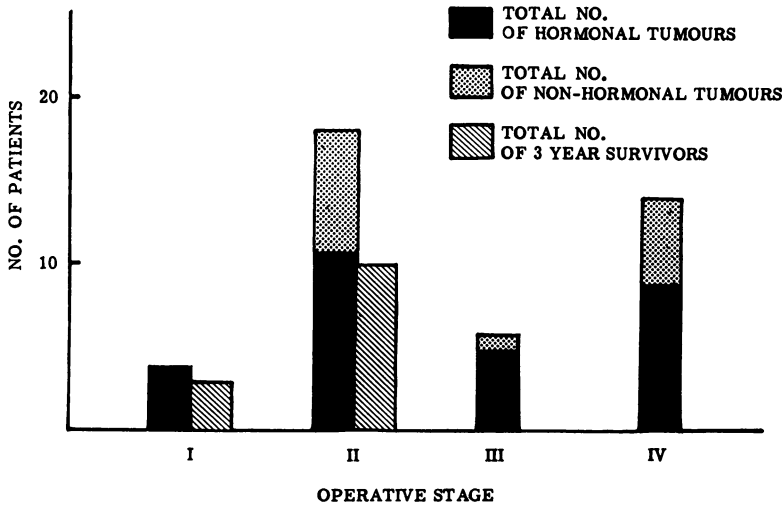
Forty-two tumours could be staged operatively, twenty-two being either Stage I or II and twenty in Stage III or IV—Table XVII. Eighty-two per cent. of the total hormonal tumours were operated upon and consequently staged, but only 65 per cent. of the non-hormonal reached surgery, the remainder being advanced growths or recognized only at post-mortem. Their failure to appear in Stage I is understandable when the anatomical position and lack of symptoms is considered. No statistical value could be placed on the operative staging of the tumours responsible for the various clinical hormonal syndromes.

In a condition of high malignancy it is reasonable to employ a three-year survival period in assessing prognosis. The thirteen survivors were found to be Stage I and II growths, that is where no infiltration has occurred. When extension locally or more distally has taken place the prognosis as measured by survival time is bad ; the average period after operation in Stage III being eight months, and in Stage IV, seven months.

The non-survivor in Stage I died after two years with metastases and it is doubtful if any further measure would have helped, but of the eight cases in Stage II who did not survive three years, six died within twenty-four hours of operation and a number of these deaths occurred at the

TABLE XVII

3 YEAR SURVIVAL PERIOD RELATED TO OPERATIVE STAGING IN 42 CASES



earlier period of the series, no doubt from electrolyte and hormonal imbalance associated with insufficiency of the other adrenal. Had this been corrected the number of three-year survivors in this group might have been higher. To better the prognosis earlier detection with a view to improving the Stage is important, but in fairness in a longer follow-up it has been found that one of the three-year survivors in Stage II has succumbed to the disease after four years, and another is dying from metastases after six years.

Prognosis from mortality results

To evaluate the prognosis from the mortality results it is first necessary to consider the nature of the surgery employed in the management of these cases. Although the number of three-year survivors—thirteen out of fifty-five—suggests a rather poor prognosis, analysis of the type of surgery performed emphasizes where improvement in prognosis could take place (Table XVIII). In 40 per cent. of all cases only laparotomy or palliative

TABLE XVIII

SURGICAL MANAGEMENT IN FIFTY-FIVE CASES OF ADRENOCORTICAL CARCINOMA

	Number of patients	Percentage
Three-year survivors	13	23·6
Surgery employed	42	76·5
Laparotomy	10	18·2
Palliative excision	12	21·8
Radical excision	20	36·4
Immediate mortality in forty-two surgical cases	11	26·2

excision was feasible, but in the twenty cases where a radical excision of the lesion was performed there were thirteen who survived for three years. Earlier diagnosis can be expected to increase the number of patients where such radical extirpation can be carried out.

The overall immediate mortality—deaths within one month of operation or in hospital—in the forty-two surgical patients is high and some improvement in prognosis would seem indicated. That this has occurred is seen by an analysis of the immediate mortality in the hormonal group of patients treated before cortisone became generally available and since (Table XIX). Reduction of immediate mortality in the non-hormonal group is likely with improved techniques which have taken place since some of the earlier cases. In the hormonal group the overall immediate mortality of 27.6 per cent. can be sub-divided into 35.3 per cent. before 1952 and 16.7 per cent. since. The advent of cortisone has thus more than halved the immediate mortality and greatly improved the prognosis in these tumours.

TABLE XIX

IMMEDIATE MORTALITY IN FORTY-TWO SURGICALLY TREATED CASES

	Number of patients	Percentage
Immediate mortality in thirteen non-hormonal cases	4	30·8
Immediate mortality in twenty-nine hormonal cases	8	27·6
Immediate mortality in seventeen hormonal cases before 1952 ..	6	35·3
Immediate mortality in twelve hormonal cases after 1952	2	16·7

Ten of the thirteen survivors are females (32.3 per cent. of the total number of female patients) and only three are males (12.5 per cent.), emphasizing the apparently worse outlook in the latter. Eight of the survivors had hormonal tumours, although only one of these was of the Cushing's type indicating the particularly bad outlook noted also by other authors (Heinbecker *et al.*, 1957). There are five survivors in the non-hormonal group giving a slightly better survival rate than the hormonal type, which is at variance with the increased malignancy noted earlier. Further study of a greater number of these tumours is required to determine if in fact two distinct types of non-hormonal tumours exist.

Treatment

The method of choice is radical extirpation of the adrenal gland after adequate pre-operative preparation. Apart from the general care associated with any major procedure specific hormonal therapy is required. The excessive production of hormones by the hormonal tumours may result in atrophy of the contralateral gland. When the sole source of adrenocortical hormones in the body is then removed by excision of the tumour, collapse and death may follow, a feature of five cases in this

series—mainly occurring before its importance was recognized. In the prevention of this 100mgms. of cortisone should be given intramuscularly pre-operatively and 100mgms. of hydrocortisone intravenously during surgery. This should be followed post-operatively by cortisone for two weeks in a dosage which is gradually diminished to 50mgms. per day in the last three to four days and combined with an ACTH gel for this period.

Although removal of the tumour is the treatment of choice the exact extent of the operation has not been defined because of insufficient experience of any single surgeon. Where the lesion is localized to the gland total adrenalectomy on the affected side may be sufficient and was performed in ten out of the thirteen survivors. The study of the disease shows that spread takes place more frequently by the blood stream than by the lymphatics and thus block dissection of the lumbar nodes has a limited value. Nevertheless, in five cases these nodes were the only site of metastases and it would seem worthwhile to combine this procedure with tumour removal. Nephrectomy appears unnecessary unless the kidney is involved. Invasion of diaphragm or spleen would require their removal in an en-bloc dissection. No orthodoxy exists as to the type of incision but a thoraco-abdominal incision with resection of the eleventh rib and an extra-pleural dissection has much to commend it in allowing adequate exploration of the liver for metastases and sufficient room for en-bloc dissections.

Radiotherapy is not considered to be of great value but there was some temporary regression in two instances and further experience will show if there is some palliative value for the more anaplastic tumours with modern techniques. More recently chemotherapy in the form of amphenone has been tried in the control of inoperable hormonal-producing tumours with some temporary success (Thorn *et al.*, 1956).

SUMMARY AND CONCLUSIONS

To recapitulate, a study of the natural history of this relatively uncommon condition has been presented in order that a better understanding of the normal process of the disease may be obtained and how it may be altered with modern treatment.

Emphasis has been laid on all aspects of diagnosis which will improve the prognosis by earlier detection. The clinical syndromes have been discussed and procrastination in their correct interpretation avoided by the maximum use of accessory investigations, the value of which has been recorded in the present series. Clinically difficult to stage, a modification of Denoix's classification has been suggested which can be utilized at operation and found to be of value in assessing prognosis. Where the tumour is confined locally the outlook is more hopeful but with spread to adjacent structures the prognosis is at once more grave, and survival time short.

Treatment of the disease must be directed towards early surgery, as other methods of radiotherapy and chemotherapy are unsatisfactory and should be reserved for palliation of the inoperable lesion. Adequate exposure is essential with full exploration of the peritoneal cavity to avoid unnecessary surgery and an extra-pleural thoraco-abdominal incision is recommended. In the absence of distant metastases unilateral adrenalectomy with local node dissection is advocated. Full steroid cover during and after surgery is vital in hormonal cases as death from contralateral adrenal atrophy is a grave hazard. The results of such treatment are more hopeful than is judged from individual case reports and have shown considerable improvement since the introduction of cortisone therapy.

Nevertheless, there are many factors about this disease that require elucidation. What is the relationship, if any, between adrenal hyperplasia, adenoma and carcinoma? Small cortical adenomas are common at necropsy and yet one meets few carcinomas. Adrenal hyperplasia is related in some instances to an increased output of ACTH yet it is doubtful if the pituitary bears responsibility in carcinomatous growths as for the most part, although not always, these tumours appear to be autonomous. Yet one cannot totally ignore that in animals malignant adrenal tumours which may be produced by castration can be prevented by hypophysectomy. Therefore it is essential that in the future management of these tumours greater emphasis must be laid on fuller steroidal studies of adrenocortical hormone production as measured at the time of surgery by adrenal vein cannulation. When circumstances permit, the intravenous administration of 25mgms. of ACTH in physiological saline during collection of the blood, with subsequent fractionation studies may clarify the issue of tumour autonomy. These findings must be correlated with the clinical and histological aspects and carefully documented. Only thus can a truly composite picture of these rare neoplasms be obtained with a subsequent lowering of their mortality.

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