TRANSIENT CUSHING SYNDROME

WITH REPORT OF A CASE

BY

HERMAN ZONDEK, M.D.

AND

HANNAH E. LESZYNSKY, M.D.

Bicur Cholim Hospital, Jerusalem, Israel

Cushing's syndrome (the designation referring to the clinical and not, as frequently used, to a pathogenic entity) is commonly regarded as a very grave illness which invariably leads to death within a few years. Drastic surgery is therefore generally accepted as the treatment of choice. Although, as a rule—especially with polysymptomatic and rapidly developing cases—the seriousness of the prognosis cannot be doubted, the general validity of this drastic therapeutic viewpoint appears to us questionable. We have seen a number of cases—the first in 1923 (Zondek, 1923)—with a definite Cushing syndrome in which the signs and symptoms of the disease regressed either spontaneously or as the result of conservative measures. Clinical amelioration was in fact so striking that active therapy was again and again postponed, until it became superfluous.

The purpose of this paper is to report, out of a total of six cases mostly occurring in the younger age groups, the case of a transient Cushing syndrome in a 54-year-old woman which appears particularly noteworthy in this respect.

Case Report

The patient was a married woman aged 54. At the age of 16 she received a "heavy blow" on the right ear which caused a haematoma with subsequent suppuration (osteomyelitis?). At 21 she suffered from malaria. She had two miscarriages and five normal deliveries, the last at the age of 28. Later she became oligomenorrhoeic and then completely amenorrhoeic. At the same time she developed great hunger and thirst and became very obese, gaining 40 kg. in six months. Her weight gradually increased, until at the age of 30 she weighed 120 kg. Hypertension allegedly up to 200 mm. Hg systolic was discovered some years later, and manifest diabetes mellitus about four years ago. At first carbohydrate metabolism was controlled by dietetic restrictions. During the few months preceding admission, increasing amounts of insulin were given without benefit. Mentally the patient was bright and cheerful.

On admission to hospital in December, 1950, at the age of 50, the patient presented a Cushing type of obesity with typical distribution of the adipose tissue and bright-red moon-face (Fig. 1). Her weight was 111 kg. There were large purple striae over the abdomen and hips. Hair was present on the upper lip, cheek, and chin. Her blood pressure was 160/90–175/90 mm. Hg. No other abnormalities were revealed by physical examination. The fasting blood sugar was 250–300 mg. per 100 ml., and glycosuria 30–40 g. a day. Acetone bodies were never present. Radoslav tests* showed reduced insulin sensitivity: 248, 231, 231, 217, 203, and 263. 247, 263, 203, 225, 203 mg. per 100 ml. Urinalysis (except for the glycosuria), blood count, E.S.R., and blood chemistry showed no abnormality. The Volhard dilution test revealed marked water retention: of 1,000 ml. of water, 275 ml. was excreted. The B.M.R. was +17%. The chest

organs were radiologically normal except for a slight dilatation of the heart to the left. X-ray films showed decalcification at the base of the skull, especially in the vicinity of the sella turcica. The eyegrounds and visual fields were without pathological findings.

The patient was put on a diet low in calories, salt, and fluids, and was given mercurial diuretics. Thereupon she steadily lost weight (13 kg. within nine weeks). At the same time her blood pressure and carbohydrate metabolism gradually returned to normal.

Second Admission

Nine months after her discharge from hospital she was readmitted for the following complaints, which had developed during the ensuing six months: pressure and pain in the right side of the head, narrowing of the right palpebral fissure, diplopia, deterioration of vision and hearing, more on the right than on the left side, numbness and a feeling of pins-and-needles in the right side of the body, mumbling speech, general apathy, and lethargy.

FIG. 1.—December, 1950, weight 111 kg. FIG. 2.—July, 1953, weight 58 kg. FIG. 3.—March, 1955, weight 97.5 kg.

On admission (November, 1951) the patient was sluggish and taciturn, in contrast to her previous vivacity. She was, however, accurate and reliable in her response to questions and investigations requiring her co-operation.

Neurological examination (Drs. A. Beller and A. Stern) revealed the following abnormalities: weakness on lateral gaze to the right, narrowing of the right palpebral fissure, weakness of the right facial nerve, decreased sensitivity to touch of the right side of the face and body, impaired hearing on the right side (audiometric examination), paresis of the right soft palate, absent patellar tendon reflexes, and ataxic gait. An electroencephalogram showed low voltage, but was still within normal limits. Pneumoencephalograms were not suggestive of a cerebral tumour. The spinal fluid showed increased pressure and contained 26 lymphocytes per c.mm. and 59 mg. of proteins per 100 ml. Nonne-Apelt, Pandey, and Wassermann reactions were negative. Besides the above-described impairment of ocular motility, there was extreme (70–80 degrees) bilateral restriction of the visual fields for white and colours.

The patient now weighed 99 kg. Her blood pressure was 115/80–140/80 mm. Hg, and the fasting blood sugar 85–113 mg. per 100 ml. There was no glycosuria. The B.M.R. was +33 to +48%. Urinary F.S.H. amounted to 200 r.u. per litre and 17-ketosteroids to 4.8 mg. per 24 hours. The Volhard dilution test again showed water retention: of 1,000 ml. of water, 280 ml. was excreted within four hours. Sodium chloride excretion was 0.7 to 1.9 g. a day. The daily urine output averaged 300 ml. a day.

*The Radoslav test, which serves the determination of insulin sensitivity, consists of the following procedure: after the fasting blood sugar is taken, 12 units of insulin are administered by the intravenous route, and thereafter blood-sugar readings at half-hourly intervals are taken during 2 to 2½ hours.

Mercurial diuretics increased the diuresis and the patient lost 7 kg. in seven weeks. During the same time she grew lively and cheerful, her gait became normal and her speech more distinct. The ocular pareses gradually subsided until ocular movements were practically free, the right palpebral fissure widened, although not attaining normal width, the motility of the right soft palate was restored, and the corners of the mouth became symmetrical. The visual fields progressively enlarged until both became normal. The reduction of sensory perception and hearing persisted, however, and the patellar tendon reflexes remained absent.

Third Admission

In July, 1953, the patient was readmitted complaining of headaches, weakness, and lassitude. Though always tired and desiring to sleep, she slept but little, either at night or during the day. During the previous five months her appetite and food intake, which had been quite normal up to then, had steadily decreased, until at the time of admission she felt an aversion towards food and fluids (during her stay in hospital her food intake never exceeded 600–700 calories a day, and this was achieved only by permanent coaxing). Weight loss during the five months preceding admission amounted to about 35 kg.

Examination revealed an almost cachectic condition (weight 58 kg.), the skin hanging down in loose folds all over the body with the exception of the legs, which showed pitting oedema (Fig. 2). The skin was pale. The pulse rate was 64–76 a minute, and the blood pressure 90/70–105/65 mm. Hg. The visceral organs showed nothing abnormal except for a moderate dilatation of the left ventricle. Apart from slight narrowing of the right palpebral fissure and slight impairment of hearing on the right side, the neurological examination was normal. Urinalysis revealed nothing pathological. The blood count showed a moderate hypochromic anaemia (R.B.C., 3,800,000; Hb, 60%; W.B.C., 5,400, with a normal differential count). E.S.R. and blood chemistry were essentially normal. The fasting blood sugar was 80–95 mg. per 100 ml. A glucose-tolerance test ran a comparatively flat course: 95, 122, 135, 124, 145, 125 mg. per 100 ml. The daily urine output ranged from 200 to 450 ml. The Volhard test again indicated water retention: of 1,000 ml., 450 and 600 ml. respectively were excreted within four hours. The sodium chloride and the nitrogen excretion were at low levels: 1.5–4.2 g. per 24 hours, and 3.37–6 g. per 24 hours respectively. The B.M.R. was –5%. Urinary F.S.H. and L.H. were less than 50 r.u. per litre, 17-ketosteroids were 4 mg. per 24 hours, and reducing corticosteroids 1.3 mg. per 24 hours. The eyegrounds showed slight hypertensive changes and the visual fields were normal for all qualities. Additional laboratory and radiological examinations helped to exclude the existence of malignancy.

Fourth Admission

In March, 1955, the patient was admitted once more. She reported that without any obvious reason her food habits had radically changed about four months previously. She had developed ravenous appetite and thirst, feeling hungry even a short time after a substantial meal. She voluntarily stated that her urine output was very small despite the great amounts of liquid drunk during the day and also at night. Her weight had steadily increased. Mentally she was apathetic and inactive, after having gone through a

short period of great activity and high spirits. In contrast to the sleeplessness at the time of her last admission, however, she slept a lot, both at night and during the day.

Examination on admission revealed a weight gain of 39 kg. (weight 97.5 kg.), with the result that she was almost as obese as on her first admission (Fig. 3). Pitting oedema of the legs was present as before. The pulse rate varied between 64 and 80 a minute, and the blood pressure between 130/80 and 150/90 mm. Hg. Physical and neurological examination failed to reveal any essential change. Urinalysis, blood count, E.S.R., and blood chemistry were normal. The fasting blood sugar ranged between 113 and 141 mg. per 100 ml., and a glucose-tolerance test ran a mildly diabetic course: 122, 171, 184, 179, 187, 178, 155 mg. per 100 ml. The B.M.R. was +34%. The daily urine output ranged between 200 and 350 ml. Sodium chloride excretion was likewise low, averaging 0.5 g. a day. The Volhard dilution test again demonstrated water retention: of 1,000 ml., 300 and 600 ml. respectively were eliminated during four hours. Urinary F.S.H. was 111 r.u. per litre; L.H., 50 r.u. per litre; 17-ketosteroids 4.2 mg. per 24 hours, and reducing corticosteroids 1.2 mg. per 24 hours. X-ray examination of the heart and skull gave the same results as before. The hypertensive changes in the eye-grounds had not progressed, and the visual fields were normal for both white and colours. There was a positive Graefe sign.

Comment

There were four more or less distinct phases in the patient's illness, which had but one common feature—namely, a pronounced tendency towards water and salt retention. The predominant features of each phase are summarized in the Table.

Mentally the patient alternated between periods of hypoactivity and apathy and periods of heightened activity and cheerfulness. No fixed correlation could be established, however, between the emotional and bodily aspects of the illness, both varying independently of each other.

Discussion

The above case is noteworthy, for in the course of observation considerable fluctuations of the signs and symptoms took place which, among other things, led to the disappearance of a frank Cushing syndrome manifest during the first phase of the patient's illness. Spontaneous reversal or effective treatment of Cushing's syndrome induced otherwise than by direct reduction of adrenocortical or pituitary hyperfunction has been occasionally reported. In our first case (Zondek, 1923), which was included by Cushing in his first publication of the syndrome (Cushing, 1932), sudden and intense weight loss became evident shortly before the patient succumbed to an intercurrent infection. In recent years we have observed a certain number of cases in which regression of the morbid phenomena occurred either spontaneously or as the result of dietary restrictions and/or dehydrative therapy, simulating thereby the excellent results achieved by drastic adrenocortical surgery. Such reversibility of the disease process is in our opinion hardly compatible with the assumption of primary pituitary or adrenocortical pathology. In fact, post-mortem examination of H. Z.'s first patient failed to reveal signs of hyperactivity in

Predominant Features in Each Phase of Illness

Phase	Duration	Food and Fluid Intake	Weight in kg.	B.P. (mm. Hg.)	B.M.R. in % (averages)	Carbohydrate Metabolism	Urinary F.S.H. (r.u. l.)	Water-Salt Metabolism	Clinical Remarks	Treatment
I	Several (?) years	Excessive	111	160–170/90	+17	Manifest diabetes		Retention	Cushing syndrome	Dehydrative therapy
II	ca 6 months	Normal	99	115–140/75	+40	Normoglycaemia	200	"	Cerebello-pontine syndrome; bi-temporal hemianopsia	" "
III	ca 8 "	Anorexia	58	90–105/70	–5	"	<50	"	Anorexia nervosa; insomnia	None
IV	ca 4 "	Excessive	97.5	130–150/80	+34	Latent diabetes	111	"	Hypersomnia	"

either gland. Rather, transient forms of the disease point to a third pathogenic site which, *per exclusionem*, should be looked for in the hypothalamus.

The fact that disorders in whose pathogenesis the pituitary is involved may result from hypothalamic as well as from primary pituitary malfunction (Zondek, 1924) is nowadays generally accepted. This also applies to Cushing's syndrome, an eventual hypothalamic origin of which has been postulated by several workers. Hypothalamic regulation of corticotrophin secretion has been shown by manifold animal experiments and clinical observations (Hume and Wittenstein, 1950; de Groot and Harris, 1950, 1952; Schunk and Cornelius, 1951; Fortier, 1952; Harris, 1952; Brobeck, 1952; Hume, 1952; Slusher and Roberts, 1954). Structural or functional damage to hypothalamic centres in man may arise from direct injury of the hypothalamic area or from cerebral lesions in the area of the fourth ventricle through compression of the Sylvian aqueduct (Zondek, 1926a). The latter possibility is demonstrated by two cases of Heinbecker (1944) in which the Cushing entity coexisted with increased intracranial pressure. In one of his patients a meningioma in the region of the second cervical vertebra had produced complete block of the spinal canal. Removal of the tumour resulted in the disappearance of the Cushing syndrome. Crispell and Parson (1952) reported the case of a man with a cerebellar astrocytoma with marked hydrocephalus internus who eventually developed the typical features of Cushing's syndrome. A similar case was reported by Fruhling *et al.* (1952).

Although absolute proof of hypothalamic origin of the Cushing manifestations in the present case is lacking, there is a good deal of circumstantial evidence. The second phase was dominated by transient neurological and ocular abnormalities. Their selection and nature permit a fairly accurate localization of the cerebral area involved, the former being suggestive of a process in the cerebello-pontine angle, and the latter of damage to the optic chiasma. Structural—for example, neoplastic—lesions at either site were ruled out in view of the transient nature of both processes and on the strength of negative encephalographic studies. Rather does the disappearance of the clinical manifestations subsequent to dehydration therapy favour the assumption of circumscribed cerebral oedema, which, acting on the neighbouring tissues in the manner of neoplastic lesions, is accordingly termed "pseudo-tumour" (Nonne, 1914). On the strength of these deductions a diagnosis of circumscribed serous meningitis of the cerebello-pontine angle was made, which conclusion concurs with the findings in the spinal fluid and the anamnestic data. A similar line of thought may be applied to the genesis of the Cushing manifestations, since they too were relieved by dehydration therapy.

The alternating occurrence of obesity and emaciation during the later stages of our patient's illness is also compatible with a hypothalamic origin. Experimental evidence accumulated during past decades has established beyond doubt that the hypothalamus is specifically concerned in the pathogenesis of both abnormal weight gain and weight loss (Aschner, 1912; Camus and Roussy, 1913, 1920; Bailey and Bremer, 1921; Smith, 1927; Keller *et al.*, 1936; Hetherington and Ranson, 1939, 1940; Hetherington, 1940; Brobeck *et al.*, 1943; Heinbecker *et al.*, 1944). One of us (Zondek, 1925, 1926b) reported cases of obesity of presumably hypothalamic origin, some of which were associated with a marked tendency towards water and salt retention (water-salt obesity), which also was a dominant feature in the present case.

Alternating obesity and emaciation without tangible disease was reported by several clinicians (Zondek, 1926c; Nonnenbruch and Feuchtinger, quoted by Weller, 1952), and attributed to disturbances of hypothalamic regulation. This conforms with the conception of one of us (Zondek, 1952, 1953) that disturbances of hypothalamic regulation are notably unstable in nature. With regard to the problem at hand, this phenomenon is well documented by experimental

investigations of Anand and Brobeck (1951). In rats and cats electrolytic lesions in the ventromedial nuclei result in ravenous hunger and subsequent obesity, whilst bilateral destructive lesions in the extreme lateral portion of the lateral hypothalamus completely inhibit food intake to the point of starvation.

On the strength of these observations it may be postulated that normal food intake is regulated by a delicate balance between two hypothalamic feeding centres, any disturbance of which will lead to either hyperphagia, with consequent weight gain, or anorexia, with consequent weight loss. Our patient behaved like a Brobeck animal, inasmuch as she alternately displayed voracious hunger with extreme weight gain, and anorexia with extreme weight loss. In her case, however, functional rather than structural damage to hypothalamic feeding centres may be postulated, which hypothesis readily agrees with the varying effects of cerebral oedema.

The hypothalamic nature of our patient's illness is also supported by a great number of other clinical manifestations which were as unstable in nature as those mentioned, and control of which by hypothalamic function is well documented by a wealth of experimental and clinical observations. These were disturbances of carbohydrate and basal metabolism, of sexual and vasomotor function, of sleep rhythm, and of the emotional state. To deal with them individually is beyond the scope of this paper.

The case here recorded, as well as similar observations (see above), permits the conclusion that in cases of Cushing's syndrome in which there is no evidence of tangible disease of the pituitary or the adrenals the possibility of an extraglandular—that is, hypothalamic—origin should be borne in mind. It appears that prognosis greatly differs with cases of glandular and extraglandular origin. Of late it has been advocated to treat Cushing's syndrome by drastic resection of the adrenals even if gross pathological abnormalities are lacking. We feel that, especially in the presence of a marked tendency towards water and salt retention, a more conservative attitude is indicated in cases in which primary hypothalamic disorder is suspected.

Summary

The case is reported of a 54-year-old woman who, when first seen, had a frank Cushing syndrome (typical obesity with moon-face, hypertension, red striae, insulin-insensitive diabetes, secondary amenorrhoea, and mild hirsutism). The basal metabolic rate was +17%. A notable feature was a marked tendency towards water and salt retention. Dehydration therapy resulted in weight loss and complete disappearance of the Cushing signs. However, the tendency towards water and salt retention remained manifest throughout the whole course of observation. After a short period of well-being neurological abnormalities suggestive of a cerebello-pontine lesion associated with a pronounced bilateral hemianopsia developed. An organic cerebral process was excluded by various encephalographic investigations. Dehydration therapy resulted in further weight loss and almost complete regression of the neurological and ocular phenomena.

About a year later a phase of anorexia associated with considerable spontaneous weight loss (about 35 kg.), hypotension, fall of the B.M.R. and of gonadotropin excretion became manifest which lasted around eight months. Again a year later the patient experienced a spontaneous change to the other extreme: voracious hunger and thirst accompanied by rapid gain in weight (39 kg.), moderate rise in blood pressure, rise in gonadotropin excretion, hypermetabolism, and latent diabetes mellitus—that is, though obese, she did not display the symptomatology of Cushing's syndrome. The patient

also suffered from disturbances of sleep rhythm during the later two stages. During the whole course of observation she was mentally very unstable without exhibiting signs of genuine psychotic alterations.

The majority of the morbid phenomena as well as their fluctuability point to hypothalamic involvement, and their response to dehydrative therapy to cerebral oedema affecting various centres during the different stages (pseudo-tumour cerebri) as the underlying cause. This hypothesis is also readily compatible with the appearance and regression of the neurological and ocular manifestations.

On the strength of this and similar observations made by us, it is suggested that in cases of Cushing's syndrome in which evidence of gross pituitary or adrenocortical pathology is lacking a hypothalamic origin of the condition be taken into account. Such cases may respond well to conservative therapy—that is, drastic dietary restrictions and dehydrative measures—especially when a marked tendency towards water and salt retention is present, and may even regress spontaneously.

REFERENCES

- Anand, B. K., and Brobeck, J. R. (1951). *Proc. Soc. exp. Biol. (N.Y.)*, **77**, 323.
 Aschner, B. (1912). *Arch. ges. Physiol.*, **146**, 1.
 Bailey, P., and Bremer, F. (1921). *Arch. intern. Med.*, **28**, 773.
 Brobeck, J. R. (1952). *Ciba Foundation Colloquia on Endocrinology*, **4**, 148.
 ———, Tepperman, J., and Long, C. N. H. (1943). *Yale J. Biol. Med.*, **15**, 831.
 Brooks, C. McC., Lockwood, R. A., and Wiggins, M. L. (1945). *Fed. Proc.*, **4**, 9.
 Camus, J., and Roussy, G. (1913). *C.R. Soc. Biol. (Paris)*, **74**, 1386.
 ——— (1920). *Endocrinology*, **4**, 507.
 Crispell, K. R., and Parson, W. (1952). *Amer. J. Med.*, **13**, 247.
 Cushing, H. (1932). *Bull. Johns Hopk. Hosp.*, **50**, 137.
 de Groot, J., and Harris, G. W. (1950). *J. Physiol. (Lond.)*, **111**, 335.
 ——— (1952). *Ciba Foundation Colloquia on Endocrinology*, **4**, 103.
 Fortier, C. (1952). *Ibid.*, **4**, 124.
 Frühling, L., Boitelle, G., and Dubois, M. (1952). *Ann. Endocr. (Paris)*, **13**, 916.
 Harris, G. W. (1952). *Ciba Foundation Colloquia on Endocrinology*, **4**, 106, 115.
 Heinbecker, P. (1944). *Medicine (Baltimore)*, **23**, 225.
 ———, White, H. L., and Rolf, D. (1944). *Amer. J. Physiol.*, **141**, 549.
 Hetherington, A. W. (1940). *Endocrinology*, **26**, 264.
 ——— and Ranson, S. W. (1939). *Proc. Soc. exp. Biol. (N.Y.)*, **41**, 465.
 ——— (1940). *Anat. Rec.*, **78**, 149.
 Hume, D. M. (1952). *Ciba Foundation Colloquia on Endocrinology*, **4**, 87.
 ——— and Wittenstein, G. J. (1950). *Proc. 1st Clin. ACTH Conf.*, p. 134. Blakiston, Philadelphia.
 Keller, A. D., Noble, W., and Hamilton, J. W., jun. (1936). *Amer. J. Physiol.*, **117**, 467.
 Nonne, M. (1914). *Neue Deutsche Chirurgie*, **12**, 107. Enke, Stuttgart.
 Schunk, J., and Cornelius, H. V. (1951). *Z. ges. exp. Med.*, **117**, 497.
 Slusher, M. A., and Roberts, S. (1954). *Endocrinology*, **55**, 245.
 Smith, P. E. (1927). *J. Amer. med. Ass.*, **88**, 158.
 Weller, O. (1952). *Ärztl. Wschr.*, **7**, 818.
 Zondek, H. (1923). *Die Krankheiten der endokrinen Drüsen*, p. 371. Springer, Berlin.
 ——— (1924). *Dtsch. med. Wschr.*, **50**, 364.
 ——— (1925). *Ibid.*, **51**, 1267.
 ——— (1926). *Die Krankheiten der endokrinen Drüsen*, Springer, Berlin.
 (a) pp. 199, 204; (b) p. 198; (c) p. 369.
 ——— (1935). *The Diseases of the Endocrine Glands*, (a) pp. 268, 269; (b) p. 266; (c) p. 433. Arnold, London.
 ——— (1952). *Schweiz. med. Wschr.*, **82**, 36.
 ——— (1953). *Die Krankheiten der endokrinen Drüsen*, p. 585. Schwabe, Basel.

The many dangerous hazards to which office workers all unsuspectingly expose themselves are the subject of a pamphlet entitled *Danger! Office Staff at Work*, recently issued by the Royal Society for the Prevention of Accidents (Terminal House, 52, Grosvenor Gardens, London, S.W.1; 6d. a copy, reduced rates for bulk purchases). Danger spots in offices include trailing telephone and electric cables, fires that have no guard to prevent papers from being blown into them, scissors, pins and needles left lying around, carpets and boards that trip up visitors even though the usual occupant of the office is familiar with them, filing cabinets that catch the unwary on the shins, and even, apparently, maniacal practical jokers who pull chairs away from under people. Office workers with slippery disks or whatever else it is that causes lumbago are shown in a neat little diagram how to pick up heavy boxes. A useful reminder in conclusion is that everyone should know where the nearest first-aid box and fire extinguisher are.

WILMS'S TUMOUR: ITS TREATMENT AND PROGNOSIS

BY

L. STUART SCOTT, Ch.M., F.R.C.S.Ed.
F.R.F.P.S.

Urological Department, Western Infirmary, Glasgow;
formerly of the Royal Hospital for Sick Children, Glasgow

In a previous paper (Scott, 1954) dealing with various types of renal tumours in childhood, I noted that the overwhelming majority were of the embryonic type known as Wilms's tumour (Wilms, 1899). An analysis of the reports of the Registrar-General for Scotland for the years 1941 to 1949 shows that, of 82,007 deaths in children under 12 years of age, renal tumours accounted for 0.07% of the total deaths and 17% of the tumour deaths.

The present review of the subject was prompted by the high mortality rate found in 61 cases of Wilms's tumour at the Royal Hospital for Sick Children, Glasgow (Scott, 1954). In an effort to obtain a clearer picture of the various factors which might influence treatment and prognosis, details of 1,141 cases treated at different centres and by different methods have been abstracted from the literature. These are discussed below, together with a more detailed study of my original 61 cases plus two additional cases that have since been encountered.

Historical

Because these tumours seldom produce symptoms referable to the renal tract, the diagnosis was for many years generally made at necropsy, and, although pyelography now permits earlier diagnosis, the mortality is still about 80%.

Jessop (1877) reported the first successful nephrectomy for Wilms's tumour in a boy aged 2 years; the child survived the operation but died nine months later from a recurrence under the scar. Israel (1894) recorded the first five-year "cure." Keith (1894) stated that "in young children it is doubtful whether it is ever right to operate; indeed, such operations must be looked upon as a surgical possibility rather than as an operation of advantage to the patient." This somewhat sweeping statement is not without justification, as a perusal of the literature shows that at the end of the nineteenth century nephrectomy in children was attended by a prohibitive mortality.

For several years deep x rays had been employed in the treatment of various types of tumour before Friedlander (1916) realized their potential value as the primary treatment of renal tumours in children. Foster and Mendilharzu (1925) implanted radium needles direct into the tumour, but although this was a popular vogue for some years it failed to stand the test of time.

To-day few surgeons favour treatment by radiation alone, although for a time this appeared to hold great promise; even fewer employ surgery alone. Radiotherapy by itself may still have a limited place in the treatment of advanced cases, occasional dramatic "cures" having been reported even in the presence of pulmonary metastases (Kerr, 1939; Silver, 1947). Radiotherapy used in conjunction with surgery is now the treatment of choice, but its exact role is still controversial.