WERNER'S SYNDROME (PROGERIA OF THE ADULT)

FURTHER PATHOLOGICAL AND BIOCHEMICAL OBSERVATIONS

BY

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Clinical details of this case of Werner's syndrome have already been reported (Grant, 1957). Since then the opportunity has arisen to investigate more fully the steroid metabolism in this unusual condition and to report on the necropsy.

Results of various biochemical tests carried out on these patients in the past have been both conflicting and limited in scope, the only full study on adrenal steroids available being that of Bauer and Conn (1953). Post-mortem evidence, too, is scant. Out of 61 cases published to date, excluding the case here recorded, only the necropsy report by Oppenheimer and Kugel (1941) is available. Mavis Kelsey is quoted by Bauer and Conn (1953) as finding large adrenals with an adenoma in the cortex in necropsy. Oppenheimer and Kugel (1941) found a normal pituitary, adenomata of the adrenal and thyroid glands, and hyperactive parathyroids. Several theories of the cause have been advanced, all of which fail to explain fully the multiple facets of the syndrome. Indeed, the explanation would appear to be the problem of ageing itself.

Clinical Picture

The features of the syndrome, which vary slightly with different authors, may be summarized as follows:

1. *Premature Senility*.—This is a constant feature, starting at about 20 years of age and progressing with greying of the hair going on to baldness. Early cataracts and arteriosclerosis ensue, and the patient becomes senile between 30 and 40 years, with a piping, highly pitched voice and loss of teeth. Arterial calcification is marked.

2. *Pseudo-scleroderma*.—The skin and subcutaneous tissues atrophy, especially over the extremities, where the skin is very tight and thin and may cause contractures. Over points of pressure the tissues break down, with the appearance of ulcers. Associated occlusive vascular effects and chronic infection may lead to amputations.

3. *Characteristic Stature and Appearance*.—These patients are undersized owing to early cessation of growth. There is wasting with spindling, especially of the extremities, the nose is rather beak-like, and the features are gaunt and sharply defined. The abdomen and trunk do not share to the same extent in the wasting.

4. *Associated Endocrine Disturbances*.—Hypogonadism seems constant. Some patients have been described with mild hyperthyroidism and some with diabetes. Proptosis found in most of these patients is not due to hyperthyroidism. The condition may be confused with organic panhypopituitarism.

5. *Skeletal Disturbances*.—Arthritis, osteoporosis, and subcutaneous calcification are usual, and the latter also may lead to chronic ulcers.

6. *Hereditary Tendency*.—Since the original description, this feature has been noted by many authors, although a family history may be absent in individual cases.

The Role of Steroid Hormones and Liver Metabolism

It has been suggested by Bauer and Conn (1953) from their studies on the response to corticotrophin (A.C.T.H.) and oral compound S (17-hydroxy: 11-desoxycorticosterone) in a case of Werner's syndrome that the essential feature of this condition is a failure of the liver to detoxicate hydrocortisone.

Hydrocortisone is probably the active glucocorticoid and is normally removed from the circulation at a rapid rate (Peterson *et al.*, 1957). The details of how hydrocortisone is disposed of by the body are still obscure, although there is no doubt that the liver is of great importance. Cameron (1957) has reviewed in detail the present knowledge of the function of the liver in steroid metabolism. In liver disease hydrocortisone disappears from the circulation at a slower rate than normal, although related hydroxycorticoids—cortisone, corticosterone, and tetrahydrocortisone—disappear at normal rates, which are higher than that of hydrocortisone. Two main processes seem to be involved in the disposal of hydrocortisone—alteration in the steroid molecule, and conjugation of hydrocortisone and its metabolites, forming glucuronides. In the steroid molecule reduction takes place in ring A, and compounds of the tetrahydrocortisone, tetrahydrohydrocortisone, and dihydrocortisone type are produced. All these products appear in the urine as 17-hydroxycorticoids, mainly as conjugates, but 3–7% remain in the free form. Removal of the side chain from the hydrocortisone molecule leaves 17-ketosteroids, including weak androgens of the 11- β -hydroxaetiocholanolone type.

In a review of corticoid metabolism Jay Gold (1957) records that by chromatographic methods after cortisone infusion through a cirrhotic liver two abnormal steroids are found. These are 6- β -hydroxy-deoxycorticosterone and allopregnane 17 α ,21-diol-3: 11:20-trione, the latter being similar to cortisone except that the pregnene structure has been partially broken down. He summarizes the steps in hydrocortisone formation by the adrenal as follows: cholesterol—pregnenolone—progesterone—17-hydroxyprogesterone—compound S—hydrocortisone; and a similar scheme has been postulated by Hechter and Pincus (1954).

Bauer and Conn (1953) in an A.C.T.H. stimulation test gave 70 mg. in divided doses spread over six days to a patient with Werner's syndrome and produced a fall in circulating eosinophils, while low-control urinary 17-ketosteroids rose and then fell two days after stopping therapy. Formaldehydogenic steroids were at the upper level of normal (0.92–2.6 mg./day) during the control period and rose with A.C.T.H. to a maximum of 4.9 mg. Oral administration of 400 mg. of compound S produced a rise of 17-ketosteroids to 11.1 mg. on the first day and 18.3 mg. on the second day—a much smaller rise than expected—while formaldehydogenic steroids rose to 3 mg./24 hours after five days. The ordinary liver function tests were normal. The authors noted that the subnormal 17-ketosteroids and relatively elevated urinary formaldehydogenic

steroids with compound S administration were similar to the effects of liver dysfunction, and postulated an inability of the liver to convert compound S to 17-ketosteroids. Fajans, Louis, and Conn (1951) had studied the urinary excretion of 17-ketosteroids and formaldehydrogenic steroids following administration of compound S both orally and intramuscularly. These authors had found an increase of four to six times in the urinary 17-ketosteroids without a corresponding increase in the formaldehydrogenic steroids in two normal cases and in a case of Addison's disease. In a subject with cirrhosis, 400 mg. of compound S orally produced a rise of 17-ketosteroids of only 12 mg. as against the expected 35 mg. They concluded that the liver was responsible for the degradation of compound S to 17-ketosteroids. Bauer and Conn (1953) argued that if the liver in Werner's syndrome was unable to deal with compound S it could be similarly incapable of transforming hydrocortisone. If this process was of mild degree from birth and long-continued, excess hydrocortisone would produce an antianabolic effect, with failure to grow, atrophy of the tissues, and a tendency to diabetes instead of Cushing's syndrome. While A.C.T.H. gave clinical improvement in their patient they considered that it would eventually aggravate the condition.

Further Case Report and Method of Study

The patient, a man aged 62, was readmitted for further investigation on March 8, 1957. His general condition was similar to that previously described (Grant, 1957). In order to test further the validity of the theories referred to above, the following investigations were undertaken:

1. *A.C.T.H. Stimulation Test* (Fig. 1).—This standard test was carried out over a period of six days, involving two initial resting-days followed by four days of stimulation by a potent A.C.T.H. gel, 20 mg. b.d. intramuscularly. Urine specimens (24-hour) were measured and estimated for 17-ketosteroids and 17-ketogenic steroids by the modified Norymberski method (Appleby *et al.*, 1955).

2. *Cortisone "Utilization" Test*.—This was undertaken as in the A.C.T.H. stimulation test, with an initial period of two resting-days followed by oral cortisone acetate, 25 mg. q.i.d. for four days. Twenty-four-hour urine samples were similarly saved, measured, and estimated for 17-ketosteroids and 17-ketogenic steroids.

3. *Compound S "Utilization" Test*.—This was carried out in a similar manner to the above tests excepting that compound S, 100 mg. q.i.d., was given for one day only, after an initial rest period of two days. The results of this and of the cortisone "utilization" test are shown in Fig. 2.

4. *Additional Biochemical Investigations*.—These gave the following results. Urinary creatinine, 1,172 mg./24 hours; urinary creatin, 127 mg./24 hours; a urinary chromatogram showed a particularly raised excretion of taurine and slightly increased leucine and tyrosine; serum proteins totals, 6.0 and 7.0 g./100 ml. (albumin 3.6 and 3.6/100 ml., globulin 2.4 and 3.4/100 ml.); alkaline phosphatase, 19.3 and 23.8 K.A. units; serum calcium, 10.1 and 8.9 g./100 ml.; serum magnesium, 1.9 mg./100 ml.; serum transaminase, 16 G.O. units; blood urea, 42 mg./100 ml.

Serum Electrolyte Levels in mEq/l. Taken on 10 Occasions Between May 11, 1956, and June 2, 1957. Specimen (b) Taken When Patient on Cortisone Acetate 100 mg. Daily and Specimen (g) When on A.C.T.H. gel 40 Units Daily

Specimens	a	b	c	d	e	f	g	h	i	j
Na ..	121	140	123	121	125	124	134	126	122	120
K ..	5.7	4.9	5.2	5.1	4.3	5.3	4.1	3.5	5.4	5.0
Cl ..	105	110	85	90	95	100	95	100	105	95
CO ₂ CP ..	24.8	25.5	26	26.8	27	27.7	31.3	29.4	34	26.8

Serum electrolytes were estimated on 10 separate occasions. The results are shown in the Table. At the time of taking specimen (b) the patient was on cortisone acetate, 25 mg. q.i.d.; and specimen (g) corresponds to a time when he was receiving A.C.T.H. gel, 20 units b.d. intramuscularly. The improvement in the serum sodium level is evident. It was further noted that while the patient was on test doses of A.C.T.H. he improved greatly, his appetite returned, and he volunteered that he felt stronger.

He was discharged at his own request on May 18, to be readmitted on June 13, in an extremely weak condition. Emaciation was extreme, but otherwise his condition showed little change. His temperature was 98.4° F. (37° C.), his pulse was in normal sinus rhythm at 78/minute, and his blood pressure was 90/50. He died suddenly on June 18, 1957.

Necropsy Findings

Post-mortem examination (Dr. B. Foley and Dr. J. E. Morison) was undertaken 21 hours after death. In view of the sparsity of previous post-mortem reports the findings are given below in some detail.

Macroscopic Examination.

The physical characteristics were striking, being those of extreme emaciation and senility, with complete loss of subcutaneous fat and absence of scalp and axillary hair, with only a few fine pubic hairs remaining. Numerous

FIG. 1.—A.C.T.H. stimulation test on two occasions, with record of urinary output, of 17-ketogenic steroids (KGS), and of 17-ketosteroids (KS).

FIG. 2.—Cortisone and compound S "utilization" tests with record of urinary output, of 17-ketogenic steroids (KGS) and of 17-ketosteroids (KS).

septic lesions were noted in relation to bony prominences and joint surfaces. Both elbow-joints were dislocated and showed associated septic arthritis. The medial and lateral malleoli were ulcerated, as were the lateral borders of the feet and heels. The little toe of the left foot had sloughed away, leaving a raw infected surface. The fourth and fifth toes of the right foot had been amputated surgically. Post-mortem rigidity and lividity were present.

FIG. 3.—Physical characteristics of the patient.

The body cavities appeared normal. Pericardial fat was almost absent and the heart small, weighing only 175 g., compared with a normal weight of 300 g. There was no aortic valvular calcification, and the coronary arteries appeared normal apart from patchy calcification. The aorta showed some patchy atheroma of the arch and at its bifurcation, where there was also calcification. The lungs were consolidated in the posterior basal segments. The liver weighed 700 g. (normal 1,400–1,600 g.) and appeared atrophic on section. There was increased fibrosis of the splenic pulp, and the organ weighed only 60 g. (normal 150–200 g.) while the pancreas showed a normal lobular pattern and weighed only 60 g. The stomach, duodenum, and intestines were normal. The right adrenal weighed 2.75 g. and the left 3.4 g. (normal 5–6 g.). On section the lipid content was decreased but not entirely absent. Perirenal fat was more or less absent and each kidney weighed 80 g. (average normal 150 g.). The surface was smooth and showed only a few scattered congenital cysts. On section the renal architecture was normal. The bladder was reduced in size and showed no trabeculation. The prostate

FIG. 4.—Skin of scalp. Atrophy of epithelium and skin appendages. ($\times 125$)

was small (walnut-size) but otherwise normal. Both testes appeared small and atrophic, measuring 3.8×2 cm. The mucosa of the pharynx, oesophagus, and trachea appeared atrophic; the thyroid was very small and smooth on section; the parathyroid glands were not identified. The brain weighed 1,140 g. (average normal 1,400 g.). No atrophy of convolutions was noted.

Microscopical Examination.

The myocardium showed early "brown atrophy," the muscle bundles being generally smaller than normal, with an atrophic appearance; ischaemic fibrosis was evident, while the coronary arteries showed marked atheroma. The aortic cusp of the mitral valve was the seat of non-specific thickening with no vascularization. The lungs were emphysematous, and basal pneumonic consolidation, with areas of dense fibrosis and infiltration with plasma and small round cells, was present. Other cells had foamy cytoplasm, and fat stains were positive, suggesting lipid pneumonia. In the liver the cells in the centre of lobules showed marked atrophy, but there was no acute necrotic change; marked glycogen and slight fat vacuolation of cells was seen. The spleen showed prominence of trabeculae with atrophy of the Malpighian corpuscles. The pancreas appeared normal apart from reduction in size of the islets. The adrenal tissue had an atrophic appearance, but lipid was still present and a few small adenomata were

FIG. 5.—Testes. Complete atrophy of seminiferous tubules. ($\times 75$)

seen. Apart from occasional glomerular calcification, the kidney was normal microscopically; nothing pathological was noted in the bladder. The prostate was very fibrous, the ducts were prominent, and the glandular system was very atrophic, all the glands being small, inactive, and lined by a single layer of epithelium. A granulomatous prostatitis was noted in relation to the prostatic urethra. The testes showed thickening of the tunica albuginea; the seminiferous tubules had no lining cells, were hyalinized, and were widely separated by oedema fluid. Occasional Leydig cells were seen. There was no evidence of spermatogenesis at any phase, and the whole picture was one of extreme generalized testicular atrophy. The thyroid and parathyroid glands had normal histological appearances. The trachea and oesophagus were the seat of subepithelial fibrosis, while the pharynx showed low-grade submucosal inflammatory reaction. The brain was microscopically normal apart from marked calcification of the smaller vessels. The pituitary gland, though very congested, was otherwise normal. Skin of the scalp, chest,

thigh, foot, arm, pubis, and shin were all examined. They showed the epidermis to be stretched and atrophic, while there was a thick fibrous layer in the dermis with loss of subcutaneous fat. Skin appendages, though present, were atrophic, and there was no attempt at hair growth in the scalp and only a few fine hairs on the pubis. In sections showing muscle, the bundles seemed to be irregular in size and shape and to have an increased proportion of fibrous tissue. The bone-marrow was atrophic and gelatinous, but showed no evidence of a gross disturbance.

Summary of Necropsy Findings

Death was due to "lipoid pneumonia." There was atrophy of the skin and skin appendages, with atrophy and patchy fibrosis of voluntary muscles. The trachea and oesophagus showed submucous fibrosis, while there was gross generalized atrophy of the testes and prostate. The adrenals were atrophic, showing much reduction in weight, thinning of the cortex, and the presence of multiple small adenomata. The liver was atrophic, being only half the normal average weight, while the heart and spleen were reduced in size to a lesser extent. The pituitary gland, though congested, had a normal cellular structure. The thyroid, the parathyroid glands, and the brain were essentially normal.

Discussion

Biochemical

In the patient under consideration the results of A.C.T.H. stimulation (Fig. 1) are compatible with hypopituitarism. Initial levels of 17-ketogenic steroids and 17-ketosteroids were low, but gains of 18–19 and three times the resting level respectively were observed on two separate tests—results which are not outside the limits one would expect with a hypoplastic adrenal responding to stimulation by the method employed. The daily volume of urine of this patient was consistently small (Figs. 1 and 2), and we have been impressed by this also in a case of dystrophia myotonica. It will be noted, too, that an increased daily volume of urine resulted from both A.C.T.H. stimulation and administration of oral cortisone acetate. This we interpret as improved excretion of a water load and would further support a state of hypopituitary function with adrenal hypoplasia. No similar diuresis occurred with compound S (Fig. 2), which is known to have no metabolic effects (Terry and London, 1950) (Pearson *et al.*, 1951). Functional pituitary deficiency is further suggested by the low level of gonadotrophins (4 mouse units/24 hours) and the relatively low blood-sugars in the glucose tolerance and in the insulin sensitivity tests reported previously (Grant, 1957). On test doses of A.C.T.H. and cortisone the serum sodium increased (Table I) and the patient improved physically.

After oral administration of 400 mg. of cortisone acetate over four days and 400 mg. of compound S the total recovery of metabolites was poor (Fig. 2), especially so in the latter, the maximum output of 17-ketosteroids being 2.8 mg./24 hours, while that for 17-ketogenic steroids was 3.8 mg./24 hours. Out of 400 mg. of compound S, only 6 mg. of 17-ketosteroids and 10.4 mg. of 17-ketogenic steroids were recovered over six days. The recovery rate after cortisone was 17 mg. and 63.0 mg. respectively, levels which are lower than expected but much better than after compound S. After administration of cortisone acetate 100 mg. a day in adrenalectomized patients, the expected recovery of 17-ketogenic steroids would be approximately 40 mg. a day (Moxham and Nabarro, 1956).

The Norymberski reaction is limited to estimation of the following side-chains at C₁₇ (Butt, Kornel, and Morris, 1957):

Adequate information about the recovery of compound S metabolites was unobtainable, but one would have expected this substance to behave as hydrocortisone and to be shown up by the Norymberski technique as an increase in 17-ketogenic steroids. Chemically these steroids are similar except at the 11 position, and compound S is a precursor of hydrocortisone. The possibility also arose that compound S as an inert substance might be metabolized in a manner different from cortisone, as proportions of the ketogenic and ketosteroid fractions were almost equal. The probability is, however, that the low renal output and consequent low excretion of total steroids, which was not improved by the relatively inert compound S, led to an accumulation of this substance in the body. More time was allowed for breakdown by the liver, and this would explain the appearance of a higher proportion of ketosteroids in the urine than was the case with active cortisone, which was rapidly excreted, mainly as 17-ketogenic steroid conjugates.

We have, further, to reconcile our results with those of Bauer and Conn (1953), who found a rise in formaldehydogenic steroids from a high normal resting level after administration of compound S and following A.C.T.H. stimulation. In both subjects the 17-ketosteroid output was lower than expected, and this was especially so in our case. We also found control levels of 17-ketogenic steroids to be lower than normal, a finding which would be hard to reconcile with an increased blood level and thus an increased urinary output of hydrocortisone. After A.C.T.H. and cortisone 17-ketogenic steroids increased much more than 17-ketosteroids, but were still subnormal. We do not feel that the relatively increased proportion of 17-ketogenic steroids to 17-ketosteroids in any way negates hypopituitarism. To confirm Bauer and Conn's hypothesis that the inability of the liver to break down hydrocortisone is the basic cause of Werner's syndrome the increase would need to be much more striking. Further, the much more equal proportions of the two steroids after compound S suggest that there was no impairment in breakdown of this substance to 17-ketosteroid, and by analogy of hydrocortisone to 17-ketosteroid, in our patient. These authors, however, were estimating substances of the α -ketol and non-reducing C₂₀-C₂₁, α -glycol type as formaldehydogenic steroids (Daughaday, 1950), which include progesterone and other steroid products. It is generally agreed that the Norymberski technique is a more reliable procedure and has replaced estimation of formaldehydogenic steroids in the assessment of urinary hydrocortisone (Loraine, 1958). In this connexion it is also noteworthy that urine extracts contain substances other than steroids which yield formaldehyde on oxidation with periodic acid (Loraine, 1958), the presence of which might vitiate the result of estimations of formaldehydogenic steroids.

In our patient the urinary chromatogram showed a particularly raised excretion of taurine and slight excess

of leucine and tyrosine. Taurine has also been found as a trait in dystrophia myotonica by Lynas (1957), but further information on the clinical importance of this substance is scanty. Aminoaciduria might be taken as indicative of liver dysfunction, but it has been pointed out by Dent (1946) that gross aminoaciduria is encountered only in cases of massive liver necrosis or advanced cirrhosis, and taurine has not been noted following liver damage. The only other evidence of defective liver function is the slight reduction in serum albumin and the doubtfully significant increased excretion of 17-ketogenic steroids as against 17-ketosteroids previously discussed (Bauer and Conn, 1953).

The hereditary basis has again been stressed by Ellison and Pugh (1955), and, as they had found diabetes, skeletal decalcification, and impaired renal function with excess urinary aspartic acid, they considered the possibility in Werner's syndrome of a congenital innate defect of renal tubular reabsorption such as occurs in cystinosis and the Fanconi syndrome. They concluded, however, that there was no evidence for this concept. Our own case, too, showed no evidence of hyperchloraemic acidosis; in fact, electrolyte studies showed a pattern of salt depletion, and it was impossible to get the patient to take what might be regarded as adequate fluids orally.

Gross skeletal demineralization was found, but, apart from the increased alkaline phosphatase which has not been a constant feature in other cases described, there was no other suggestion of hyperparathyroidism. The original view of Oppenheimer and Kugel (1941) that increased parathyroid function was causal could not be confirmed in this as in other recorded cases.

Diabetes was not found in our subject, and is an inconstant finding in the literature, occurring in 11 cases out of 55 (Irwin and Ward, 1953). The metabolic disturbance which allows this to occur in the face of what appears to be pituitary underaction is as yet unexplained. It seems clear, however, that it is an effect of the syndrome rather than being in any way causative.

The increased figure for creatine in the presence of an almost normal urinary creatinine is probably due to both muscle-wasting and decreased tubular reabsorption, the latter in part due to the urinary excretion of other aminoacids (Thompson and King, 1957).

Pathological

The only previous post-mortem report is that of Oppenheimer and Kugel (1941). Here death was due to a primary hepatic carcinoma; in addition, multiple adenomata were found in the thyroid and adrenal glands, while the appearance of the parathyroid glands microscopically suggested increased activity. The prostate and testes were atrophic and the pituitary gland was entirely normal. The size of the organs was not in general reduced. A second patient described by the same authors died from a fibrosarcoma of the radius, while the second patient of Ellison and Pugh (1955) succumbed to a melanotic sarcoma. The incidence of malignancy in these patients is strikingly high. No evidence of malignant change was found in the case here presented, a few small adenomata only being evident in the adrenal gland. The steroid hormones are members of the cholanthrene-ring system and might have carcinogenic properties in a disordered state of cellular or steroid metabolism. Sugiura and Rhoads (1941) have shown the importance of a proper function of the intracellular enzyme system in the prevention of carcinoma of the liver. Such carcinogenic agents

first produce destruction of cells, which is then followed by repair (Wolbach, 1937), the hyperplasia leading to malignancy. It is agreed also that malignancy is more common in the older patient.

In the case reported here the striking changes were found in the skin and subcutaneous structures—changes quite distinct from scleroderma (Thannhauser, 1945) or dermatomyositis. The main features were the atrophy of the epidermis with flattening of papillae, the almost complete absence of skin appendages, and the absence of oedema, arteritis, or lymphocytic infiltration. The elastic tissue was preserved in the deeper dermis, but in the immediate subepidermal area it was atrophic. No homogenization or sclerosis of collagen, seen in scleroderma, was noted. However, fibrosis in the submucosa of the trachea and oesophagus was similar in location to that affected by scleroderma.

The other remarkable feature in the necropsy was the general microsplanchnia with gross atrophy of the testes and prostate of a general type, similar to that described by Oppenheimer and Kugel (1941). The testicular atrophy differed in its diffuseness from that due to mumps or other infections. The adrenal glands, markedly atrophic and containing a few adenomata, were normal in cellular structure. Such adenomata are often found in post-mortem material. The pituitary gland, though congested, showed no definite abnormality. The pituitary was also normal in the case of Oppenheimer and Kugel (1941); and in the post-mortem accounts of progeria—a very comparable condition arising in the first or second year of life—the pituitary was also normal (Mitchell and Goltman, 1940) and there was no sign of a pluriglandular deficiency (Atkins, 1954). Microsplanchnia in progeria is similar to the findings here, but arteriosclerosis seems much more severe than in the present case, so that in the original necropsy of progeria (Gilford, 1897) the coronary arteries were concluded at 18 years of age.

The thyroid and parathyroid glands were normal in structure, in contrast to the findings in Oppenheimer and Kugel's (1941) case of active adenomata of these glands. The atrophic gelatinous bone-marrow afforded no clue to its causation. Serum calcium, phosphorus, alkaline phosphatase, and calcium-balance studies of Irwin and Ward (1953) have tended to rule out the likelihood of hyperparathyroidism being causative, as suggested by Oppenheimer and Kugel (1941). Indeed, Thannhauser (1945) records a personal communication from Oppenheimer in which he states that he no longer adheres to the opinion that the parathyroid gland is predominantly involved.

The liver, at half its normal weight, and the less-marked reduction in size of the heart and spleen also illustrate the microsplanchnia seen in the organs in general, excepting the brain. There seems no adequate explanation for this atrophy other than the effects of senescence.

The post-mortem findings here do not help particularly in the problem of aetiology. This is understandable, since it would appear that we are dealing with chemical pathology related to a genetically determined defect of cell enzymes of a general type. This view does not differ greatly from that so well put by Thannhauser as "multiple germ-plasm defects manifesting themselves in abiotrophic features of various organs at different periods of life."

Conclusions

In conclusion, the data considered above suggest a diffuse interference with cellular metabolism affecting

endocrine tissues as well as those of other structures, such as liver, kidney, skin, bone, etc. The post-mortem appearances noted were those of microsplanchnia comparable to a state of severe and premature senescence. The combination of the typical skin changes with gonadal atrophy is distinctive. The biochemical investigations strongly suggest functional hypopituitarism with adrenal hypofunction in this case. The multiple features and variation around a common and unforgettable clinical pattern cannot, however, be explained on a purely endocrine basis nor by the effects of reduced function of the liver or kidney alone. The clinical picture of the syndrome varies as a result of other factors superimposed on what is probably a single inherited trait. Modifications of the final syndrome may then be largely dictated by the relative degrees of hypofunction of various vital endocrine and metabolic organs and their resulting imbalances. The basic cellular disturbance as shown in the skin, hair, and body structure remains constant and determines the typical physical features. A deficiency of synthesis in one enzyme system vital to all cells may be responsible and so set in train the diverse pathological consequences encountered. This is probably an inherited heterozygous recessive character, and an analogy may perhaps be drawn to galactosaemia, Hartnup disease and Wilson's disease—conditions in which a tissue enzyme defect has been established.

Summary

The biochemical investigations and necropsy findings are described in a male patient of 62 years with Werner's syndrome. It is suggested that the condition is due to a generalized enzyme defect which causes premature senescence.

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EPIDEMIOLOGY OF "SUDDEN, UNEXPECTED, OR RAPID" DEATHS IN CHILDREN

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Fatal disease in children after the perinatal period falls into four fairly distinct groups: (1) unnatural accidents; (2) neoplastic disease; (3) congenital abnormalities of form or function; and (4) rapid, unexpected death occurring either at home or shortly after admission to hospital. Our hospital beds are filled with the children of the first three groups, but the children of group 4 are rarely seen by a paediatrician, and even more rarely by the conventional paediatric research team, and there is a tendency to overlook them or assume that the deaths in this group are outside the responsibility of the hospital.

In Sheffield we are fortunate in that, through the co-operation of the coroner, the general practitioners, and the pathologist in charge of the local regional hospitals, virtually the whole of the natural deaths in children, from a fairly well circumscribed community of over half a million, have tended to pass through a single paediatric pathology department. The variation in the types of death probably reflects as complete a picture of infant mortality as is seen anywhere in the country.

When we first began doing necropsies for the coroner we were struck by the similarity in anatomical findings between the children referred to the coroner as possible cases of home suffocation and the children dying in hospital after a short illness. A careful study of the histories of a series of 50 such "sudden deaths" was carried out in conjunction with the hospital almoner; this confirmed the findings of Bowden and French (1951) that the majority of histories given to the coroner were incomplete. In over 90% there was a history of symptoms beginning at least 48 hours before death (Emery and Crowley, 1956). It thus seemed that it was something of "chance" whether a child died at home or in hospital. For that reason we have now surveyed the deaths of children who, from the histories available, had symptoms for 48 hours or less prior to death, irrespective of the site of death.

Material and Selection of Cases

During the seven years from June, 1949, to May, 1956, we carried out 1,250 necropsies in which the clinical histories were available and adequate for study. Of these deaths, 654 occurred over the age of 7 days. Only these are discussed in the present paper, as the pathological features causing death are likely to be different under this age.

Of the 654 children, 249 had died with a total history of symptoms for 48 hours or less, and from what appeared to be natural acute illnesses. There were a further 10 deaths from unnatural accidents, such as road accidents, and 8 children died as a result of a "cold" operation in hospital.

Variation in Proportion of Deaths During the Seven Years

The total annual number of children examined during the period of study was remarkably stable, being: 1949-50, 88; 1950-1, 92; 1951-2, 98; 1952-3, 100; 1953-4, 90; 1954-5, 99; 1955-6, 87. The proportions