1956), and it has been suggested that there is a separate exophthalmos-producing substance (E.P.S.). The physiological role of this substance is puzzling and its assay is difficult. It has been claimed that E.P.S. can be separated chemically from T.S.H. (Dobyns and Steelman, 1953), that it can produce exophthalmos experimentally, and that excess of it in the serum of patients is correlated with exophthalmos (Dobyns and Wilson, 1954; Brunish, 1958). It has yet to be established that E.P.S. or any other substance is present in excess in the serum of patients who develop pretibial myxoedema and later acropachy. The concept that excess of a pituitary hormone produces change in certain parts of a target organ, the skin, is not yet proved and is unhelpful as a basis for therapy. At present one can only say that pretibial myxoedema in the skin is one of several localized disorders, perhaps essentially similar, which may appear in Graves's disease under certain circumstances as yet obscure.

Summary

In 23 patients with pretibial myxoedema the appearance and behaviour of the lesions, and their relationship with hyperthyroidism, are described.

Minor pretibial lesions are not uncommon; they usually soon resolve after hyperthyroidism has been controlled.

Severe pretibial myxoedema, when it develops, tends to do so after cure of hyperthyroidism and in association with severe exophthalmos. When the lesions become extensive they persist and are resistant to treatment.

I thank the physicians of St. Thomas's Hospital who have allowed me to describe patients under their care.

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"Roughly the same is true about the theory either of contraceptive measures or of treatment of sub-fertility. Although each of them contains some new elements each can be developed from the basic physiological and anatomical knowledge common to all doctors. The situation is utterly different with regard to the therapy of marital problems. First, our knowledge of the natural history of marriages is most rudimentary, it does not bear comparison with physiology and still less with anatomy. Since pathology and therapy of marriage is not part of the medical curriculum it follows then that the mere fact that someone has obtained a medical qualification does not mean that he or she will possess the skill required for this kind of work. Should a doctor want to treat marital problems he must be prepared, as in any other special branch of medicine, to learn a good deal, theoretically and practically." ("The Marital Problem Clinic," Dr. M. Balint, *Family Planning*, April, 1960.)

RETINITIS PIGMENTOSA, HYPERTENSION, AND URAEMIA IN WERNER'S SYNDROME

REPORT OF A CASE, WITH NECROPSY FINDINGS

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In 1904 Werner described a peculiar disorder termed "cataract in connexion with scleroderma" occurring in four brothers and sisters. Oppenheimer and Kugel (1934) distinguished this condition from its related Rothmund (1868) syndrome and established the eponym "Werner's syndrome." In 1941 they reported the first post-mortem findings on such a case. In a comprehensive review of the condition Thannhauser (1945) emphasized that the skin changes were not true scleroderma. By 1953 Irwin and Ward listed 55 cases, and up to the time of writing the present article approximately 62 cases have been placed on record, with only one additional post-mortem description (Perloff and Phelps, 1958).

The manifestations of the fully developed syndrome may be summarized as follows: (1) Habitus: short stature, stocky trunk, and slender extremities. (2) Premature senility: appearance in the third or fourth decade of juvenile cataracts, grey hair, baldness, and arteriosclerosis. (3) Scleroderma-like changes: atrophy of skin and subcutaneous tissue, circumscribed hyperkeratosis, trophic ulcers about ankles and feet, and beaked nose. (4) Endocrine: tendency to diabetes mellitus, hypogonadism, thyroid-gland dysfunction, osteoporosis.

Only one manifestation may be prominent in the clinical picture, so that cases may be overlooked and regarded as juvenile cataracts, primary hypogonadism, scleroderma, or generalized arteriosclerosis. Our present case, the third with necropsy findings, is unusual as its presenting symptoms were uraemia and hypertension.

Case Report

A Persian Jew aged 39 was admitted to the Rambam Government Hospital on January 9, 1958, complaining of shortness of breath, persistent severe headaches, and frequent vomiting of five days' duration.

His past history revealed that as a child he was healthy. Between the ages of 18 and 19 he rapidly lost most of the hair on the top of his head without any apparent disease or illness. He had never married, as he was always poor and could not afford a wife, but he also admitted that he had never had a sexual urge or libido.

At the age of 30 his vision began to fail, gradually getting worse and worse until six years later he could only distinguish finger movements in front of his eyes. It was about this time, in December, 1954, that he was admitted to the eye department of the Rambam Government Hospital with bilateral posterior pole juvenile cataracts. After operation on the left eye his sight improved slightly, and on examination of the eyeground retinitis pigmentosa was

diagnosed. No disk changes were recorded on that examination or on others which followed. The blood-pressure fluctuated between 190 and 155 systolic and 120 and 100 diastolic. Blood urea was 20 mg./100 ml., and the urine was normal except for traces of albumin.

The family history revealed that his parents were first cousins. Two brothers died a few months after birth, of an unknown cause. His father died at the age of 73. His mother, two brothers, and two sisters were all alive and well. None was bald and none of them wore spectacles.

Examination showed him to be a small-statured, emaciated, bald, and bespectacled man, 160 cm. in height and weighing only 45 kg. He looked about 10 years older than his stated age, except for his body, which had a childish appearance with its relatively thin limbs and no hair on the chest, axillae, or pubis. His facial hair and moustache showed normal growth except for localized bald patches over the left cheek and upper lip.

FIG. 1.—Showing baldness of the head and outer halves of the eyebrows.

The top of his head was completely bald, and on the sides the hair was sparse and thin. There was baldness of the outer halves of the eyebrows, and the nose was beaked (Fig. 1). A number of teeth were missing; others were loose and about to fall. His voice was weak and hoarse.

He had a mature posterior cortical opacity of the right lens, obscuring detailed vision of the respective eyeground. The operated left eye revealed retinitis pigmentosa, but no other

vascular or disk changes. He was almost blind in his right eye, and the vision in the left eye was limited to 4/50.

The skin was waxy pale, atrophic, and dry. Over the bony prominences of the ankles and feet it appeared glossy and tight, and could not be moved freely. One got the impression of there not being enough subcutaneous tissue between the skin and bones. On the thighs, gluteal regions, and lower back were circumscribed areas of dry, scaly, hyperpigmented skin. Other areas looked ichthyotic. The finger-nails showed fine longitudinal striations.

The chest was well developed, showing a slight asymmetric prominence over the praecordium to the left of the sternum. The lungs were slightly hyperresonant on percussion, but the breath sounds were normal. The heart was normal in size, with the apex beat in the fifth intercostal space within the mid-clavicular line. There was a soft grade I apical systolic murmur. A2 was accentuated. The pulse was regular 80/min., and blood-pressure 160–170/80–90. The abdomen was soft, flabby, and slightly protruding. The liver and the spleen were not enlarged on palpation. The thyroid gland was not enlarged and no nodules could be felt in it. The testicles were small like those of a child of 12 years. The penis was normal in size and appearance. Examination of the central nervous system revealed no abnormality.

Clinical Course and Laboratory Data

During the first week the patient continued to vomit and was in a state of severe dehydration and metabolic acidosis. Blood urea was 203 mg./100 ml., potassium 7.8 mEq/l., sodium 140 mEq/l., chlorides 100 mEq/l., calcium 9.7 mg./100 ml., phosphorus 6.7 mg./100 ml. The urine contained

1% albumin but no pathological sediment. Specific gravity measurements showed an isosthenuria with a maximum of 1006.

He was put on intravenous infusions to combat acidosis, and in an effort to shift the high serum potassium he was given 10 units of insulin half an hour before the main meals. At 11.40 p.m. of the second day after commencement of insulin he was found in a deep coma, covered with cold sweat. After 10 ml. of 50% glucose intravenously he rapidly regained full consciousness.

About two weeks after admission his condition improved, he ceased vomiting, and his blood electrolytes were restored to normal. Blood urea fluctuated between 120 and 160 mg./100 ml., urea clearance was 7.2%, and blood proteins were 6.1 g./100 ml., with 3.8 g. albumin. Cholesterol in blood was 246 mg./100 ml. Haemoglobin was 4.7 g./100 ml. R.B.C., 2,600,000; W.B.C. 12,000 (normal differential count). The haematocrit was 23%, M.C.V. 88 cubic μ , M.C.H. 30 μ g., M.C.H.C. 27%; thrombocytes 130,000. The bone-marrow was normal. The Khan serological test for syphilis was negative.

Retrograde pyelography and presacral insufflation gave the radiological impression of a small left kidney. Methylene blue injected intravenously was not excreted from either kidney after 20 minutes. Kidney biopsy was unsuccessful on two occasions and further increased our suspicion that the kidneys were small and inaccessible.

The following endocrinological examinations were carried out: 17-ketosteroids were found to be 14.8 mg. per 24 hours. No eosinophils could be found in the peripheral blood on repeated absolute counts. The F.S.H. was 24 u./l. The B.M.R. was -12% and the P.B.I. 3 μ g./100 ml. The intravenous glucose-tolerance test showed a normal curve, but when performed by giving glucose orally a flat curve was obtained—namely, 95, 95, 108, 105, and 110 mg./100 ml. at half-hour intervals.

The electrocardiogram showed signs of strain on the left ventricle. An x-ray film of the skull revealed oxycephaly. X-ray films of the cervical spine showed no signs of osteoporosis. On fluoroscopy the left ventricle seemed slightly enlarged and the aorta wide for his age. No signs of arteriosclerosis were detected in the arteries of the legs.

The patient went slowly downhill. The blood urea remained high, reaching at times 220 mg./100 ml.; his blood-pressure gradually increased to 240/130; and finally he developed heart failure with pulmonary oedema. His vomiting returned and he lapsed into uraemic coma and died on March 12, 1958.

Post-mortem Findings

External examination accorded with the above clinical description.

Brain: Oedematous, with increase in amount of cerebrospinal fluid in the subarachnoid spaces. **Heart** (weight 370 g.): Both ventricles hypertrophic; aortic valves fenestrated, otherwise normal. Coronaries widely open. Approximately 100 ml. of clear fluid in pericardial sac. Severe fibrotic and atheromatous plaques in the aorta. Ostium of right renal artery occluded and does not permit entrance of probe (Fig. 2). **Respiratory system:** Trachea

FIG. 2.—Showing the small contracted kidneys and detail of right-renal artery obstruction.

and bronchi contain thick, purulent mucus; lungs emphysematous and oedematous. *Liver* (weight 1,500 g.): Dark brown in colour. Biliary system normal. Pancreas and gastro-intestinal tract—no abnormalities. *Kidneys*: Both very small (right 65 g., left 85 g.). Capsule strips easily. The external surface of left kidney is granular, of right fairly smooth. Small scattered cysts visible on external surface. On cut surface, parenchyma atrophied; no evident differentiation between cortex and medulla. *Bladder*: Mucous membrane inflamed. *Spleen* (weight 30 g.): Grossly normal. *Genital organs*: Prostate not enlarged; testicles very small (weight 5 g.). *Endocrine glands*: Hypophysis normal in shape and size. Thyroid smaller than normal; cherry-sized, white, hard nodule in left lobe; scattered white pea-sized nodules in right lobe. Adrenals of normal appearance. Parathyroids not enlarged.

Histological Examination

Nervous System.—No changes.

Respiratory System.—Small foci of bronchopneumonia.

Cardiovascular System.—Myocardium: few small perivascular cuffings by round cells. Aorta: intimal thickening and fibrosis. Right renal artery occluded by organized thrombus. In vessel wall, evidence of atheromatotic changes.

Digestive System.—Gastro-intestinal tract normal. Liver normal in structure; slight irregularity in shape and size of liver cells with many mitotic figures. Fine brownish pigment (lipofuscin) in several Kupffer cells. Pancreas: inspissated secretion in slightly dilated ductules.

Urinary System.—Glomeruli mostly obsolete and fibrotic. In remainder, slight thickening of capillary basement membrane, with fibrotic thickening of Bowman's capsule in some. Tubules generally atrophic, with areas of compensatory hypertrophy in patchy fashion. In atrophic tubules the basal membrane thickened and fibrotic. Several tubules showed cystic dilatation and contained hyaline casts and birefringent crystals (sodium urates; leucine?). Interstitial connective tissue increased and fibrotic. Diffuse round-cell infiltration, marked especially in the cortical zone and cortico-medullary junction. The interlobular and arcuate arteries revealed hypertrophy of the media and intima with splitting of the internal elastic membrane. The lumina narrowed. No manifest changes in the afferent arterioles. Bladder: haemorrhagic areas and acute inflammation of the mucous membrane.

Genital System.—Seminiferous tubules of various sizes, generally smaller than normal. Good spermatogenic activity in about two-thirds of tubules, but rather incomplete (no spermatozoa). The remaining tubules small and obliterated, partially or completely by loose connective and elastic tissue. The tubules widely separated by loose connective tissue. Groups of small Leydig cells visible in the vicinity of tubules. Prostate: Glandular lumina distended by large amyloid bodies. Several solid cords of transitional epithelium. Slight round-cell infiltration in stroma.

Endocrine Glands.—Hypophysis of normal size. Cell population normal. Pinhead-sized chromophobe adenoma in anterior lobe. Adrenals: small areas of nodular hyperplasia in fascicular zone; glomerular and reticular zones well preserved; scanty lipoids. Thyroid: irregularity in shape and size of vesicles; papillary adenocarcinoma in left lobe and small nodules of papillary adenocarcinoma in right lobe.

Spleen normal structure; small foci of haemopoiesis in sinusoids.

Skin from the extremities showed slight atrophy of the epidermis with moderate hyperkeratosis.

Discussion

The unusual appearance of the patient stimulated the search for a common cause of his cataracts, premature senility, and hypogonadism. Though hypertension and uraemia were not features of any of the reviewed cases

of Werner's syndrome, their known predilection to generalized arteriosclerosis induced us to consider the attractive possibility that the hypertension and uraemia might be secondary to arteriosclerotic changes in the renal vessels. On post-mortem examination bilateral vascular contracted kidneys were found in spite of the fact that only the right renal artery was occluded. This points to a slow occlusive process—as enough time must have elapsed for collateral compensatory circulation to develop.

The functional and anatomical study of the endocrine system in this case and in the two previously reported post-mortem cases (Oppenheimer and Kugel, 1941; Perloff and Phelps, 1958) shows that no fundamental or characteristic glandular deficiency exists in Werner's syndrome.

None of these cases showed any structural abnormality of the pituitary gland, and the F.S.H. in our case was normal. The pin-head sized chromophobe adenoma is a common finding in post-mortem examinations and no significance can be attached to its presence.

Histologically the thyroid parenchyma was normal, except for the small nodules of papillary adenocarcinoma in the left lobe and the papillary adenocarcinoma in the right lobe. The protein-bound iodine of 3 $\mu\text{g.}/100\text{ ml.}$ is in the low range of normal and may be indicative of a mild hypothyroidism. This impression is further increased by the flat oral glucose-tolerance test and by the hypoglycaemic episode, which cannot be attributed only to the small dose of insulin which was given several hours beforehand.

The two consistently recurring endocrine abnormalities in Werner's syndrome are diabetes and hypogonadism. Only the latter existed in our case, and was manifested clinically by small testicles, impotence, and lack of libido. The normal masculinization with damage of part of the seminiferous tubules, normal Leydig cells, incomplete spermatogenic activity, and normal F.S.H. speak for a selective tubular injury of testicular origin. Tubular degeneration may be seen in chronic renal insufficiency, but in our case the sexual disturbances appeared long before his kidneys showed signs of failure. The patient stated that at no time did he ever experience sexual urge, whereas at the age of 36, when in hospital for the first time, his blood urea was still only 20 mg./100 ml.

The thyroid adenocarcinoma found in our case deserves comment, as it strengthens the impression that there is a relative increase in the incidence of neoplasia in these cases. Our case added to six other malignancies in 63 cases of Werner's syndrome (Agatston and Gartner, 1939; Oppenheimer and Kugel, 1941; Schott and Dann, 1949; Müller and Andersson, 1953; Ellison and Pugh, 1955), brings the incidence of malignancy to 11.1%.

The perivascular cuffing by round cells in the myocardium, the inspissated secretions in the pancreatic ducts and the anaemia are manifestations of uraemia. The increase in mitotic figures in the liver may be a manifestation of old age, though the presence of lipofuscin pigment in the Kupffer cells points to a post-necrotic regenerative process.

The retinitis pigmentosa, which occurred also in the case reported by Kleeberg (1949), is interesting and

deserves special comment. This disease is a primary degeneration of the neuro-epithelium of the retina on a hereditary basis, the importance of blood relationship among parents for the manifestation of the disease having been established (Nettleship, 1907-8).

Cataracts often complicate retinitis pigmentosa and are always present in cases of Werner's syndrome. If we accept the view that retinitis pigmentosa belongs to a group of hereditary diseases which have this in common, that the cells and tissues affected become prematurely senile (Verhoeff, 1931), then retinitis pigmentosa and the cataracts, common to the two diseases, are further evidence that Werner's syndrome is a heredo-degenerative disease of unknown origin. (It will be noted that our patient's parents were first cousins.)

From the foregoing it would appear that premature senile changes, rather than endocrinopathies, offer the best explanation for the functional and structural changes described in Werner's syndrome.

Summary

The clinical and post-mortem findings in a case of Werner's syndrome with uraemia and hypertension are described.

The renal failure was found to be due to vascular contracted kidneys and arteriosclerotic occlusion of the right renal artery.

The presence of retinitis pigmentosa in Werner's syndrome is an interesting finding which, together with other evidence, points to a heredo-degenerative disease in widely distributed body cells and tissues, affected by inherent characteristics which result in their degeneration.

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"Unlike Russian doctors, who are merely members of a branch of the Medical Workers Trade Union, Chinese doctors still retain their association. But though its journals continue to print some work of an international standard—which the *Chinese Medical Journal* presents in excellent English—the incessant political exhortations of some of the association's officers force one to conclude that they see themselves as primarily the representatives of government, not of the doctors who may elect them."—From a lecture by Dr. T. F. Fox, editor of the *Lancet*, at the 87th Annual Meeting of the American Public Health Association (*Amer. J. publ. Hlth*, 1960, **50**, suppl., 28).

TREATMENT OF CHRONIC FURUNCULOSIS

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Recurrent furunculosis is often caused by reinfection with staphylococci from the patient's carrier sites. Hobbs *et al.* (1947), Valentine and Hall-Smith (1952), and Tulloch (1954) have shown that the causative staphylococci often come from the patient's own nose. Gould and Cruikshank (1957) and Copeman (1958) have had considerable success in preventing recurrences of furunculosis by the use of antiseptic nasal creams.

Staphylococci from sites other than the nose may also cause furunculosis. Superficial lesions of the skin, such as eczema, otitis externa, and blepharitis, are sometimes colonized by staphylococci and may be important sources of reinfection. Areas of normal skin also are sometimes colonized by staphylococci, especially the perineum (Hare and Ridley, 1958; Ridley, 1959). We observed cases of recurrent furunculosis which were caused by staphylococci from the perineum.

We report here the results of treating chronic furunculosis by disinfecting the patients' anterior nares and other carrier sites and by eradicating staphylococcal carriage from members of their families.

Methods

The patients investigated were 58 adults who came to the dermatological out-patient department between January, 1957, and June, 1959, with histories of recurrent furunculosis of at least six months' duration. Several had suffered from boils and styes for years. Alternate patients were selected for the control and the test groups. 15 patients defaulted. After spending six months as controls, 13 patients were transferred to the test group. There were altogether 33 test cases and 23 controls, most of whom were followed up for at least six months from the beginning of treatment. A few were observed for only four months. Freedom from furuncles during this period was regarded as a cure.

At the first attendance swabs were taken from a furuncle and from the anterior nares, and also from the ears and eyelids when indicated by the history or clinical findings. During the later part of the study perineal swabs were also taken. Further swabs were taken during and after treatment, usually at monthly intervals; and also from the relatives of some patients, as described below.

The bacteriological methods were described by Alder *et al.* (1955). Staphylococci were phage-typed by the method of Williams and Rippon (1952).

Treatment.—All the patients were instructed to swab the boil-bearing areas twice a day with a 1 in 3,000 aqueous solution of mercuric chloride. No other treatment was used for the control cases. The test cases were