are used we would suggest that greater emphasis should now be placed on El Tor vaccines than on those prepared with *V. cholerae* (Mukerjee, 1964).¹

Summary

Since 1962 classical cholera has been limited to India and Pakistan; but cholera El Tor, which began to spread in pandemic form after 1961, is involving increasingly large areas in the West Pacific region and South and South-East Asian countries. It is rapidly extending to areas in India and Pakistan, where classical cholera was already endemic, and in many of these areas it has progressively displaced cases due to classical cholera. Laboratory experiments to study the interaction of *V. cholerae* and *V. eltor* have shown that in mixed cultures *V. eltor* is capable of eliminating *V. cholerae* within a short time both *in vitro* and *in vivo*. These findings provide a possible explanation of the observed alteration in the pattern of cholera outbreaks in the Indo-Pakistan subcontinent. Because of the greater epidemic and endemic potentialities and speed of dissemination of cholera El Tor there is a likelihood that in the near future El Tor infections may spread further westward to the Middle East countries and from there to Southern Europe. Consequently it is suggested that containment measures, particularly the organization of mobile diagnostic and treatment services, should be undertaken in the threatened areas in anticipation of possible outbreaks. As *V. eltor* is now the causative organism of cholera in most areas, and since a better degree of protection is obtainable with vaccines made of El Tor vibrios, it is suggested that more emphasis should be placed on El Tor vaccine than on the classical cholera vaccine.

Most of the observations relating to spread of El Tor infection in India and other countries were made during the course of phage-typing of vibrio strains referred to our Centre from various laboratories. Our grateful thanks are due to the workers and chiefs

¹ It has recently been reported that in the Philippine field trials El Tor vaccine conferred comparatively longer protection against the disease than *V. cholerae* vaccine (Azurin, 1965).

of these laboratories for their valued co-operation. We are particularly thankful to the World Health Organization and the Health Directorate of the Government of India. Owing to their sustained help we have been able to follow up regularly the progress of cholera infection in different areas. We are indebted to Dr. K. Patricia Carpenter, Director, International Shigella Centre, London, for opportunities of testing the El Tor strain isolated in Bahrain and for providing the relevant information concerning the patient. The annual incidence of cholera cases in Calcutta was supplied by the Office of the Director of Health Services, New Delhi. Dr. A. Narayanaswami, a colleague in the Institute, deserves our gratitude for his helpful suggestions.

ADDENDUM.—Since the above paper was prepared cholera outbreaks have been reported from Afghanistan, Nepal, and Iran during June, July, and August this year. The causative vibrios from the first two countries were received for test in our laboratory and found to comprise both classical and El Tor types. Cholera outbreaks with a high fatality rate due to El Tor vibrios were also reported from a number of provinces in Iran in July and August this year (*Wkly. Epidem. Rec.*, 1965a). Bahrain was also declared a cholera-infected area on 12 August 1965, after another case of cholera had been notified on 11 August (*Wkly. Epidem. Rec.*, 1965b). On 21 August localized outbreaks of cholera due to imported cases were reported from Uzbekistan, in U.S.S.R. (*Wkly. Epidem. Rec.*, 1965c).

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Abnormalities of Development Associated with Hypothalamic Calcification after Tuberculous Meningitis

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Any bacterial meningitis, including tuberculous meningitis (TBM), may be associated with neurological complications, such as epilepsy, hemiplegia, paraplegia, optic atrophy and blindness, deafness, mental retardation, and hydrocephalus. Attention to these complications has recently been drawn by the *British Medical Journal* (1964).

Diabetes insipidus may also follow TBM (Acheson and Smith, 1964; Lorber, 1958a; Hay, 1960). Infrequently sequelae have included other endocrine disorders, such as the so-called "Fröhlich syndrome" (obesity, hypogonadism, retarded growth), sexual precocity, and simple obesity (Lincoln *et al.*, 1960; Wasz-Höckert and Donner, 1963). These endocrine manifestations have been recorded mainly in the Continental literature (Allimant and Peiffert, 1952; Peruzzi, 1958; Lorenz, 1959).

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Intracranial calcification, presumably as a result of mineral deposition in small tuberculomata, may also follow tuberculous meningoencephalitis, but the occurrence of endocrinal dysfunction in association with intracranial calcification is apparently uncommon.

In this paper we describe three cases of endocrinal syndromes that followed tuberculous meningitis, two with obesity and hypogonadism, and one with precocious sexual development. All three were associated with radiological calcification in the suprasellar region, confirming the probability that damage to the hypothalamus was the cause of the disorder in each case.

Methods

Urinary 17-hydroxycorticosteroids (17-OHS) were determined by the procedure of Appleby *et al.* (1955), and 17-oxosteroids (17-OS) as described by the Medical Research Council

(1951). Gas chromatography of urinary neutral steroids as trimethylsilyl ethers was carried out on a 12-foot (30-cm.) column, the phase being QF1, 1% on 120–140 mesh Gas Chrom P (Lewis and Stewart, 1962). Bone age was assessed by the standards of Greulich and Pyle (1959). Urinary gonadotrophins were assayed by the mouse-uterine-weight method (Dekanski, 1949).

Case 1. "Fröhlich's Syndrome"

The patient, a youth aged 17 (Fig. 1), had recovered from TBM at the age of 7 years, and had been attending the Endocrine Clinic of the Groote Schuur Hospital for three years before his admission. At his first attendance in 1960, when his height was 54 in. (137 cm.), it was noted that his penis and testes were very small and that he had intracranial calcification (Fig. 2). Bone age was 12 years. Between 1961 and 1963 he received 20 months' therapy with

FIG. 1.—Case 1. Patient aged 17. Note general immaturity.

thyroxine (0.1 mg. b.d.) and androgens. He grew $1\frac{3}{4}$ in. (4.5 cm.) in 10 months on thyroxine alone, then $2\frac{1}{2}$ in. (6.7 cm.) in 10 months on thyroxine and androgen combined. His gonads and penis enlarged, his voice deepened, and pubic hair appeared. An orgasm, with ejaculation, was first experienced at the age of 16; he never shaved. His scholastic standard was normal for his age; he was the shortest boy in his class.

He was admitted to the medical ward for investigation in 1963 after discontinuing all therapy for three weeks. He was an intelligent, cheerful boy of short stature, but obese. His height was $58\frac{1}{2}$ in. (148.5 cm.), weight 104

lb. (47.2 kg.), facial and axillary hair were absent, and pubic hair was sparse. Bone age was between 14 years 10 months and 16 years 4 months.

Examination of the cardiovascular, respiratory, gastro-intestinal, and central nervous systems did not reveal any abnormality. White-cell count and erythrocyte sedimentation rate were normal. Electrocardiogram was normal. Blood urea was 15 mg./100 ml., serum cholesterol varied from 293 mg./100 ml. when not taking thyroxine to 207 mg. while on thyroxine. The level of protein-bound iodine in plasma in 1961 was 4.75 μ g./100 ml. and in 1963 it was 4.5

FIG. 2.—Case 1. Calcification in sella turcica and suprasellar region.

μ g./100 ml. 131 I thyroidal uptakes were 18% at six hours and 39% at 24 hours. Urinary follicle-stimulating hormone (F.S.H.) excretion was less than 6 mouse uterine units. Urine osmolality (307 mOsm/l.) exceeded that of plasma (294 mOsm/l.) after 18 hours of fluid deprivation; this excluded diabetes insipidus. Water-diuresis tests were normal (97% of 750 ml. was excreted within four hours). The mean urinary excretion of 17-OHS was 13.3 mg./24 hours and of 17-OS 8.9 mg./24 hours, both within normal limits. Oral metyrapone (Metopirone), 750 mg. four-hourly for 24 hours, caused an insignificant increase in the urinary excretion of 17-OHS (from 16.0 to 19.6 mg./24 hours). Testicular biopsy showed failure of maturation of the cells with absence of spermatogenesis. After the necessary investigations had been completed the patient was discharged on injections of a long-acting androgen preparation (Sustanon) every three weeks and L-thyroxine 0.3 mg./day.

Case 2. "Fröhlich's Syndrome"

The patient was a youth aged 19 (Fig. 3). At the age of 10 he suffered from TBM, which was treated with P.A.S., isoniazid, and streptomycin. Six months after his admission, and while still in hospital, it was noted that he was becoming very obese and that his appetite was voracious. Since then the obesity increased, and he was eventually admitted to the Groote Schuur Hospital for investigation for failure of sexual development.

There was a complete absence of subjective sexual feelings; he had erections but no ejaculation. There was no polyuria, nor did he feel the cold excessively.

On examination the patient was obese, the obesity being confined to the trunk, hips, and face. His hands and feet were small and slender. There was scanty pubic hair, but the face, chest, and axillae were hairless. There was no gynaecomastia. The scrotal skin was thin and poorly pigmented, and the penis pre-pubertal in size. Both testes were present, but measured only 0.5 by 0.5 cm. in diameter.

The patient's height was 65 in. (165 cm.), span $65\frac{1}{2}$ in. (166 cm.), head-to-pubis measurement $33\frac{1}{2}$ in. (85 cm.), and foot-to-pubis measurement $31\frac{1}{2}$ in. (80 cm.). His weight on admission was

FIG. 3.—Case 2. Patient aged 19. Obesity and lack of sexual development.

FIG. 4.—Case 2. Calcification in sella turcica and suprasellar region.

178 lb. (80.7 kg.). The rest of the clinical examination was not contributory.

Radiological investigations revealed suprasellar calcification (Fig. 4), and the patient's bone age lay between 13 and 14 years. Plasma protein-bound iodine level was 6.0 $\mu\text{g.}/100\text{ ml.}$ The ^{131}I thyroidal uptake at six hours was 34% and at 18 hours 51%. In addition the red-blood-cell triiodothyronine uptake was also normal (19.5%). The mean 24-hour urinary 17-OHS and 17-OS excretions were 19.9 and 12.3 mg. respectively. Diuresis following a water-load was normal. Glucose-tolerance test was within normal limits. Twenty-four-hour urinary F.S.H. excretion was between 3 and 6 mouse uterine units.

The urinary 17-OS excretions were fractionated, and the gas chromatogram revealed the chief urinary neutral steroid to be dehydroepiandrosterone, the proportions of androsterone and etiocholanolone being lower than normal for the patient's age (Johnsen, 1956a).

Metrapone tests confirmed normal pituitary function with respect to A.C.T.H. production, the 17-OHS excretion reaching a level of 28.9 mg./24 hours after metrapone stimulation. Cells obtained from buccal smear were chromatin-negative. Testicular biopsy revealed no spermatogenesis. The tubules were lined by a single layer of undifferentiated cells and resembled infantile testes, the interstitial cells being spindle-shaped and inactive.

The patient was treated with Sustanon every three weeks, and showed good response.

Case 3. Sexual Precocity

The patient, a boy aged 9, developed miliary tuberculosis and TBM at the age of 8 months and was treated in hospital for a period of 18 months. At the age of 8 years he developed generalized organ tuberculosis with hepatosplenomegaly and adenopathy, and was once again admitted to hospital for treatment. By the time he was 9 years old a marked increase in size of his testes and penis had occurred (Fig. 5). There was no axillary or facial hair, although pubic hair was well grown.

FIG. 5.—Case 3. Patient aged 9. Well-developed genitalia and developing secondary sex characters.

He was grossly retarded mentally and of normal stature (height 43 in.; 109 cm.), with a well-developed musculo-skeletal system. The penis was 6 in. (15 cm.) long and testes were of adult size. No other abnormalities were found on examination. Bone age was that of 11 years, and

x-ray examination of the skull revealed a considerable amount of calcification in the suprasellar region and overlapping the sphenoid ridge on the right side (Fig. 6). Urinary 17-OS estimations were 5.9 and 5.1 mg./24 hours, and the urinary 17-OHS 5.7 and 7.8 mg./24 hours. On gas chromatography there was a prominent dehydroepiandrosterone peak, followed by one corresponding to epiandrosterone; the androsterone and etiocholanolone peaks were small. There was an excellent response to oral metrapone, the basal 17-OHS urinary excretion of 7.8 mg./24 hours rising to 20.6 mg./24 hours.

Radiiodine uptakes (31% at 6 hours and 33% at 24 hours) were normal, as was the level of protein-bound iodine (3.0 $\mu\text{g.}/100\text{ ml.}$). Urinary F.S.H. was 12 mouse units in 24 hours. Urine osmolarity was within the normal range. A testicular biopsy showed evidence of spermatogenesis. The tubules were lined predominantly by Sertoli cells. Germinal cells were present, but in reduced numbers. These showed maturation to spermatid level. Clumps of mature Leydig cells were present in the interstitial tissues.

Discussion

Hypothalamic Disease

The location of the intracranial calcification taken in conjunction with the clinical pictures incriminates the hypothalamus as the specific area involved in our cases.

There is no doubt that hypothalamic disease *per se* may be associated with abnormalities of sexual development, taking the form either of precocious puberty or of hypogonadism. This has been experimentally shown in animals. Basal hypothalamic lesions situated behind the optic chiasma advance the onset of puberty in young female rats (Donovan and van der Werff ten Bosch, 1959; Horowitz and van der Werff ten Bosch, 1962). Lesions of the arcuate nucleus and of the amygdaloid nucleus may also accelerate sexual development (Elwers and Critchlow, 1960), while the fact that electric stimulation of the amygdala delays puberty complements this finding (Bar-Sela and Critchlow, 1962). In a recent review Reichlin (1963) stated that these results suggested that the anterior hypothalamus and its interconnexions exert a tonic inhibitory control over gonadotrophin secretion in the prepubertal animal and that hypothalamic lesions, by reducing the size of the area from which pituitary-inhibiting stimuli arise, may initiate precocious puberty.

Sixty cases with various lesions in the hypothalamus found at necropsy were collected from the literature by Bauer (1954). Precocious puberty had occurred in 24. Among these 24 cases, 17 showed a localized lesion, 14 of which were in the posterior hypothalamus, with nine affecting the mamillary bodies. How-

FIG. 6.—Case 3. Calcification in sella turcica and suprasellar region.

ever, in nine other cases diffuse inflammatory periventricular and encephalitic lesions were found. Neoplasm affecting the hypothalamus was the most frequent lesion associated with precocious puberty. One case of tuberculous meningo-encephalitis was described. There were also 19 cases with hypogonadism, craniopharyngioma being the commonest associated condition. The predominant location of the lesions in cases of gonadal depression was the inferior (tubero-infundibular) and the more anterior region of the hypothalamus. Of the 19 hypogonadal cases 16 had lesions in the floor of the third ventricle. Kahana *et al.* (1962) also stress the importance of central hypothalamic mechanisms in the regulation of gonadotrophin, thyrotrophin, and adrenocorticotrophin secretion by the anterior pituitary. Their impressive series of cases show beyond any doubt the profound influence of third-ventricle tumours and internal hydrocephalus on sexual maturation.

Fröhlich's Syndrome

The name of Fröhlich's syndrome, characterized by obesity, gonadal underdevelopment, a female habitus (in males), and associated sometimes with delayed skeletal growth and diabetes insipidus, has become linked with lesions involving the hypothalamic area. (The eponym should *not* be used for children who are simply fat and slow in developing.)

The first report appears to have been by Babinski (1900), who described the case of a girl of 17 with obesity and retarded sexual development resulting from a craniopharyngioma; and in 1901 Fröhlich, in Vienna, collected records of similar cases and described that of a boy of 14 years who had an extensive pituitary tumour with resulting hypogonadism, obesity, and involvement of the optic nerves leading to almost total blindness.

Although craniopharyngiomas, because of their position in relation to the hypothalamus, have been most frequently reported as causing the Fröhlich syndrome, the identical clinical picture has been seen in other conditions—for example, following encephalitis (Eaves and Croll, 1930) and in pinealoma (Cleghorn *et al.*, 1938).

It is likely that the retarded skeletal growth seen in this syndrome is a result of decreased growth-hormone production by the anterior pituitary gland, which itself may be under the influence of a primary hypothalamic centre.

Sexual Precocity

Sexual precocity, as in Case 3, associated with intracranial lesions is more common in boys than in girls. Seckel (1946) and Seckel *et al.* (1949) stressed that such precocious sexual development is always isosexual. The gonads are usually well developed, with spermatogenesis in males and hyperplasia of the Graafian follicles and consequent menstruation and ovulation in females. Precocious puberty has been described in association with a number of diverse conditions affecting the central nervous system, but it is apparent that, possibly excepting localized tumours of the pineal glands, which constitute a rare cause of this syndrome, most of the lesions described have involved the hypothalamus either directly or indirectly by pressure effects in conjunction with an occluded ventricular system. Thus hamartoma of the hypothalamus (Richter, 1951), tumours (Weinberger and Grant, 1941), lesions of the floor of the third ventricle (Nelson, 1959), encephalitis (Ford and Guild, 1937), and TBM itself have all been implicated (Lorber, 1951, 1952; Allimant, and Peiffert, 1952; Bauer, 1954; Lorenz, 1959; Wasz-Höckert and Donner, 1963).

Calcification

Calcified intracranial tuberculomas were rare before the introduction of effective antituberculous drugs. Lorber (1952) reviewed the literature over the past 100 years and was able to find only 49 proved or suspected cases of intracranial calcification in cerebral tuberculomas. Later he found pathological intracranial calcification during life on x-ray examination of the skulls of 63 children who had recovered from TBM (Lorber, 1958b). Serial x-ray films revealed the gradual development of calcification within three years after the onset of the tuberculous meningitis in 49 children (more than four-fifths of the total) in his series. The calcification did not disappear in any of the cases. The commonest site of the calcification was the basal meninges, less often intracerebral.

Lorber also found that the incidence of calcification was a little less in patients who were treated with isoniazid and streptomycin than in those with streptomycin alone or with streptomycin plus P.A.S., but this was not verified by others (Todd and Neville, 1964). The use of adjuvants—for example, streptokinase

—also seemed to reduce the incidence of meningeal calcification in selected groups. Lorber (1952) made the observation that it was likely that tuberculous meningitis was becoming the commonest cause of intracranial calcification in children. Todd and Neville (1964) stress that in many cases the development of calcification is an indication of the severity of the original illness. Heikel and Wasz-Höckert (1963) found intracranial calcification in 26% of 103 patients who were examined 6 to 12 years after the onset of the disease, and other authors reported similar findings (Lincoln *et al.*, 1960; Todd and Neville, 1964).

Among all the cases of post-TBM calcification reviewed by Lorber (1952) were three with sexual precocity but none with hypogonadism and dwarfism or Fröhlich's syndrome. Todd and Neville (1964) mention two with "delayed puberty." It seems likely to us that such sequelae of TBM are not rare, but may not always be recognized. In our first patient (Case 1) we initially failed to recognize the connexion between the backward development and the intracranial calcification.

Urinary Steroid Excretion

17-OS excretion was within the normal range in both cases of Fröhlich's syndrome, but the gas-chromatographic fractionation in Case 2 showed that the chief component of urinary neutral steroid glucuronosides was dehydroepiandrosterone with only small androsterone and etiocholanolone peaks. This corresponds to the pattern shown in male patients with hypogonadism by Johnsen (1956b), using column chromatography—namely, a selective reduction particularly in androsterone (a testicular product), with a relative increase in dehydroepiandrosterone (an adrenal product).

The patient with sexual precocity (Case 3), who was 9 years of age, had evidence not only of virilization but also of Leydig-cell development. Normally at this age androgen secretion has begun to rise (Hamburger, 1948), but the mean urinary 17-OS output of 5.5 mg./24 hours is above the physiological range (Hamburger, 1948). Dehydroepiandrosterone was excreted in greater quantity than androsterone or etiocholanolone, and the chromatogram also showed a peak with the retention time of epiandrosterone.

The androgenicity of the various 17-OS fractions varies widely (Dorfman and Shipley, 1956); it is therefore possible that a relatively small increase or decrease in production of a potent androgen such as testosterone could lead to virilization or hypogonadism without striking quantitative or qualitative changes in urinary 17-oxosteroids (Van de Wiele and Lieberman, 1960; Dorfman *et al.*, 1963). The normal total 17-OS output in our cases of Fröhlich's syndrome, and the absence of gross changes in the steroid excretion in the case of sexual precocity (which contrasts with far higher excretion levels in virilizing adrenal hyperplasia), may be related to differences in biological activity of adrenal and testicular androgens.

Summary

We record three cases of endocrine disturbance following tuberculous meningitis, associated with intracranial calcification in the suprasellar region. Two patients showed hypogonadism, with absent puberty, delayed bone-maturation, and obesity from hyperphagia. In one of these linear growth was defective and there was evidence of partial hypopituitarism. The other was of good stature and showed no features of hypopituitarism except for the hypogonadism. The third patient was severely retarded mentally and underwent early sexual development, having matured by the age of 9.

In discussion we consider the relation of the hypothalamus to sexual development, the condition known as "Fröhlich's syndrome," and the occurrence of intracranial calcification following tuberculous meningitis.

Gas-chromatographic studies of the urinary androgenic steroids were performed and their significance has been considered.

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Nutritional Studies on the Entrants to an Old People's Home, with Particular Reference to Folic-acid Deficiency

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Since the introduction of reliable techniques for the detection of deficiency of folic acid there has been a gradual recognition that certain patients develop nutritional deficiency of this substance, with resultant megaloblastic anaemia. Most observers had previously felt that folic-acid deficiency was not common in well-nourished communities such as ours, and that it was confined to patients who could not absorb folic acid, who showed increased metabolic demands for folic acid, or who were taking drugs which interfered with its action. Nutritional deficiency causing a megaloblastic anaemia has been recognized in this country in middle-aged women (Gough *et al.*, 1963) and in other patients (Forshaw *et al.*, 1964). It seemed reasonable to suppose that the elderly might be particularly prone to develop nutritional deficiency of this substance, because of diminished financial resources, reduced mobility interfering with shopping, and apathy over food consequent upon old age and loneliness. It was therefore decided to survey a group of elderly subjects entering an old people's home which was run by the Welfare Committee of Bristol Corporation. The survey was

conducted during 1962-3, when 51 patients were seen. These were compared with a similar group of aged control subjects who were without apparent evidence of underlying disease. These patients were in the National Health practice of one of us (J. L. P.), and all volunteered for the study. The practice in question contains a fairly high percentage of retired elderly middle-class patients.

Patients Studied

Fifty-one consecutive patients were seen on arrival at the municipal home. Their ages ranged from 59 to 95, and 45 were 70 years and over. There were 17 men and 34 women. Two patients over 70 years old were uncertain of their exact age. A full clinical examination of the patients was performed, including a rectal examination. The weight was recorded and portable chest radiographs were also taken. An inquiry into each patient's financial, social, and nutritional background was made. If clinical and radiological examination showed no evidence of organic disease likely to cause folic-acid deficiency, the following tests were performed.

1. After 15 g. of oral L-histidine the urine was examined for formiminoglutamic acid (Figlu), using electrophoresis on cellulose acetate (Kohn *et al.*, 1961). Excretion of Figlu was estimated by

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