FOUR CASES OF DIABETES INSIPIDUS AND PULMONARY DISEASE

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The syndrome of diabetes insipidus may arise from many different lesions of the hypothalamo-hypophyseal mechanism. Destruction of the posterior lobe of the pituitary gland, the hypothalamo-hypophyseal tract, or the supra-optic nuclei bilaterally will produce the symptoms of polyuria and polydipsia, provided the anterior lobe of the pituitary gland remains functionally intact. It is a rare affection. In the majority of cases the pathological cause of the diabetes insipidus can be deduced during life, but there remains a small group of cases in which this is not possible.

This communication is concerned with the association of diabetes insipidus with diffuse pulmonary disease in four patients. The first patient was undoubtedly suffering from sarcoidosis in that he fell ill with fever, facial palsy, and uveoparotitis (Heerfordt), recovered, and later developed pulmonary disease and diabetes insipidus. The latter necessitated treatment with pitressin for 18 months. The second and third patients suffered from permanent diabetes insipidus and chronic pulmonary "fibrosis" of obscure origin. The third patient showed progressive intellectual deterioration and his electroencephalogram was abnormal. In the fourth patient diagnosis is not yet established, but sarcoidosis cannot be excluded.

SARCOIDOSIS

Case I.—A man aged 35 years, an accountant, in August, 1946, when 31 years of age, developed an acute left facial palsy of peripheral type. It was at first considered that he was suffering from acute poliomyelitis, as his daughter had been taken ill with this disease three weeks earlier. However, no further paralysis developed and within two days there was painful bilateral swelling of the parotid and submaxillary glands. He ran a low fever for seven to 10 days and three weeks after the onset of his illness developed bilateral acute iridocyclitis. Thereafter he made good progress except for one further episode of iridocyclitis.

During 1947 his general condition improved, but there was probably one mild recurrence of unilateral iridocyclitis. Early in 1948 he consulted his doctor because of shortness of breath, and was found to have bilateral enlargement of the hilar lymph nodes. He was investigated at a nursing-home, but no further abnormalities were disclosed. He had no cough, and the little sputum obtained was negative for tubercle bacilli, even after culture and guinea-pig inoculation. The E.S.R. was 9 mm. in one hour.

In July, 1948, he came under my observation. He described how he had recently been troubled with increasing thirst and polyuria. At first the polyuria was nocturnal and he would rise from his bed to urinate three or four times every night. This symptom was soon followed by excessive thirst. Investigation in hospital showed that he was suffering from true diabetes insipidus. Under controlled observation he voided seven to 15 pints (4 to 8.5 litres) of urine daily and drank roughly equal amounts. The specific gravity of the urine was usually in the neighbourhood of 1005. He was pale, but not significantly anaemic (R.B.C. 4,275,000 per c.mm.). On routine examination of the nervous system there was no abnormality. Power, tone, reflexes, and sensation were normal. The cerebrospinal fluid was normal. He was noted to be noticeably short of breath, and the fingers were not clubbed. There was no enlargement of the lymph nodes and the spleen could not be felt. The E.S.R. was 12 mm. in one hour. A radiograph of the skull was normal, but one of the chest revealed diffuse, coarse fibrosis of both lungs with slight enlargement of the hilar lymph nodes (Fig. 1). Radiographs of the hands and feet were normal.

In July, 1948, he was first given an injection (1 ml.) of pitressin tannate in oil. It had an immediate and pronounced effect and for nearly 48 hours he was relieved of his intolerable thirst. Subsequent observation confirmed the diagnosis of diabetes insipidus and he developed no further symptoms. He left hospital shortly afterwards and for the next three months was content and happy when he was receiving 1 ml. of pitressin tannate in oil every other day. Repeated examination and radiographs of the limbs disclosed...
no further abnormalities and his general condition improved.

He was last seen in October, 1949, when his general condition had considerably improved and there had been further lessening of his thirst and polyuria.

In this case there was no previous history of pulmonary disease and the radiological discovery of enlargement of the hilar shadows was unexpected. Clinical examination of the chest at that time revealed no abnormality despite his complaint of shortness of breath. The latter is unusual in pulmonary sarcoidosis at that stage of the disease. Six months later there was little hilar node enlargement, but the lung markings were considerably accentuated and there was coarse mottling. There was never any evidence of tuberculosis, the sedimentation rate remained normal, and the Mantoux reaction negative to 1 in 200 O.T. At that time, 23 months after the original illness, he developed polyuria and polydipsia. He was a neurotic character and the possibility that his thirst was hysterical was entertained. Nevertheless, he did not merely excrete the excess of the water which he drank, and the first injection of pitressin gave dramatic relief for nearly 48 hours.

Kourilsky (1950) has questioned the view, long held by clinicians, that in diabetes insipidus thirst is a consequence of the dehydration resulting from polyuria. Careful clinical investigations suggest that there may be considerable dissociation between polydipsia and polyuria. In Kourilsky’s cases the polydipsia fell into four groups: (1) pure polydipsia of hypothalamic origin; (2) polydipsia resulting from partial destruction of the posterior lobe of the pituitary gland, when pitressin has a more or less definite action, and despite restriction of water intake there is no relative decrease in polyuria; (3) polydipsia of pituitary origin remaining when the polyuria has stopped. Kourilsky points out that such cases were at first considered as psychogenic, but their organic nature he believes established. The persistence of thirst depended on the existence of conditioned reflexes. (4) Pure polydipsias which were completely uninfluenced by treatment with posterior pituitary extracts. In two cases examined at necropsy, of pulmonary tuberculosis and arteriosclerotic cerebral softening respectively, the supra-optic hypothalamic tract was normal. Kourilsky believes that because of the associated organic disorders it is a mistake to call these cases “psychogenic polydipsias.” In my patient no effect followed the injection of normal saline.

Diabetes Insipidus in Sarcoidosis.—Case 1 is a typical example of that variety of sarcoidosis commonly known as uveoparatosis or Heerfordt’s syndrome. In his original paper entitled “Febris Uveo-parotidea Subchronica” Heerfordt (1909) published an account of three cases, the last of which, a man of 25 years, developed polydipsia and polyuria (diuresis 5,000 ml. daily) with multiple cranial nerve palsies a month after the onset of parotitis.

At least 18 well-established instances of diabetes insipidus developing in patients with sarcoidosis have been reported (Table I). In a report on 300 cases of sarcoidosis Ricker and Clark (1949) made no mention of polydipsia and polyuria. Twenty-two cases came to necropsy and the pituitary was involved in one. Two patients died of Addison’s disease. There are many further reports in which dryness of the mouth and thirst with or without frequent micturition are mentioned (Brewerton, 1910; Guillaum, 1922; Jackson, 1925; Parker, 1926; Soutter, 1929; Merrill and Oaks, 1931; Palmer, 1940). In cases without polyuria, of course, dryness of the mouth and excessive thirst are most likely to result from the bilateral involvement of the parotid and submaxillary glands.
**TABLE I**

**DIABETES INSIPIDUS IN SARCOIDOSIS**

<table>
<thead>
<tr>
<th>No.</th>
<th>Author</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Skin</th>
<th>Bones</th>
<th>Lungs</th>
<th>Lymph Nodes</th>
<th>Parotid Glands</th>
<th>Eyes</th>
<th>C.N.S.</th>
<th>Hypothalamo-hypophyseal Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cameron and Dawson (1942)</td>
<td>F</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>Fibrosis</td>
<td>Multiple nodes spleen***</td>
<td>—</td>
<td>Bilateral iritis (recurrent)</td>
<td>0</td>
<td>Thirst. Polyuria (112 oz. daily)</td>
</tr>
<tr>
<td>2</td>
<td>Elshout (1942)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diabetes insipidus</td>
</tr>
<tr>
<td>3</td>
<td>Flandin and others (1936)</td>
<td>M</td>
<td>56</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Diabetes insipidus 2 years. Intake and output 15 litres daily. Controlled by pitressin</td>
</tr>
<tr>
<td>4</td>
<td>Folger (1936)</td>
<td>F</td>
<td>34</td>
<td>Red papules</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Enlargement of left</td>
<td>Iridocyclitis</td>
<td>L. arm weak. L. face numb. L. facial palsy</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Franceschetti and de Morsier (1941)</td>
<td>M</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>Hilar lesions Fibrosis</td>
<td>0</td>
<td>Bilateral enlargement</td>
<td>Iridocyclitis</td>
<td>0</td>
<td>Diabetes insipidus. Adiposogenital dystrophy. Hyper-somnia</td>
</tr>
<tr>
<td>7</td>
<td>Giesing (1916)</td>
<td>M</td>
<td>21</td>
<td>0</td>
<td>0</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Bilateral enlargement</td>
<td>Iridocyclitis</td>
<td>L. facial and recurrent laryngeal palsies</td>
</tr>
<tr>
<td>8</td>
<td>Harrell (1940)</td>
<td>M</td>
<td>26</td>
<td>Nodular lesions</td>
<td>Swollen finger joints Radiographs normal</td>
<td>Hilar involvement miliary changes</td>
<td>Generalized involvement</td>
<td>Bilateral enlargement</td>
<td>0</td>
<td>L. 6th nerve palsy. Headaches</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>Heerfordt (1909)</td>
<td>M</td>
<td>25</td>
<td>0</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Bilateral enlargement</td>
<td>Iridocyclitis</td>
<td>Multiple cranial nerve palsies</td>
</tr>
</tbody>
</table>
### TABLE I (continued)

<table>
<thead>
<tr>
<th>No.</th>
<th>Author</th>
<th>Sex</th>
<th>Age (yrs.)</th>
<th>Skin</th>
<th>Bones</th>
<th>Lungs</th>
<th>Lymph Nodes</th>
<th>Parotid Glands</th>
<th>Eyes</th>
<th>C.N.S.</th>
<th>Hypothalamo-hypophyseal Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Jersild (1939)</td>
<td>M</td>
<td>15</td>
<td>Multiple lesions</td>
<td>0</td>
<td>Hilar enlargement. Military</td>
<td>Generalized</td>
<td>Bilateral enlargement</td>
<td>Iridocyclitis</td>
<td>0</td>
<td>Diabetes insipidus</td>
</tr>
<tr>
<td>11</td>
<td>Kuhlefelt (1917)</td>
<td>F</td>
<td>31</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Constant diuresis</td>
</tr>
<tr>
<td>12</td>
<td>Lemming (1940)</td>
<td>F</td>
<td>32</td>
<td>&quot;Erythema nodosum&quot;</td>
<td>0</td>
<td>Hilar enlargement. Military</td>
<td>Cervical</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Constant polyuria (average 3 litres daily)</td>
</tr>
<tr>
<td>13</td>
<td>Lesné and others (1935)</td>
<td>M</td>
<td>10</td>
<td>Lupus pernio</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Obesity and diabetes insipidus. Intake 3.5 litres daily. Output 3-4 litres daily. Controlled by pitressin</td>
</tr>
<tr>
<td>15</td>
<td>Longcope (1941)</td>
<td></td>
<td></td>
<td>No details published</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diabetes insipidus. Necropsy confirmation</td>
</tr>
<tr>
<td>16</td>
<td>Schüpbach (1936)</td>
<td>M</td>
<td>35</td>
<td>0</td>
<td>0</td>
<td>Hilar lesions</td>
<td>—</td>
<td>Bilateral enlargement</td>
<td>Iridocyclitis</td>
<td>Facial palsy</td>
<td>Diabetes insipidus. Polyuria (6 litres daily)</td>
</tr>
<tr>
<td>18</td>
<td>Tillgren (1935)</td>
<td>M</td>
<td>47</td>
<td>Lupus pernio</td>
<td>—</td>
<td>Hilar changes and &quot;reticulation&quot;</td>
<td>Cervical</td>
<td>0</td>
<td>0</td>
<td></td>
<td>Necropsy, sarcooid infiltration of post-pituitary</td>
</tr>
</tbody>
</table>

--- = not recorded. 0 = normal.
The many ways in which the nervous system can be affected in sarcoidosis have been examined by Colover (1948). He reviewed 115 cases from the literature and reported three further examples. The structures most likely to be affected are the optic nerves and retinal nerves, the facial, glossopharyngeal, and vagus nerves, the pituitary gland, and the peripheral nerves. Meningoencephalitis and meningomyelitis occur in subacute and chronic forms and the brain and spinal cord may be infiltrated by sarcoid tissue or be affected by tumour-like masses in the dura mater. Hydrocephalus and adhesive arachnoiditis have been observed at operation. The cerebrospinal fluid may react by a pleocytosis and an increase in protein content.

In 12 of the 18 reported cases of sarcoidosis causing diabetes insipidus (Table I) the primary manifestation took the form of uveoparotid fever. In four cases (Nos. 3, 12, 13, and 18) there was no such syndrome and the sarcoid lesions involved, apart from the pituitary mechanism, only the skin, bones, and lungs. In Case 13 (Lesné, Launay, and Sée, 1935) lesions were present in the skin and phalanges; there was doubtful pulmonary involvement. In Case 18 (Tillgren, 1935) there was hilar node enlargement and pulmonary "reticulation" as well as characteristic lesions in the skin and phalanges. Case 3 (Flandin, Parat, and Paumeau-Delille, 1936) showed only characteristic cutaneous manifestations for two years before the appearance of polyuria. In Case 12 (Lemming, 1940) there was a history of erythema nodosum and cervical adenopathy in addition to pulmonary changes.

In these published cases, then, there were no examples of an association of pulmonary and pituitary disease only.

**Other Hypothalamo-hypophyseal Syndromes in Sarcoidosis.—**Reported cases of other hypothalamo-hypophyseal syndromes in sarcoidosis are summarized in Table II.

In at least six recorded cases of sarcoidosis of the nervous system hypersomnia or lethargy was a feature (Colover, 1948). The distinction from ependymitis lethargica in such cases is difficult (Waldenström, 1937). Haas and Joseph (1908) reported iridocyclitis and parotitis in a boy showing infantilism; the patient described by Rogers and Bodman (1926) developed narcolepsy; Parker's case (1926) was observed to have loss of the pupillary accommodation reflex; Doub and Menagh (1929) described the case of a man aged 30 years who showed the characteristic cutaneous lesions of sarcoidosis, with swelling of the fingers and typical radiological lesions in the metacarpals and phalanges, and developed a Frohlich's syndrome with impotence, decreased sugar tolerance, and impaired mentality. In Toulant and Morard's case (1936) Heerfordt's syndrome was associated with retarded growth and infantile genitalia. Kraus (1942) described the case of a woman aged 41 years with polyuria, amenorrhoea, hypothyroidism, and genital dystrophy in whom at necropsy there was sarcoid infiltration of the infundibular area of the hypothalamus and the pituitary stalk and gland. Glass and Davis's (1944) patient was a man aged 54 years who became progressively ill with weakness, anaemia, and failing vision. He became eunuchoid in appearance, with testicular atrophy. There was acute infiltration of the hilar zone of the right lung and later of both lung fields. The course of the illness was febrile and progressive. There was almost complete absence of steroid hormones in the urine, and radiological examination of the skull showed early intrasellar calcification. At necropsy the lungs and pituitary gland were seen to be invaded by a granulomatous process that was considered to

### Table II

**Other Hypothalamo-hypophyseal Syndromes in Sarcoidosis**

<table>
<thead>
<tr>
<th>No.</th>
<th>Author</th>
<th>Sex</th>
<th>Age (yrs.)</th>
<th>Manifestations of Sarcoidosis</th>
<th>Hypothalamo-hypophyseal Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toulant and Morand (1936)</td>
<td>M</td>
<td>17</td>
<td>Heerfordt's syndrome</td>
<td>Infantilism. Dysgenitalia</td>
</tr>
<tr>
<td>2</td>
<td>Rogers and Bodman (1926)</td>
<td>F</td>
<td>61</td>
<td>Heerfordt's syndrome. Polyneuritis</td>
<td>Narcolepsy</td>
</tr>
<tr>
<td>3</td>
<td>Haas and Joseph (1908)</td>
<td>M</td>
<td>15</td>
<td>Uveoparotitis</td>
<td>Infantiilsm</td>
</tr>
<tr>
<td>5</td>
<td>Doub and Menagh (1929)</td>
<td>M</td>
<td>30</td>
<td>Skin lesion. Digits swollen. Cystic lesions</td>
<td>Frohlich's syndrome. Reduced sugar tolerance</td>
</tr>
<tr>
<td>7</td>
<td>Glass and Davis (1944)</td>
<td>M</td>
<td>54</td>
<td>Pulmonary</td>
<td>Eunuchism. Atrophic testes. Absence of urinary steroid hormones</td>
</tr>
</tbody>
</table>
be of sarcoidal or tuberculous character. Curtis, Taylor, and Grekin (1947) reported the case of a man aged 25 years, with pulmonary and cutaneous sarcoidal lesions, who became acutely ill with headache, fever, facial palsy, papilloedema, aphasia, and stupor. He survived, but there was permanent mental change. Sarcoidal infiltration of the pituitary gland, its stalk, and the adjacent hypothalamic tissue has been observed at necropsy by Reis and Rothfield (1931), by Schaumann (1941), by Longcope (1941), by Kraus (1942), and by Glass and Davis (1944).

**Sarcoidosis and Tuberculosis**

Case 2.—In 1942 a man, then aged 28 years and serving in the R.A.F., reported sick with headaches. The details of this stage of his illness are not available, but it was discovered that his blood Wassermann reaction was positive. The C.S.F. was normal and its Wassermann reaction was negative. There was no history of acquired syphilis and two brothers also proved to have positive Wassermann reactions. For several years he received routine courses of antisyphilitic treatment and his headaches rapidly subsided. He left the R.A.F. in 1946 in category A1 after 10 years’ service. About one year later he tried to re-enlist, but he was rejected because a routine radiological examination disclosed “pulmonary fibrosis.” The sputum was negative, the Mantoux reaction was negative to 1 in 100 O.T., and the E.S.R. was 20 mm. in one hour.

Soon afterwards he first became aware of shortness of breath on exertion. He had no cough, there was no haemoptysis, but occasionally he had sharp stabbing pains in the right side of the chest. He remained in much the same condition until early in 1947, when he began to be troubled with excessive thirst and the passing of large amounts of urine. He lost about 28 lb. (13 kg.) in weight in a year, and before receiving pitressin injections he passed large quantities of pale urine every half-hour by day and night. He was first admitted to hospital in 1948 and later came under my observation. His general condition was poor and he had lost strength. He was pale, with a moderate hypochromic anaemia (Hb 80%). He was not dyspnoeic at rest, but rapidly became so on mounting stairs. There was considerable clubbing of the fingers (Fig. 2) and toes, but no cyanosis. The cardiovascular system was normal. Chest expansion was 24 in. Clinical examination of the lungs revealed no abnormality. Radiography showed diffuse bilateral miliary mottling without enlargement of the hilar lymph nodes (Fig. 3). There was scanty sputum, and tests for tubercle bacilli were repeatedly negative. He was intelligent and co-operative and showed no evidence of intellectual or personality changes. There was blunting of pinprick sensation over the right side of the face and forehead, with a reduced corneal reflex; the pupils were slightly unequal but reacted normally. The optic discs and visual fields were normal. The blood Wassermann reaction was negative, and the cerebrospinal fluid was normal. Radiographs of the skull, hands, and feet were normal, and an air encephalogram showed a normal ventricular system with no excess of air over the cortex. The only abnormality of the skin, apart from dryness, consisted of areas of fat atrophy on the outer aspects of both thighs where he was accustomed to administer pitressin injections. Without treatment he voided 10 to 20 pints (5.7 to 11.4 litres) of urine daily. The effect of 1 ml. of pitressin tannate in oil lasted 18 to 24 hours. Plasma globulins were normal. The blood cholesterol level was 235 mg. per 100 ml. Intravenous pyelography was normal. The Mantoux reaction was positive to 1 in 1,000 O.T. Sarcoidosis had been diagnosed before he was referred to me.

Calciferol (150,000 units daily) by mouth for three months exerted no influence on his lesions. The dyspnoea was more marked and at times he was cyanosed. There had been no evidence of spontaneous pneumothorax, and it was considered advisable to induce pneumothorax artificially as in Case 3. The honeycomb appearance of the lungs on the radiograph was not as marked as in Case 3, and tomograms did not assist in deciding whether there were cystic changes in the lungs. Lateral radiographs

**Fig. 2.—Clubbing of fingers in Case 2.**
and over the right side of the face and forehead. The cerebrospinal fluid was normal.

The question that naturally arose was whether the diabetes insipidus, the pulmonary fibrosis, or both, were syphilitic in origin. In rejecting this explanation the following points were borne in mind. First, the patient's syphilis was undoubtedly congenital and only discovered on routine investigation for headaches in his twenty-ninth year. The nervous system and the cerebrospinal fluid were then normal. Secondly, by the time the pituitary disorder developed, the blood Wassermann reaction had become negative. The cerebrospinal fluid remained normal. Thirdly, the later development of unilateral involvement of the fifth cranial nerve can hardly be attributed to syphilis in these circumstances.

It is difficult to imagine that such uncommon and separate manifestations of congenital syphilis would make their appearance during the third decade in this manner. Much more likely is it that both pulmonary and pituitary symptoms are a manifestation of another disease. The possibilities will be considered in the discussion that follows the description of Case 3.

Case 3.—In 1944 a man, then aged 30 years and serving in the Army in East Africa, began to suffer from excessive thirst. On his admission to hospital it was estimated that fluid intake varied between seven and 14 pints (four to eight litres) and urinary output between eight and 20 pints (4.5 to 11.4 litres) daily (specific gravity of the urine 1000–1010). He passed urine every two hours during the day and usually three times at night. Apart from the evidence of loss of weight he appeared to be well, but a radiograph of the chest showed diffuse, fine miliary infiltrations of the lungs. There was no enlargement of the hilar lymph nodes. No Mantoux test was possible at this stage, but six examinations of sputum were negative for tubercle bacilli. The E.S.R. was 9 mm. in one hour. The skin was normal. Radiographs of the skull and of the hands and feet disclosed no abnormality. The blood urea level was 24 mg. per 100 ml. A blood urea clearance test showed 118% of normal renal function in the first hour and 62% in the second hour (mean 90%).

He was invalided home with a diagnosis of diabetes insipidus and was discharged from the Army in 1945. In May, 1945, round, scaly erythematous lesions, some of them nodular, appeared on the skin of the hands, right thigh, and abdomen. They varied in size from a threepenny piece to a shilling. The Mantoux test was negative to 1 in 100 O.T. The E.S.R. at this time was 9 mm. in one hour. He was then first troubled by shortness of breath on exertion and there were occasional asthmatic attacks and bouts of rhinorhoea. Biopsy and histological examination of one of the skin nodules showed "zones of round-cell infiltration..."
tion in the deep layers of the cutis with macrophages, endothelial cells, lymphocytes, and plasma cells." An intramuscular injection of 1 ml. of pitressin controlled the polyuria for 24 to 48 hours.

In January, 1947, he developed a small, left-sided pneumothorax. At this time the radiographic changes in the lungs had progressed, but there was no evidence of hilar enlargement and the appearances were those of extensive fine miliary mottling with fibrosis. The Wassermann reaction was negative, the C.S.F. normal. Sputum examinations were negative for tubercle and the Mantoux test (1:1,000 O.T.) was still negative: higher concentrations were not used.

He came under my observation in May, 1949. He was now noticeably inefficient at his work. His memory for recent and remote events was poor, speech was at times slurred and indistinct, and his aptitude for figures was very much below that of the average bank clerk. He was frequently anxious and irritable, and yet at other times would laugh foolishly and show lack of insight. Radiography of the chest revealed diffuse coarse reticulation (Figs. 4 and 5).

In July, 1950, the Mantoux test (1:1,000 O.T.) was positive. He produced no sputum. No changes had developed in the bones of the hands or feet. The blood cholesterol level was 283 mg. per 100 ml.; the blood Wassermann reaction was negative. There was no evidence of cutaneous xanthomatosis. In January, 1951, there was a further small left-sided pneumothorax. This absorbed and chest expansion and air entry remained good. He still experiences considerable dyspnoea on effort, and occasionally adventitious sounds are heard in both lung bases.

His wife described how his personality had deteriorated. He was now facile and rather child-like in his attitude to his illness. At times he was pleasant and co-operative, but sometimes there were bouts of temper or anxiety or depression. He was not disorientated and there were no hallucinations or delusions. Tests of intellectual function revealed a fairly gross deficit. Speech was slow, monotonous, and at times slurred. There were no narcoleptic attacks, but he was generally somnolent by day. There were no significant abnormalities on routine examination of the nervous system. Lumbar puncture revealed a normal cerebrospinal fluid pressure (120 mm.) with a free rise and fall on jugular compression; protein content of the cerebrospinal fluid was 50 mg. per 100 ml.; the Wassermann reaction was negative. A lumbar air encephalogram showed that the ventricular system was normal and there was no excess of air over the hemispheres. An electroencephalogram showed considerable abnormality; there was a clearly defined moderate potential theta
rhythm with a predominant frequency of 64 cycles per sec.; slower waves in the theta band were also present. This activity appeared bilaterally in all leads, the amplitude in the frontal leads being lowest. Low potential delta waves appeared as little more than a base-line sway, also bilaterally. There was no alpha rhythm in the record.

Intravenous pyelography and urinary concentration and dilution tests were normal. The third urinary specimen of the concentration test showed a specific gravity of 1030. There was a mild normocytic anaemia (4,120,000 R.B.C. per c.m.m.). The plasma globulins were normal.

Calciferol by mouth (150,000 units daily) was prescribed. This dosage was reached gradually and without side-effects.

In May, 1951, an artificial pneumothorax was induced on the right side, but the honeycomb appearance of the compressed lung was not much enhanced.

At that time the film illustrating a pneumothorax he had experienced a few months previously was not available to me (Fig. 6). It shows, however, some accentuation of the honeycomb appearance of the compressed left lung.

No abnormality has been discovered in the skeleton on careful radiological examination.

In neither Case 2 nor Case 3 can a diagnosis of sarcoidosis be established. In Case 2 there was no tissue available for biopsy (liver puncture was not performed). In Case 3 sarcoidosis was considered to be the interpretation of the histological changes observed in a skin nodule several years previously, but the specimen has not been available to me. In neither case have any cutaneous lesions developed during my period of observation. There was no adenopathy or enlargement of liver or spleen. There were no cystic lesions in the bones. Serum proteins were normal. None of these factors, however, can be taken to exclude the possibility of sarcoidosis, and the literature, as already stated, contains many examples of diabetes insipidus occurring in sarcoidosis.

Writing of pulmonary sarcoidosis, Scadding (1950) described several different radiological appearances: (1) enlargement of hilar lymph nodes without detectable lung changes; (2) bilateral enlarged lymph nodes with diffuse mottling in the lungs; (3) diffuse pulmonary infiltration without gross evidence of hilar lymph node enlargement; (4) fine reticulation; (5) fibrosis, emphysema, and bulla formation. Scadding continues:

"Correlating my own experience with reports in the literature, I think the earliest intrathoracic lesion of sarcoidosis is usually hilar lymph-node enlargement, which may be shortly followed or more rarely accompanied by a more or less diffuse pulmonary infiltration varying from a fine micro-nodular type resembling miliary tuberculosis to coarser irregular mottling. Possibly some cases start with the pulmonary infiltration without a preceding stage of hilar lymph-node enlargement. Infiltrations of either type may either clear completely so far as radiographic appearances are concerned, or persist for a variable time with a variable amount of replacement by fibrosis. This fibrosis most frequently takes the form of irregular coarse strands, usually in the middle zones, with gross emphysematous changes elsewhere, or it may more rarely be of much finer type giving rise to a fine reticulated appearance in the radiograph. This latter appearance may easily be missed on inspection of the radiograph; it is accompanied, however, by a considerable diminution in the patient's vital capacity and correspondingly severe functional disability. In the cases which present the picture of fibrosis and emphysema tubercle bacilli may eventually appear in the sputum, although the radiographic appearances may not show any immediate corresponding change."

The good general condition, the insensitivity to tuberculin, and the clinical course of the affection are points that indicate that the pulmonary process in any given case is more likely to be sarcoid than tuberculous. "But it must be admitted, states Scadding, "that the differentiation between chronic miliary tuberculosis and sarcoidosis is..."
many instances little more than a verbal one.” It will be remembered that the Mantoux reaction was considered to have been negative in the early stages of the disease in Cases 2 and 3 of this report, but in each case it was positive when the patient came under my care. The ultimate development of tuberculosis is, of course, frequent in sarcoidosis, but it is very improbable that the early invasion of the thalamo-pituitary region was tuberculous. Diabetes insipidus occasionally develops as a terminal event in tuberculosis, and it is known that bronchogenic carcinoma can present with the syndrome of diabetes insipidus (Peabody and Olsen, 1951).

Examination of the literature concerning diabetes insipidus in sarcoidosis has not disclosed any case in which the lesions were confined to the pituitary region and the lungs. Clubbing of the fingers, which was observed in Case 2, is an uncommon finding in pulmonary sarcoidosis which has progressed to fibrosis. In Case 3, the progressive mental deterioration and the advance of the cerebral lesion with apparent paresis of the pulmonary disturbance are difficult to reconcile with a diagnosis of sarcoidosis. The radiological appearance of the lungs in Case 2 has not altered during the past four years.

It is therefore considered that sarcoidosis is not the likely explanation of the syndrome in these two cases.

Case 4.—A 32-year-old carpenter was admitted to hospital in January, 1952, because of loss of weight, dyspnoea on exertion, and excessive thirst with polyuria. He was well until two years previously, and had never worked in a dusty atmosphere. In February, 1950, he developed a perianal abscess which required drainage. The chest was not radiographed at the time. He recovered and remained well until a year ago, since when he had lost 28 lb. (13 kg.) in weight. His appetite deteriorated and he became short of breath on exertion. In October, 1951, he was referred to a chest clinic, and radiography showed pneumonic consolidation in the right mid-zone. He was febrile, and was sent home to bed under the care of his own doctor. A second radiograph taken a month later showed that the area of consolidation had resolved.

When admitted to hospital two months later he was sallow and his skin was rather dry. He had recently been troubled with excessive thirst. At night he would retire to bed with two jugfuls of water, and during the 24 hours he estimated that he drank about 12 pints of water in addition to fluids taken at mealtimes. There was increasing polyuria. He remained alert, cheerful, had no difficulty in concentrating, and his memory remained good. His sleep rhythm was unchanged, and there was no somnolence by day.

His eyes were prominent, but he said they had always been so (confirmed by photographs). The tip of the spleen could be felt, and a few small lymph nodes were palpable in the axillae. The fingers were not clubbed. Chest expansion was less than 1 in., but there were no adventitious sounds. Neurological examination revealed no abnormality: C.S.F., normal; E.E.G., normal. The specific gravity of the urine was 1005 to 1008, and there was no glycosuria. The average daily intake of fluids was 10 to 12 pints. The glucose tolerance curve was normal, the fasting blood sugar 80 mg. per 100 ml. The blood cholesterol level was 208 mg., the serum albumin 3.4 g., and globulin 1.9 g. per 100 ml.; albumin-globulin ratio 1.8:1.0. The blood Wassermann reaction was negative. The E.S.R. was 33 mm. in one hour. Thymol turbidity was 3 units. Leucocytes were 5,000 per c.mm. (neutrophils 60%, lymphocytes 26%, monocytes 13%, eosinophils 1%). Haemoglobin was 96%. The Mantoux test was positive (1 in 100 O.T.). No tubercle bacilli were found in the sputum.

Radiography of the skull and skeleton gave normal results, and of the chest (Fig. 7) fine pin-head mottling evenly distributed throughout both lung fields; no cysts were detected, the hilar shadow was normal, and there was no pneumothorax. Tomography disclosed no further lesions.

The sternal marrow was normal, with no excess of eosinophils (Dr. Roger Seale).

The patient's general condition is good. Pitressin tannate, 1 ml. in oil, given intramuscularly, controls the thirst and polyuria for about 36 hours. Diagnosis is not established. The patient would not permit biopsy of an axillary lymph node. Sarcoidosis cannot be excluded, and inability to demonstrate pulmonary cystic changes does not of course exclude a granulop-
matous or xanthomatous process in the lungs. The case is regarded as falling into one or other of the categories discussed in this paper.

"Honeycomb Lungs" and Diabetes Insipidus

Oswald and Parkinson (1949) have drawn attention to what they termed "honeycomb lungs." The condition is characterized by thin-walled cysts distributed uniformly throughout the substance of both lungs, varying in size up to a maximum of 1 cm. in diameter. They have collected 16 such cases. In six the pulmonary lesions formed part of a general medical disorder. In the other 10 cases the disease seemed to be solely pulmonary. They believed that their cases represented "a single variety of cystic disease" of the lungs. Distinctive clinical features included spontaneous pneumothorax, frequently bilateral, and progressive right heart failure which was almost invariably the cause of death. They pointed out that xanthomatosis, tuberous sclerosis, biliary cirrhosis, and pituitary disorders have been reported in association with the radiological picture of "honeycomb lungs." The latter, they concluded, occurs in a variety of diseases in which there is diffuse interstitial pulmonary infiltration, but the radiological appearances are remarkably constant. "Throughout both lung fields a reticular pattern is seen, varying from fine to coarse." The honeycomb appearance was accentuated by collapse of the lung during pneumothorax, and in four cases was clearly demonstrated by tomography. The authors pointed out that similar, but not identical, appearances may be caused by pneumoconiosis, lymphangitis, carcinomatosis, and chronic miliary tuberculosis. In a personal communication Oswald (1951) states that sarcoidosis does not give rise to "honeycomb lungs. Histological studies of "honeycomb lungs" were made by Cunningham and Parkinson (1950).

What is particularly interesting about these cases of "honeycomb lungs" is the occasional association with pituitary disorder. One of their patients (Case 5) was a pituitary dwarf; no abnormality was found in the central nervous system. Another patient (Case 6) had diabetes insipidus. He was 36 years of age and had had diabetes insipidus for nine years. There had been one spontaneous pneumothorax and the fingers were clubbed. In this case, on different occasions, enlarged cervical lymph nodes, palpable liver and spleen, and a soft mass behind the left sternomastoid were noted. Radiography of the lungs showed a coarse reticulation and mottling throughout. No biopsy was performed and he died with:

**TABLE III**

**"HONEYCOMB LUNGS" ASSOCIATED WITH PITUITARY DISORDERS**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Spontaneous Pneumothorax</th>
<th>Right Heart Failure</th>
<th>Pulmonary Retraction</th>
<th>Bone Erosions</th>
<th>Pituitary Disorders</th>
<th>Miscellaneous Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weidman and Freeman (1924)</td>
<td>M</td>
<td>9</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Skull</td>
<td>Diabetes insipidus</td>
<td>Ravenous appetite</td>
</tr>
<tr>
<td>Oechsli and Miles (1934)</td>
<td>M</td>
<td>22</td>
<td>+</td>
<td>Cause of death</td>
<td>+</td>
<td>-</td>
<td>Diabetes insipidus</td>
<td>Fröhlich's syndrome</td>
</tr>
<tr>
<td>Berg and Zachrisson (1941)</td>
<td>M</td>
<td>30</td>
<td>+</td>
<td>Nil</td>
<td>+</td>
<td>-</td>
<td>Diabetes insipidus</td>
<td></td>
</tr>
<tr>
<td>Ackermann (1944)</td>
<td>F</td>
<td>25</td>
<td>+</td>
<td>Nil</td>
<td>+</td>
<td>Pevis and long bones</td>
<td>Diabetes insipidus</td>
<td></td>
</tr>
<tr>
<td>Oswald and Parkinson (1949) (Case 5)</td>
<td>M</td>
<td>15</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Nil</td>
<td>Pituitary dwarf</td>
<td></td>
</tr>
<tr>
<td>Oswald and Parkinson (1949) (Case 6)</td>
<td>M</td>
<td>38</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Diabetes insipidus</td>
<td></td>
</tr>
<tr>
<td>Oswald and Parkinson (1949) (Case 8)</td>
<td>M</td>
<td>12</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Nil</td>
<td>Diabetes insipidus (temporary)</td>
<td>Necropsy, cystic lungs and xanthomatosis.</td>
</tr>
<tr>
<td>Lewis and Smart (1951)</td>
<td>M</td>
<td>21</td>
<td>Nil</td>
<td>Nil</td>
<td>+</td>
<td>Nil</td>
<td>Diabetes insipidus</td>
<td></td>
</tr>
<tr>
<td>Spillane (Case 2)</td>
<td>M</td>
<td>36</td>
<td>Nil</td>
<td>Nil</td>
<td>+</td>
<td>Nil</td>
<td>Diabetes insipidus</td>
<td>Mantoux reaction changed from negative to positive</td>
</tr>
<tr>
<td>Spillane (Case 3)</td>
<td>M</td>
<td>36</td>
<td>+</td>
<td>Nil</td>
<td>+</td>
<td>Nil</td>
<td>Diabetes insipidus</td>
<td>Progressive dementia, Abnormal E.E.G. Mantoux reaction changed from negative to positive</td>
</tr>
</tbody>
</table>

* = not recorded.
DIABETES INSIPIDUS AND PULMONARY DISEASE

out further information coming to light. Another of Oswald and Parkinson's patients (Case 8), a boy of 12 years, complained of polyuria. His daily urinary output varied from four to six litres (S.G 1001). Treatment with pituitrin improved the polyuria (full details not available). Cystic lungs were found at necropsy. Oswald and Parkinson found reports of three cases in the literature in which diabetes insipidus was associated with "honeycomb lungs," one patient, in addition, suffering from Fröhlich's syndrome (Oechsli and Miles, 1934; Berg and Zachrisson, 1941; Ackermann, 1944). The first of these cases came to necropsy and the lungs showed a diffuse honeycomb structure with interstitial fibrosis. Histologically the pituitary was said to "resemble parathyroid tissue," but no details were given. The patient, a man aged 22 years, had several episodes of pneumothorax and death resulted from congestive heart failure with cyanosis. The authors were undecided about the aetiology of the pulmonary cystic condition. They noted an absence of inflammatory reactions in the lungs and raised the question of the congenital origin of the cysts.

XANTHOMATOSIS

It is well known that diabetes insipidus may result from xanthomatous changes in the pituitary gland as in Hand–Schüller–Christian disease. Pulmonary xanthomatosis is not so widely recognized. The radiological signs of "honeycomb lungs" have been observed in xanthomatosis with and without evidence of pituitary, skeletal, and cutaneous involvement. The pulmonary changes may result from diffuse infiltration with lipoid material or from widespread interstitial fibrosis and cyst formation (Oswald and Parkinson, 1949). Writing of the lipoidoses, Thannhauser (1950) describes a case of diabetes insipidus in which there were disseminated xanthomatous lesions of the skin without cranial or pulmonary involvement. The blood cholesterol was normal. He does not mention diabetes insipidus in cases of generalized xanthomatosis of the normocholesterolaemic type, but stressed the radiological similarity of the pulmonary disease to that of miliary tuberculosis.

Lewis and Smart (1951) state that Weidman and Freeman (1924), in reporting the necropsy of a case described by Griffith (1922), were the first to describe cystic lung changes with diabetes insipidus. The case was that of a boy of 9 years who had jaundice, xanthomatous lesions of the skin and the skull, and diabetes insipidus. The blood cholesterol was 397 mg. per 100 ml. At necropsy the posterior pituitary was fibrotic and xanthic; there was a small interpeduncular xanthic tumour. The lungs were said to cut like a rubber sponge and showed large alveoli, emphysematous bullae, fibrosis, and patches of xanthic deposit. Oswald and Parkinson referred to Griffith's paper but not to the necropsy. Lewis and Smart reported the case of a man, aged 21 years, with diabetes insipidus, "honeycomb lungs," and a normal blood cholesterol. They believe that such cases come into the category of normocholesterolaemic xanthomatosis as classified by Thannhauser.

In Cases 2 and 3 of this report no xanthomatous lesions of the skin were observed. Extensive radiological investigation revealed no abnormalities of the skeleton. In Case 2 the blood cholesterol was 235 mg. per 100 ml. and in Case 3 it was 283 mg. per 100 ml. The latter figure is high.

TUBEROUS SCLEROSIS

"Honeycomb lungs" in tuberous sclerosis was first described by Berg and Vejlens (1939), but diffuse cyst-like changes in the lungs with infiltration by fibrous and myomatous tissue was described by von Stossel (1937). In two patients with progressive dyspnoea and cyanosis (one with pneumothorax), with enlargement of the hilar shadows and a miliary radiological appearance, von Stossel found at necropsy lung surfaces like "hob-nailed livers." He considered that there was a diffuse pulmonary "muscular cirrhosis."

Diabetes insipidus was not present in any of the cases of tuberous sclerosis since described in which there were signs, radiological or pathological or both, of diffuse "myomatosis" of the lungs (Berg and Zachrisson, 1941; de Fine Licht, 1942; Rosendal, 1942; Samuelsen, 1942; Paliard, Plaucli, Galy, and Papillon, 1946; Berg and Nordenskjöld, 1946; Oswald and Parkinson, 1949). Adenoma sebaceum, epilepsy, subungual fibromata, phakomata, and bony changes are inconstant in these case reports.

Berg and Zachrisson (1941) described three cases of cystic lung changes in tuberous sclerosis. The first two came to necropsy and the characteristic lesions of tuberous sclerosis were found in various organs. But the third case, a man of 30 years, also had diabetes insipidus with a history of a spontaneous pneumothorax. He was still alive and well and the radiological appearances of the lungs resembled miliary tuberculosis and cystic disease. There were no other abnormalities. The possibilities of sarcoidosis and xanthomatosis were not considered. There was certainly no proof of tuberous sclerosis, which was the presumptive diagnosis.

Ackermann (1944) also considered his case to be one of tuberous sclerosis. A man, aged 25 years,
had diabetes insipidus for two years. He developed chest trouble and entered a tuberculosis sanatorium. Radiography of the chest revealed an "irregular honeycomb pattern" and he later had a spontaneous pneumothorax. Lipoid metabolism was normal. The skull was normal. However, there were multiple cystic changes in the pelvis and long bones, which may occur in tuberous sclerosis (Sutton and Liversedge, 1951), so that a diagnosis of normocholesterolenaemic xanthomatosis, excluded by Ackermann, was not really justified.

The diagnostic difficulties encountered in "honeycomb lungs" are well illustrated by the case reported, with necropsy, by Samuelsen (1942). A man, aged 49 years, was for several years in a tuberculosis sanatorium, believed to be suffering from miliary tuberculosis. Cystic lesions developed in the phalanges and were revealed by radiography. The diagnosis was then altered to one of sarcoidosis, but after death typical lesions of tuberous sclerosis were discovered in the brain and kidneys. The lungs showed diffuse fibrosis and nodular interstitial thickening with accumulation of pigment.

Rosenfeld (1942) patient with "honeycomb lungs" was thought to be suffering from pulmonary tuberculosis or sarcoidosis, but at necropsy there was diffuse pulmonary myomatosis and cystic dilatation of alveoli and bronchioles. The final diagnosis was in doubt. In this case, as in that of de Fine Licht (1942), there were no other changes at necropsy, but both authors noted the resemblance to the pulmonary pathology in cases of proved tuberous sclerosis.

As far as I know diabetes insipidus has not been described in tuberous sclerosis.

SUMMARY

Four cases are described in which there was an association of diabetes insipidus and diffuse pulmonary disease.

The first case was one of sarcoidosis, a disease in which diabetes insipidus and other hypothalamic-hypophysal syndromes occur from time to time. Following a characteristic uveoparotitis with facial palsy, the patient developed hilar lymph node enlargement and later coarse pulmonary fibrosis and diabetes insipidus.

In the second and third cases diabetes insipidus was associated with diffuse pulmonary disease which caused a fine reticular pattern, of the "honeycomb" type, on the radiograph. It was more evident in Case 3 in which pneumothorax, artificial and induced, enhanced the "honeycomb" appearance of the pulmonary radiograph. In addition, in Case 3, there was mental deterioration.

In neither case were there any bony lesions on radiological examination. The blood cholesterol levels were 235 and 283 mg per 100 ml respectively. It is suggested that these two cases are examples of xanthomatosis affecting the lungs and the pituitary region, and the differential diagnosis from sarcoidosis is discussed. In the fourth case no cystic changes have been demonstrated in the lungs. The Mantoux reaction is positive.

The general question of the aetiology of cases of diabetes insipidus (and other hypothalamic-hypophysal syndromes) associated with "honeycomb" lungs is considered in the light of these case reports and of similar ones in the literature. Necropsy studies will be necessary to confirm the true nature of such cases, but they are presumably examples of disordered lipoid metabolism.

I am indebted to Dr. Arthur M. Jones for his help in the interpretation of the radiographs and for his kind co-operation. Dr. H. A. Evans responded to my request to induce a pneumothorax in Case 3, and I am very grateful. Dr. A. J. Thomas kindly referred Case 4 to me. Mr. H. A. Griffiths, of the Department of Clinical Photography, Llandough Hospital, Penarth, provided the clinical photographs and prepared the illustrations.

REFERENCES

ADDITIONAL

Since this paper was submitted for publication Case 3 has died. The relevant post-mortem changes were as follows (Dr. W. Jones Williams):

Axillary and pubic hair was sparse.

There was moderate atheroma of the coronary vessels and aorta, and an ante-mortem thrombus in the aorta at the origin of the left testicular artery.

Both lungs were cystic. Cysts were numerous, up to 2 cm. in diameter, giving a honeycombed appearance (Fig. 8). There was bronchopneumonia in the lower lobes. Microscopically between the cysts interstitial fibrosis and eosinophils were seen. The mediastinal gland showed lymph stasis and numerous eosinophils.

The left kidney showed numerous small cortical infarcts.

The testis was small, and histology showed atrophy of the tubules with no mature sperms and with an increase of fibrous tissue.

Yellowish flecks were seen in the hypothalamus. The pituitary gland and stalk and frontal lobes were macroscopically and microscopically normal. Histology of the hypothalamus showed replacement by "granulomatous" tissue, consisting of islands of "endotheliod" cells, perivascular lymphocytic cuffing, and numerous eosinophils.

The sella turcica appeared normal macroscopically, but the histology showed an increased number of eosinophils. A similar picture was found in the sternal marrow. Fat stains of the various organs showed no increase in the lipid content.

The changes in the hypothalamus were considered to be indicative of an eosinophilic type of granuloma of unknown cause but similar to those previously described. The picture in some areas was reminiscent of sarcoidosis.

REFERENCES
