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Part I.—Original Articles.

MORGAGNI'S SYNDROME: A CLINICAL AND PATHOLOGICAL STUDY.

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IN recent years attention has been drawn afresh to a group of cases in which there is a hyperostosis of the flat bones of the skull, associated with various mental changes and signs of endocrinological disturbances. In 1761 Morgagni mentioned the existence of hyperostosis of the inner table of the skull, and referred to its association with virilism and obesity. Morgagni's brilliant observation was neglected until recently, when it was proposed to name the condition Morgagni's syndrome. F. Morel (1931) published his monograph on frontal hyperostosis of the skull, and expressed the opinion that hyperostosis frontalis interna is a well-defined disease. He suggested that the proliferation of bone is provoked by adhesions between the dura and the inner table of the skull. As characteristics of the syndrome he described obesity, polyphagia, polydipsia, disturbance of sleep, weakness of muscles, loss of sight, headaches, and sometimes epileptic fits. In his opinion a pituitary disturbance is the primary cause of the disease. Shortly before Morel, R. M. Stewart (1928) described cases of insanity with localized calvarial hyperostosis. He found sclerosis of the anterior lobe of the pituitary, which he considered was the responsible cause. Schiff and Trelles (1931) suggested that there might be a

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relationship with Dercum's disease. Dressler (1927) and Greig (1928) dealt with the pathology of the bony changes. Greig suggests that a disturbance of the calcium and phosphorus metabolism is the causative agent. Critchley (1931), dealing with the neurology of old age, emphasized the importance of hyperostosis frontalis interna. A very extensive series of skulls taken from the average hospital population was investigated by Sherwood Moore (1936), 6,650 in all. In his case material there was 1·4 per cent. of hyperostosis. He tried to classify hyperostosis into four forms.

Cases have been described by Van Bogaert (1930), Yolton (1930), Pende (1931), Fattovich (1938), Fracassi and Morelli (1936), Cassatti (1936), Levirot (1937), Roger (1938), Carr (1936). Some of these authors have discussed methods of treatment. F. Henschen (1927) has published a monograph on this subject. Of special interest is a contribution by Moniz (1938), who made arteriographic investigations in his cases, and suggested that a considerable degree of inter-cranial pressure was responsible for the physical symptoms. All contributors have stressed the vast predominance of female patients.

A survey of the literature shows that there is unanimity of opinion that a syndrome exists as a clinical entity consisting of changes in the frontal bone, alterations in the mental state, and signs of endocrine dysfunction. However, the character of the disease is still obscure. It appears to have been rarely diagnosed during life without the help of the radiologist, and from the psychiatrical and neurological point of view the disease is still insufficiently defined. There is no doubt that many cases do not show the complete syndrome and remain undiagnosed during life, either because the disease does not develop, or because it is so slowly progressive that death intervenes from some other cause before it is advanced. Many authors have assumed that the disease is one of later years; this statement obviously must be corrected.

Our case material is small, but by reason of its special nature it seems to throw some light on the essential problems. Moreover, we had the opportunity of performing an autopsy and obtaining the pathological material of a patient in whom the syndrome was well advanced.

CASE 1.—Mabel B—, aged 31, married. Admitted 5.i.39.

General appearance.—Emaciated woman, height 5 ft., weight 5 st. 8 lb. Complexion rather sallow.

Skull.—Narrow, with a high forehead, rounded from side to side. X-ray examination of the skull revealed a marked generalized thickening, greatest in the frontal and parietal regions. There were no localized endostoses. In places the skull was more than twice the normal thickness.

Skeleton.—Apart from flat chest and bow legs there was no skeletal abnormality. The teeth were mostly decayed.

Physical examination revealed patches of fibrosis with altered breath sounds in both lungs. Heart sounds were faint. Blood pressure 110/80. Urine: sp.gr. 1020, trace of albumen. Blood count: R.B.C. 3,250,000; W.B.C. 5,937; Hb. 60 per cent.; C.I. 0·9. No abnormal cell forms. C.S.F. without abnormality. Wassermann reaction in C.S.F. and blood negative.

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Central nervous system.—Full investigation was rendered difficult by the attitude of the patient. She was hypersensitive all over and was frightened of being touched. There was a certain diffuse tenderness of her skull. Pupils equal and regular, reaction to light and convergence normal. Fundi normal. Her speech was slow and drawling, but there was no typical dysarthria. No affection of the cranial nerves. No stiffness of the neck. Abdominal reflexes present. Upper extremities: no paralysis, tonus normal. Superficial and deep sensibility not obviously disturbed. Tendon reflexes brisk, equal. Slight ataxia in finger-nose test. No adiadochokinesis. Lower extremities: reduction of power with slight spasticity, left worse than right. Deep and superficial sensibility intact. Knee and ankle jerks exaggerated, left more than right. Patellar clonus on both sides. Plantar response: left extensor, right variable. Slight ataxia in heel-knee test. Sensibility: there was no localized loss of any form of sensibility, but there was tenderness along the course of the great nerves of the lower extremities. There was also a diffuse hypersensitivity present as far as could be ascertained on every part of the surface of the body. Kernig's and Lasègue's signs were positive on both sides. Romberg's sign was slightly positive, but inconstant. Gait: shuffling and somewhat spastic. All movements were executed rather slowly and with some difficulty.

Mental state.—On admission she appeared to be dull, sometimes semi-stuporose. She would not reply to questions unless they were repeated and put to her with emphasis. She frequently gave the impression that she did not comprehend questions. She had evidently poor powers of concentration. When approached she cried out: "Don't touch me!" or "Don't hurt me!". She was obviously very much afraid of being touched. At one time she said that any form of touch caused her pain. She was unable to tell her address, or the age or occupation of her husband. She had no idea of time, and imagined that she had been in hospital for several months. She gave her own age as 13. She did not know how long the Great War had lasted, nor the name of the King. At no time while under observation, even by dint of great concentration, could she answer such questions as: What is the difference between a lake and a river? or between a child and a dwarf? etc. Her answer was: "I don't know." She was unable to perform simple calculations.

The patient remained under our observation for ten weeks, when she was transferred to another hospital. During that time her mental condition showed no real improvement. However, she became a little more responsive and co-operative as the members of the staff gained her confidence and as her nutrition improved. At first she was rather difficult to manage, but later, when less apprehensive, she could be dressed without difficulty and would feed and wash herself. At the best, one could say that her conversational powers were much retarded and that her ability to co-operate and concentrate were slight. She would, however, take part in examinations, but soon became fatigued. There were no signs of aphasia, apraxia, or agnosia.

Case history.—As far as could be ascertained she was of a normal standard of intelligence for her station in life. She had worked as a domestic servant in a vicarage for five years, apparently giving satisfaction and holding her post until her marriage in 1935. Menses had been irregular or absent for some considerable time. She had never been pregnant. We were informed that she showed signs of physical and mental changes about two years before admission to hospital. The earliest symptoms complained of appeared to be pains in the limbs. It also appeared that the mental state deteriorated most rapidly just before admission. We were unable to discover any details of the family history of the patient.

Case summary.—The case is a woman, aged 31, who developed within two years a rather rapidly progressive dementia of the organic type, without any signs of antecedent infection, neoplasm, vascular or renal disease. There was no sign of mental disorder or intellectual abnormality before the onset of this

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illness. Accompanying the mental changes were signs of an organic lesion of the central nervous system, producing symptoms of a pyramidal disorder and a certain degree of ataxia. Further, there was marked hypersensitivity of the surface of the whole body, greatest on the lower extremities. The characteristic signs of a meningeal irritation were present in the lower limbs. The only possible common cause for the mental and physical symptoms was found in the skiagram of the skull. This skiagram showed that the vault of the skull was enormously and diffusely thickened, most markedly so in the frontal and parietal regions.

CASE 2.—Rósalama R—, aged 65. Admitted 24.iv.39.

General appearance.—Well-preserved woman who did not look her age. Skin and complexion dark, sunburnt colour, with freckles on face and arms. There was an operation scar in the mid-abdomen. She had obviously been fat and had lost weight. She gave the impression of having a serious physical illness. No signs of virilism.

Skull.—Rather narrow forehead, rounded from side to side. An exostosis, the size of a pea, in the midline, 2 in. above the saddle of the nose. No other external skeletal abnormality. Skiagram showed great thickening of the vault of the skull with numerous endostoses in frontal region. The bone was dense, and the thickening involved the parietal bone to some extent. Sella normal. It was impossible to obtain a satisfactory skiagram during life because of the restlessness of the patient. After death X-ray photographs were taken of the skull and of the vault of the skull after its removal at the autopsy. We reproduce only the antero-posterior and lateral views of the latter as they shows most clearly the special nature of the bony change (Fig. 1).

Physical examination revealed advanced fibrotic process in both lungs, considered to be tuberculous. The heart showed no gross abnormality. Peripheral arteries somewhat thickened. Abdomen full and tender.

Central nervous system.—Owing to restlessness and confusion a complete examination was impossible. The fundi could not be examined. A lumbar puncture could not be performed. The skull was very tender, especially in the frontal and parietal regions, less so posteriorly. There were signs of an old iritis with consequent small pupils, bound down by posterior synechiae. No abnormalities of the cranial nerves. Abdominal reflex absent (operation scar). Upper extremities: no paralysis, muscles rather hypotonic. Tendon reflexes: slight response. Pseudo-athetotic spontaneous movements of the fingers on extending arms. Lower extremities: no gross paralysis. Hypotonia of the muscles. Knee and ankle jerks absent on both sides. Plantar reflex normal. Sensibility: a proper investigation was impossible, but no gross disturbances of sensibility were noticed. The gait could not be examined, as the patient was too ill to stand.

Blood pressure 100/70. Wassermann (blood) negative. Urine: sp. gr. 1014, trace of albumen, no other abnormalities.

Mental state.—On admission the patient was somewhat confused. She answered the first questions with " I don't know," but on being pressed she gave her age as 70, and the length of time she had been in hospital as six months. Her orientation in time was considerably disturbed, while her orientation in space was intact. When her attention could be adequately engaged, she appeared to be able to recognize individual members of the staff. She was very depressed, cried and moaned. She accused herself of wickedness and said that she had neglected her duties and that she feared everything. She answered the question: " What have you done ? " with: " The most awful things." She said that people were against her because of her wickedness. She was restless and complained that she was unable to sleep. There were no signs of aphasia, apraxia, or agnosia.

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Progress.—Her physical state deteriorated rapidly. Her confusion deepened, and towards the end contact could not be established. Four days before her death she adopted a posture in which her legs were drawn up on the abdomen with knees flexed, her arms to a much less degree. Passive flexing and extension of neck met with a definite resistance. At this stage she showed a marked resistiveness to being handled and appeared to experience hypersensitivity to touch and painful stimuli. She died on May 22 after a short period of unconsciousness.

Case history.—She had a normal childhood. She was married at the age of 19. At that time she was a well-built woman, free from any noticeable physical defects or illness, except for the small exostosis described above. She was a self-willed and rather suspicious person. She always suggested that her husband, while he was away—if only for the evening—might be conducting an illicit love affair. As his work sent him all over the world, frequently without her, she found ample grounds for development of her suspicions. At least 20 years before admission to hospital her jealousy had developed into a system of delusions, and if she saw him speaking to any youngish female acquaintance, she concluded that he was speaking to one of his illegitimate children. Some years later she expressed the belief that her husband was trying to poison her, and that he would eventually do so for the sake of some other woman. She interpreted any physical complaint as a sign of poisoning. Her paranoid attitude became more general during the last few years, and for long periods of time she remained in her bedroom. She was always anxious to convince her daughters of the truth of her suspicions. There is no reason to assume that she ever experienced hallucinations, and, apart from her behaviour connected with her paranoid ideas, she appears to have been able to conduct herself reasonably well, until just before an operation in December, 1938, when she was investigated for an attack of cholecystitis, and found to have a small contracted and irremovable gall-bladder. She did not recover fully from her physical illness after the operation, and she continued to lose weight. Her mental state had apparently altered. She now showed the symptoms of deep depression. She refused to take food, and would not use the furniture in the house, believing that it had not been paid for. If left alone she would throw her food at the wall or throw the furniture about. She would strip herself of her clothes and stand naked, crying that she had to be burned for her sins. As she had become impossible to manage at home and was losing strength, she came under our care. According to the statement of her relatives, she had never shown these melancholic features prior to the operation, but her temperament inclined towards moodiness and depression—a characteristic observed in other members of her family.

We were informed that she began to put on weight in her early third decade and was excessively fat until after the operation in 1938. She had borne four children, of whom the first died at the age of four of diphtheria and a second committed suicide two years ago. The other two children are alive.

The family history of this case and of Case 3 are considered together below.

The full post-mortem findings will be considered later.

Summary of the case.—It is evident that psychotic changes had existed in this patient for at least the last 20 years of her life. Earlier in her life she showed a morbid suspiciousness, which had not yet found a definite object. The fully developed case must be regarded as one of pure paranoia (Kraepelin). Severe melancholic symptoms did not appear until six months before her death, after an abdominal operation, when her physical state was deteriorating. When she first came under our care she had, in addition to these psychotic symptoms, signs of definite organic changes in the nervous system, with loss of reflexes of the lower limbs and symptoms of meningeal irritation. During the last six months of her life she suffered from intense headaches, apart

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from which there were no other signs of increased intracranial pressure. The skiagram revealed an advanced degree of hyperostosis frontalis interna.

CASE 3.—Thelma M—, aged 32. Daughter of Case 2. Admitted 22.v.39.

General appearance.—Well-made woman, height 5 ft., weight 11 st. 2 lb., fat, the fat distributed over the whole body, reaching its maximum on buttocks and thighs. Fingers and toes small and rather pointed. Pale, greasy skin. High complexion. Growth of dark hair on upper lip and on cheek in front of the ears. No other signs of virilism. Teeth and skeleton normal. External and internal genitalia normal.

Skull.—Forehead rather prominent and rounded from side to side, similar to that of her mother, but with no exostosis. Skiagram: marked hyperostosis of similar degree and distribution to that of her mother (Fig. 2).

No abnormality in heart, lungs, genito-urinary system.

Central nervous system.—Cranial nerves normal. Pupils and fundi normal. Abdominal reflex present. Upper extremities: no abnormalities. Lower extremities: knee and ankle jerks exaggerated. No clonus. Plantar response: left doubtful extensor, right flexor. Oppenheim's both extensor. No paralysis, no ataxia, no disorder of sensibility.

Urine normal. No polydipsia, no polyphagia. Sleep normal. Wassermann and Meinicke (C.S.F.) negative. Water output normal. Blood calcium 11·5 mg. per cent. Inorganic phosphate in blood 3·0 mg. per cent.

Mental state.—The patient was talkative and ready to discuss her case in great detail. The important points of her statement were as follows. She had a normal childhood and girlhood. She had always been accustomed to understand that her father and mother disagreed, that her father was unfaithful and that he wanted to poison her mother. She asserted that she had not been entirely normal for 15 years. She is aware that she suffers from a familial disease of bone. After marriage there were difficulties with her husband. The charges she made against him resembled those that her mother made against her father, and were probably copied. Her sister committed suicide as the result of similar difficulties with her husband.

About three years ago her menstrual life became irregular, and since then she has only an occasional menstrual period with small amount. At the same time she has been growing fatter, losing her looks, and suffering more and more from dizziness and the inability to think clearly.

Before coming to our care she had been treated at two other mental hospitals since February, 1938. She had been becoming increasingly difficult to manage at home. She held a system of delusional ideas against her husband, believing that he was habitually unfaithful to her. These ideas brought her into conflict with female acquaintances of her husband, whom she threatened and attacked. Frequent examination confirmed the impression that she was strongly under the influence of her mother, and that she had always taken her mother's part in any disagreement with her father. According to her, her two sisters also shared all the suspicions of their mother. They had adopted her delusional ideas. From the time of her engagement her mother endeavoured to estrange her from her fiancé, and later suggested to her that her son-in-law, the patient's husband, was unfaithful and going to poison her.

There were no signs of dementia, and apparently no hallucinations. Her intellect was that of a normal woman. After her mother's death she was rather depressed, showing that she had lost the very person to whom she had turned for advice and grievance. In a few days she talked quite dispassionately about her mother's life and character. While in hospital, up to the present, she has shown no initiative nor any desire to occupy herself in any other way than by writing letters. These letters are full of disjointed paranoidal ideas. A very striking feature of her mental state is her childishness and the light-hearted way in which

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she laughs as she tells the story of conflicts between her parents, her husband and herself, and the attempts at poisoning.

The patient has one child, 10 years of age.

Summary of the case.—This patient was admitted to the mental hospital on account of aggressive behaviour derived from paranoid ideas. The main features of her mental disorder were morbid jealousy of imagined rivals, and the conviction that poison was being used against her mother and herself. There were no hallucinations and no other psychotic symptoms. Her history and physical state showed that she had gained in weight in the last three years. There was virilism and a history of menstrual disturbances. There was no evidence of a disorder of the central nervous system, apart from exaggeration of tendon reflexes. The blood calcium level was slightly raised. At her present age of 32, X-ray of the skull showed a hyperostosis almost identical in degree and distribution with that seen in her mother at 65. Her delusions corresponded in a remarkable degree with those of her mother. It appears that she did not develop any delusional ideas of her own.

Family History of Cases 2 and 3.

As far as we have been able to ascertain up to the present other cases of mental disorder have occurred in this family. These investigations have not yet been completed, as the family is widely scattered, but it is hoped that it will be possible to do so at a later date. For the purpose of this paper we can produce the following facts :

Case 2 : Her father was a man of ability and intelligence, but subject to violent tempers and of a highly suspicious and intolerant nature. His brother died as the result of an accident, and at the post-mortem examination some unexpected condition of the bones of his skull was found. We cannot say what this condition was, but we were informed that an unsuccessful attempt was made to obtain compensation for an old head injury. It is possible that the real condition was hyperostosis.

Case 2 had four daughters. One died in childhood. The second is alive. She has always shared certain of the paranoid ideas of her mother. She frequently writes to her sister (Case 3) letters of similar paranoidal content to the patient's own. She is abnormally suspicious about her husband's behaviour. The third daughter was killed by a railway train in circumstances highly suggestive of suicide. She is stated to have been subject to periodic bouts of depression, but in addition she believed in every respect in her mother's delusional ideas and found it impossible to live with her own husband. The fourth daughter is Case 3.

Amongst the children of Case 2's sister one son has a skull very similar in external appearance to that of Cases 2 and 3, with, in addition, an exostosis on the forehead, similar in position and size to that of Case 2, but with no gross thickening of the internal table.

Case 3 has one daughter, 10 years old. X-ray examination of this child's skull shows early bony changes similar to those of her mother, but naturally very much less marked (Fig. 3). Her grandfather has informed us that the prominent traits of her character closely resemble those of her mother and grandmother. In fact he has said, " She is going to go in just the same way as her mother."

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This brief family history is obviously too incomplete to justify any definite conclusions from the point of view of genetics. We feel, however, that it suggests that in our cases heredity is an important factor in the production of the hyperostosis, which appears to be the expression of a dominant gene in this family. Associated with the hyperostosis is a strong hereditary tendency towards the formation of paranoid ideas. We are not justified in assuming that any linkage between the hereditary factors is responsible for these two hereditary conditions.

Discussion of the Clinical Findings.

Our case material consists of three cases, of which one has died under observation. In Case 1 the hyperostosis was more diffuse and appeared to be an encroachment on the internal volume of the cranium, without marked local endostosis. This case corresponds with what Sherwood Moore (1936) has described as diffuse hyperostosis. We feel that we are justified in agreeing with Moore's opinion that such a case is one form of calvarial hyperostosis, of which Cases 2 and 3 are another form. It would obviously be incorrect to regard all cases of hyperostosis as occurring solely in connection with the frontal bone, though no doubt, as in Cases 2 and 3, the greatest degree of hyperostosis is seen in the frontal region. We are of the opinion that the proposal by some authors to find a term applicable to all types of this condition is justified, in consideration of the fact that the hyperostosis appears to be but rarely confined to the frontal bone, and that hyperostosis can only be regarded as one part of a syndrome in which there are various other factors. Therefore we have elected to employ the name "Morgagni's syndrome." Our cases, as well as others reported, indicate that a fully developed syndrome is not commonly seen, and that in view of the slowly progressive nature of the disease the great majority of cases present an incomplete picture.

Many authors refer to obesity as the most important single symptom and as indicating an endocrine abnormality. Two of our cases, however, showed that a co-existing wasting disease may mask this feature, so that at the time of the examination the patient presented the opposite appearance. There was in two cases advanced and progressive non-tuberculous fibrosis of the lungs, and in the second, chronic disease of the gall bladder. Our case material is too small to justify any sweeping statement, but we feel that for some reason, perhaps that of an impaired metabolism, these patients are of delicate constitution and might be the subjects of chronic infections.

As to neurological and mental symptoms, the question arises whether they are derived primarily from the pressure of endostosis upon the brain. Our case material is rather special, in that the patients came under care primarily because of symptoms of mental disorder. The neurological disturbances were

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not prominent in the clinical picture. Nevertheless, it is of importance to ascertain if there are neurological features peculiar to cases of this sort, which might assist in the making of a diagnosis or at least in suggesting that X-ray investigation of the skull should be made, for as far as we know none of the mental changes can be regarded as specific. Even the opinion of the radiologist himself may be uncertain, especially in cases where the hyperostosis is diffuse and without a very definite localization. Furthermore, the ability to recognize such features would be of assistance where the differential diagnosis lay between a meningioma causing hyperostosis and a genuine calvarial hyperostosis.

The neurological symptoms evident in our material were not the same in each case. In Cases 1 and 3 we found pyramidal symptoms, which in the first case produced a spastic gait, while in Case 3 there was no impairment of motor function. In Case 2, however, the most advanced, there was loss of tendon reflexes. The fact that the pyramidal symptoms in Case 1 were the most marked, and that there was a degree of ataxia, might be explained by the fact that the thickening of bone was more extensive and diffuse. The case history suggests that the symptoms developed in a period of not more than two years.

Cases 1 and 2 were more advanced than Case 3, and they had one striking feature in common, namely, signs of meningeal irritation. Furthermore, there was a noticeable hypersensitivity in both cases, resembling what is frequently seen in cases of acute meningitis. Therefore we feel justified in suggesting that where this type of hypersensitivity, with signs of menigeal irritation, is found in patients not suffering from an acute meningitis, calvarial hyperostosis should be considered as a possibility. Probably a chronic irritation of the dura by the attached endostoses produces these symptoms, and it is noteworthy that in Case 3, where headache was absent and neurological disturbances slight, there were no signs of meningeal irritation.

Regarding the mental signs of this syndrome, the existing literature contains no symptom that could be described as pathognomonic, and various forms of mental disorder have been reported. There are obviously four possibilities concerning the relationship between mental disorder and calvarial hyperostosis, namely: (1) that the mental disorder is nothing more than an accidental accompaniment; (2) that the mental disorder is the result of interference with the function of the brain by direct action of the bony condition; (3) that the mental disorder, like the bony changes, results from some common cause responsible for the whole syndrome; (4) that some combination of conditions (2) and (3) may be responsible for the mental changes.

With regard to the first possibility, although it cannot be disproved with absolute certainty, the accidental co-existence suggested is so little in keeping with experience that it must be regarded as improbable. Dealing with the second possibility, one finds that most authors believe that such mental

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symptoms as occur are the results of the direct action of endostosis on the brain. For a variety of reasons this simple explanation cannot be accepted without reservation.

It appears justifiable to conclude that in advanced cases some form of mental disorder is a part of the syndrome. This may seem quite obvious if one considers that in this syndrome the endostoses encroach upon the surface of the brain, and especially as the frontal lobes are usually the first and the most seriously to be involved. But if the mental changes were simply the result of this encroachment, one would not expect to find such an enormous variation in the form of the mental symptoms and of the development of some of the ensuing psychoses. We find reliable references to the occurrence of schizophrenic and melancholic states as well as of confusion and dementia, made by various contributors on this subject.

Case 1 of our three cases showed an intellectual deterioration with restriction of knowledge and interest in almost all spheres of life. Not more than two and a half years before she came under our observation she was apparently of normal intelligence. The deterioration of her intelligence greatly resembled that of presenile or senile dementia, although she had not yet reached 30. Nothing in her history pointed in any way to schizophrenia. We therefore regard her case as that of an organic dementia. She consistently showed one special feature, namely, that she was extremely sensitive to any form of approach. Her reaction was one of fear and she cringed away when one approached the bed. This attitude apparently did not result from psychotic fears, but from painful experience through physical hypersensitivity, which, as we mentioned before, resembled that of meningeal irritation. The combination of dementia and fear of being touched gave a picture of an anxious frightened child.

The second case had been the subject of a pure paranoid psychosis for many years. There is no doubt that this psychosis deepened and developed more as she got older, but at the time we saw her first she was physically very ill and features of confusion and melancholic depression were prominent.

In Case 1 the clinical symptoms could perhaps have been explained quite simply by a diffuse damage to the brain surface as a whole. In Case 2 neither the paranoid psychosis nor the melancholic symptoms could be attributed to local pressure. Her intellectual powers were obviously never impaired until shortly before her death, when she was seriously ill and running a temperature. There was no evidence of senile mental changes.

There was only one special feature common to both Cases 1 and 2—an apprehensive attitude with fear of being touched. It is fair to suggest that the hypersensitivity occasioned the same mental attitude, the hypersensitivity itself probably being the result of persistent irritation of the dura. Perhaps this hypersensitivity explains why one author thought that this syndrome was akin to Dercum's disease (Schiff and Trelles, 1931).

The third patient, who showed no signs of meningeal irritation nor of

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hypersensitivity, did not display this apprehensive attitude. Although obese, she had no painful deposits of fat.

In this connection it is worth referring to another case under our care. This patient suffers from extensive Paget's disease of the skull and other bones. In her we found considerable hypersensitivity of the meningeal type, and her attitude is childish and apprehensive to a degree, comparable to Cases 1 and 2. We therefore consider that this same hypersensitivity is the result of irritation of the dura. Furthermore, this similarity is of interest, as certain authors take the view that hyperostosis and Paget's disease are akin.

Case 3, the daughter of Case 2, presented paranoid features almost identical with those of her mother. She shared her mother's delusional ideas, and also expanded and transferred them to her own environment. One feels that she developed no delusions of her own. Her psychosis was, therefore, a communicated paranoia. It is likely that her psychopathic constitution is similar to that of her mother, so that she was from the beginning highly susceptible to influences likely to assist the development of the psychosis. We cannot easily estimate how far the constitutional factor and how far the psychological factor of dependency on her mother were responsible; the fact that since the death of the mother six months ago she does not appear to have lost any of her paranoid ideas, suggests that the constitutional factor was the more important of the two.

Having now reviewed the psychiatric aspects of our case material, it seems advisable to consider the third and fourth of the possibilities mentioned above. Our observations as a whole suggest the conclusion that the pathologically abnormal environment of the brain and endocrine dysbalance, producing an alteration in the individual as a whole, activates the abnormal elements in the psychopathic constitution and gives rise to the psychosis, if not actually determining its exact shape. It is reasonable to expect an abnormal but totally different mental picture where the mental constitution is of another type. In this way one can explain the diverse appearances of the mental disorders associated with the syndrome. This hypothesis does not exclude the assumption that in certain cases mental symptoms may be secondary to the mechanical effect of bony changes on the brain, such as has been seen in Case 1.

We will refer to this and to the problem of the influence of the endocrinological factor when the post-mortem findings in Case 2 have been described and discussed.

Post-Mortem Examination of Case 2.

External appearance : A somewhat wasted woman, with a rather dark sunburnt appearance of the skin and many freckles on forehead, face and arms.

Skull : Corresponding to the external boss in the middle of the forehead there was found a well-defined exostosis. The bone as a whole was abnormally dense and offered great resistance to the saw. From within, the inner table of the whole frontal bone and of the adjacent bones, extending back in a fan-shaped fashion as

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far as the occiput, was thickened, the maximum thickening occurring round the midline of the frontal bone (Fig. 4). In the affected region the diploë seemed to be absent, and there was a great mass of irregular endostoses with a smooth surface, to which the dura was firmly adherent. More posteriorly, that is from about the vertex backwards, no endostoses occurred; diffuse thickening of the calvarium alone was seen. The dura was only adherent to the endostosis. The calvarium was removed at the average level necessary for extraction of the brain. The weight of this part of the cranium plus the attached dura was 675 gr., that is, almost double the weight of a corresponding area of bone in the average case material. The dura was thickened, its interior surface being smooth; the external, when detached from the bone, presented a rough appearance. There were no other bony changes observed inside the skull. The sella was normal.

Brain: There was a moderate diffuse flattening in the frontal region corresponding with the projections on the inside of the frontal bone, and a certain degree of gyral atrophy in this region (Fig. 4). Otherwise there were no gross pathological features. The vessels were thickened to an extent consistent with the age of the patient. No signs of advanced arterio-sclerosis. No internal or external hydrocephalus. Pituitary gland of normal size and appearance.

The *spinal cord* and its meninges appeared normal.

Skeleton: A small exostosis of the size of half a pea was found on the anterior surface of the body of the third dorsal vertebra. *Lungs:* Both lungs were of uniform mottled grey colour and of almost leathery consistency. They showed an advanced long-standing fibrotic condition, with emphysema in both apices. Enlarged mediastinal glands. *Heart:* muscle flabby, with a degree of fatty infiltration and a slight amount of atheroma of the aorta. No persistent thymus. *Liver:* greasy appearance. *Gall bladder:* small, shrunken. *Pancreas:* smaller than normal. *Kidneys:* no abnormalities.

Adrenals: Both were similar and rather large; the external surface of each rough and nodular. Cut sections showed numerous nodules, 1–2 mm. in diameter, some just outside, others attached to the cortex. The cortex thickened as a whole. Medullae normal.

Alimentary tract: as a whole normal. *Spleen* normal. *Uterus and ovaries:* atrophic according to the age. *Thyroid:* small and hard. *Parathyroids:* four in number, the sizes being—left upper gland 5 : 2 : 2 mm. The three others were unusually small, being about 2 : 2 : 1 mm. in size.

*Histological findings.**

Skull: The examination of the thickened part showed a marked increase of the bony substance. As the result of the increase of the ground substance the lamellae appeared to be increased in size, but the lamellar structure was normal. The inner table was markedly thickened, the diploë being either missing or reduced by thickening of the bony bars. No centres of new bone could be perceived. The lamellae of bone gave the impression of being absolutely quiescent. The external table showed no pathological features except for the exostosis, which showed the same structural features as the inner table, i.e. increase of the ground substance between quiescent lamellae. The pathological character of the thickened parts of the skull was emphasized by the fact that the process of decalcification of even small portions of bone was not complete in less than four months.

Meninges: The *dura mater* related to the bony growths was in many places inseparable from the bone, but there were no elements of dura within the bony tissue. The dura was homogeneous. It was not possible to distinguish between the two layers generally described, of which the outer layer is usually richer in blood vessels. The large venous sinuses which are seen in the normal dura between the two layers were not obvious. They were of small volume and sparsely distributed. The strands of the fibrous tissue ran in all directions. Elastic fibres were

* In the interest of economy the microphotographs for publication have been restricted.

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scarce. There was a noticeable increase in the number of connective-tissue cells, especially near the inner surface. There was no marked active proliferation of blood vessels, but as a whole the vascularization seemed richer than usual. The walls of some of the middle and small arteries were thickened; several of them showed early hyaline degeneration. Endothelium of all vessels normal. A number of arteries and capillaries showed a moderate infiltration with lymphocytes. There was no acute disintegration of the dura tissue, but there was a remarkable number of fat cells in the dense connective tissue. There was no calcification of the dura. The parts of the dura mater not adjacent to the hyperostotic parts of the skull showed no abnormality. There was a moderate degree of diffuse thickening of the *leptomeninges*, especially over the frontal parts of the brain. In many places a slight infiltration consisting of lymphocytes and some few plasma cells could be found. These cells were found between the fibres of the leptomeninges and surrounding some of the small arteries and the capillaries. But nowhere could this infiltration be seen to continue to the brain tissue.

Brain: Because there were no clinical localizing symptoms, it was necessary to examine a very large number of portions taken from all the important areas of the cerebral cortex as well as of the other parts of the brain. The staining methods employed were: Nissl's stain (cresyl violet), Kultschitsky-Wolter's and Spielmeyer's stain for myelin sheaths, Mallory's gold-orange aniline-blue stain, Bielschowsky's and Braunmühl's silver impregnation, the modifications of Hortega's silver carbonate and of Cajal's gold sublimate methods for glia staining (Globus, Penfield), the Turnbull blue method for iron deposits, and Herxheimer's lipoid stain. The following are the results of these examinations:

Cerebral cortex: There was no gross lesion in any part of the cerebral cortex. There was no sign of inflammation. But there were signs of a diffuse pathological process. This was found in the frontal region of both hemispheres (less pronounced in the gyrus frontalis anterior), and to a certain extent in the parietal lobes and to a very slight degree in the temporal and occipital lobes.

The pathological changes affected all elements of the nervous tissue. Many of the ganglion cells, chiefly those of the third and fifth layer, to a less degree the small pyramidal cells of the fourth and the cells of the sixth layer, showed a considerable degree of shrinking. Many cells showed an elongated nucleus, sometimes of triangular shape. The nucleus as a whole, or at least the parts surrounding the wall of the nucleus and the wall itself, stained darkly. The tigroid substance appeared more compact. The cellular processes, especially the apical processes of the pyramidal cells, were tortuous. There were no incrustations in the cells. A number of cells showed swelling. In such cells the Nissl bodies appeared fragmented and in parts of the cell body had disappeared. In many of the swollen cells part of the protoplasm was vacuolated. Silver impregnation revealed in the shrunken cells thickening of the intracellular fibres, and in some of the swollen cells fragmentation of the fibrillae. There was no sign of the Alzheimer type of neuro-fibrillary change. There were no senile plaques. There was a considerable quantity of lipofuscin in the cells of the cortex, especially in the larger pyramidal cells. The amount of lipofuscin was considerably greater than one would expect to find in a healthy subject of 65. Clusters of oligodendrocytes surrounded many of the larger ganglion cells. The amount of satellitosis was excessive. In some places there were advanced stages of neurocytophagia. Faintly stained remnants of ganglion cells (cell shadows) could be seen. Small glial elements similar to those forming clusters round the ganglion cells formed long chains parallel to the myelin sheaths, in both cortex and white matter.

A survey of the cyto-architecture revealed that in the frontal and to a less degree in the parietal cortex there was undoubtedly a diffuse loss of ganglion cells, especially in the third, fifth, and to some degree in the sixth layer. In some places a dropping out of ganglion cells was apparent, involving the second to fifth layers and occurring in patches. There were many disorientated cells, especially pyramidal.

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The apical dendrite of these cells was not directed radially to the surface, but was sometimes turned through 45°, and even in some cells through 90° from the normal. This alteration in some places made it difficult to distinguish between the individual layers.

The axis cylinders were swollen in many parts of the cortex, most markedly so in the three outer layers. Spindle-shaped enlargements were rather common. The apical processes of the pyramidal cells showed corkscrew shapes and irregular spiral twists. The alteration of the axis cylinders corresponded with the amount of cell affection. In the cornu ammonis axis cylinder changes were not marked.

There were marked pathological changes in the myelin sheaths in the outer layers of the cortex; they were demonstrated in the tangential layer and the supraradial feltwork (lamina suprastriata), and to a lesser extent in the outer Baillarger stripe and lamina interstriata. A great percentage of the fibres showed local distension and swellings, frequently leading to ballooning. In many places a fragmentation into globules of large size could be found. In some parts of the cortex, especially of the frontal lobes, one got the definite impression that the number of the myelin sheaths was reduced, but there were no localized patches of demyelinization.

There was a considerable increase in the number of all glial types, most markedly of the fibrillary and protoplasmatic astrocytes, which were increased not only in the white matter but also in the deeper layers of the cortex. The number of the protoplasmatic astrocytes attached to the external walls of the smaller vessels was definitely increased. Fragmentation of the processes of the protoplasmatic astrocytes (clasmatodendrosis) could be seen in a limited number of cells in the deep cortical layers. Many of the astrocytes revealed a swelling of the cell body. The number of the oligodendrocytes was increased, more especially in the white matter. In the cortex one could find many swollen oligodendrocytes. Their appearance as satellites has been described above.

There was a moderate proliferation of microglial cells, some cells showing a marked hypertrophy and signs of disintegration, and some being distended by globules of fat (gitter cells). Some of the enlarged microglial cells contained granules of iron pigment. These pathological changes were greatest in the frontal and to a lesser extent in the parietal lobes.

Other parts of brain: There were no marked changes in the walls of the *blood vessels*, except where some of middle size showed slight signs of early arteriosclerosis, about the average for the age. There was only a small degree of iron pigment in the walls of the smaller blood vessels of the cortex, and inside the bodies of the microglial cells. The *thalamus*, *corpus striatum* and the *globus pallidus* did not show marked pathological changes, except an increase of lipofuscin in the larger cells, with satellitosis of these cells and a proliferation of glial elements, especially of the protoplasmatic astrocytes. There was no considerable loss of cells. The substantia nigra was normal. The walls of the medium-sized blood vessels of the globus pallidus were degenerated, and were in part replaced by a homogeneous material which stained darkly with haematoxylin. This was the pseudo-calcium commonly seen in the walls and smaller vessels of the globus pallidus in patients past middle age. In the neighbourhood of these vessels balls of a similar material were seen in ganglion and glia cells and free in the tissue.

No pathological changes were found in the immediate neighbourhood of the *third ventricle* and the *aqueduct*. These regions were investigated carefully, as disturbance of sleep has been described as a characteristic symptom in these cases. The cell groups of the *tuber cinereum* were studied in serial sections. There were noticeable degenerative changes in the supra-optic nuclei, especially in the anterior and middle parts. These cells showed diffuse tigrolysis and some were shrunken. The distribution of the tigroid peculiar to the cells of this nucleus was not to be seen. The cell wall was ill-defined, the cells—normally round or oblong—showed a variety of atypical shapes, some being polygonal with regular or irregular angles. The cells were obviously reduced in number. In places cell-shadows could be seen and advanced neurocytophagia. There was a marked increase of small glial elements in the vicinity of the ganglion cells of this nucleus. Both sides of the tuber were

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equally involved. The other nuclei of the tuber showed a slight degree of similar cell changes, but without obvious loss of cells.

There were no pathological changes of importance in the *medulla* and *cerebellum*. The cells of the inferior olives showed an increase of lipofuscin.

Spinal cord : Representative specimens were taken throughout the spinal cord. There were slight signs of meningeal irritation, as shown by infiltration of some of the meningeal vessels. Some nerve roots at various levels showed slight lymphocytic infiltration, but there was no degeneration of root fibres. There was no systematic or diffuse loss of myelin sheaths. A number of the large ganglion cells of the anterior horns showed a considerable degree of dissolution of tigroid, so that in some cells the protoplasm was quite homogeneous. However, there were no signs of damage of the nucleus. The deposit of lipofuscin into the protoplasm of these cells was very substantial.

Endocrine organs.

Pineal body : Normal size. No cavum pineale. The epithelial cells formed a syncytium, partly of trabecular structure. The ill-defined protoplasm of the cells showed granulation, chiefly of basophil and to less degree of oxyphil character. There was a moderate amount of calcareous concretions.

Pituitary gland : Normal size. It was examined in serial sections, stained either with haematoxylin and eosin, or Mallory's aniline-blue gold-orange. Anterior lobe : acidophil and basophil cells were well stained and of various sizes. The majority of both types, but more especially of the acidophil, were of large size with well-defined cell walls, typical granular protoplasm, and darkly stained nucleus. In many cells there was a vacuole near the nucleus. The basophil cells were irregularly distributed, but the acidophil cells tended to occur in homogeneous groups, especially in the lateral parts of the anterior lobe, where there was a vast predominance of these cells. These areas were less vascular than elsewhere. In some places there were small vesicles containing colloid.

In the left posterior quadrant of the anterior lobe there was a conspicuous circumscribed area, well defined from the surrounding tissue (Fig. 5). It was an oval body, about 3 mm. long, and with a cross section of 2 mm. and 1 mm. It was composed exclusively of eosinophil cells, smaller and more compactly arranged than those of the surrounding tissue. The arrangement of these cells was not very well defined but, on the whole, they tended to form columns radiating approximately from the centre towards the periphery of the body when viewed in cross section. Between some of these columns there was a homogeneous colloid substance, which stained pinkish with eosin and light blue with Mallory's stain. In the centre of the body in the cross section was a small irregular space containing droplets of colloid. The outline of this body was distinct, and there were circular connective fibres surrounding it, while inside there was no connective tissue. The tissue immediately surrounding the periphery of the body was rather loose and showed signs of pressure, as can be seen in Fig. 5. This body could be seen quite clearly with the low power and even with the naked eye in the stained sections.

There were large groups of nuclei set in dense heaps, situated chiefly in the centre of the anterior lobe and along its periphery, and to a lesser degree between the chromophil cells. These nuclei were embedded in a syncytium of protoplasm which stained pale, and in some places showed no cell walls. In some of the cell heaps, however, small cells with distinct walls, some of which contained acidophil granules, could be distinguished. The densest concentration of these cells was at the centre of the anterior lobe, where they occupied the whole space intermingled with thick strands of fibrous tissue. The amount of protoplasm in these dense cell heaps was small considering the size, and most of these nuclei were obviously the nuclei of chromophobe cells, of which the protoplasm was pale and the cell body ill-defined. A few lymphocytes were seen.

With regard to the proportion of the number of these types of cells, it is not possible to make more than approximate statements. It is quite certain that the

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eosinophils were greatly in excess of the basophils, and the impression was given that what is considered to be the normal ratio of 3 to 1 was exceeded. The chromophobe cells appeared to be at least as numerous as the chromophils together, or even more so.

The vascularization of the gland was rich. There was a marked increase of connective tissue, especially in the centre of the gland, where the groups of glandular cells were separated by thick connective tissue, rather poor in fibroblasts. Connective-tissue fibres radiated towards the periphery, where they formed a loose tangential layer between the gland cells. These fibres merged into what appeared to be a normal capsule. In spite of the considerable amount of connective tissue, one did not get the impression that there had been a reduction in gland substance as a result of proliferation of connective tissue.

The pars intermedia was well developed, showing a number of large vesicles containing colloid which stained partially blue and partially purplish-red with Mallory's stain. In the periphery of the anterior lobe adjoining the pars intermedia were masses of colloid substance between the anterior lobe cells, which seemed to drown these cells in colloid. These concentrations of colloid were free and were not contained in vesicles with any discernible wall. The colloid in this part of the anterior lobe appeared to be the same as the colloid of the pars intermedia. The posterior lobe was rather small. It showed no pathological changes. In one place *a group* of small basophil cells was seen in the tissue of the posterior lobe.

Parathyroid glands: As described above, there were four glands, three of which were unusually small, and the left superior of normal size. The structure of the three smaller glands was similar and was as follows: There was a dense mass of cells with darkly stained small round nuclei and rather indistinct cell walls. The protoplasm of these cells, stained with haematoxylin and eosin, was faintly bluish or not stained at all. In many cells of the latter type a halo of unstained protoplasm could be seen next to the nucleus. The cells described showed all characteristics of the so-called chief cells, being either clear or what has been described as *Wasserhelle cells*. In some places these cells formed small vesicles, but on the whole they formed a compact uninterrupted mass. Colloid was present between many of the cells in small droplets. Among these cells were single cells, rather small, with well-defined walls and a granular protoplasm which stained distinctly with eosin. These cells resembled the smaller eosinophil cells of the anterior lobe of the pituitary. Furthermore, there were large well-defined cells arranged in groups of various sizes. The size of these cells exceeded not only that of the chief cells but also that of the oxyphil cells described above. Their protoplasm was granular and stained rather pale with eosin, so that they could be easily distinguished from other oxyphil cells. These two types of oxyphil cells (Welsh cells) obviously represented what was described as the dark and pale oxyphil cells. While the number of the dark oxyphil cells was not very large, the amount of cell groups composed of pale oxyphil cells definitely exceeded what is usually found in the normal individual of this age. These cell groups were more numerous and larger than normally. As many as 50 to 80 cells could be counted in one group. There was no colloid between the cells in these groups. The gland tissue was interrupted in many places by globules of fat consisting of typical large fat cells. Strands of fibrous tissue interrupted the compact tissue.

The upper left parathyroid showed a structure quite different from that of the three others. It consisted entirely of large oxyphil cells of considerable size with very well defined walls (Fig. 6). The protoplasm of about half of these cells was densely granular and stained pale red with eosin. The other cells showed fewer granules, which in many cells were concentrated around the nucleus, and in others loosely distributed in the cell body. There was a number of cells without granules, so that the protoplasm appeared to be quite empty. The walls of all these cells were well defined and appeared to be thickened. This thickening was more obvious in those cells which contained little or no granular protoplasm. No cells contained vacuoles. The tissue of this gland was not interrupted by fat, so that the whole

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gland presented a homogeneous appearance and was constructed of large cells, which obviously represented pale oxyphil cells in different stages of disintegration of the protoplasm. There was no colloid between or in the cells. The vascularization of this gland was poor. There was no proliferation of connective tissue.

Adrenals : The three layers of the adrenal cortex could be easily distinguished. The numerous nodules described in the macroscopic findings were composed of cells of the glomerular and fascicular cortex. The majority of these cells were of normal size ; some of them, however, were enlarged. They were all of normal structure. These cortical growths were sufficiently numerous to produce a considerable increase of cortical tissue, which could be assessed as about one-quarter of the normal cortex. The medulla did not show pathological changes.

Thyroid gland : There was a considerable diminution in total colloid. The vesicles were comparatively small, many of them atrophic, and the number of vesicles with signs of activity reduced. There was an increase of interstitial fibrous tissue, which seemed to invade the rather atrophic vesicles.

Ovaries : There were the usual signs of atrophy corresponding to the age of the patient. No pathological changes.

Pancreas : No pathological changes. The islets of Langerhans showed a normal structure.

Other organs.

Lungs : The lung tissue appeared to be completely disorganized. There was a massive proliferation of fibrous tissue between the alveoli, which were grossly distorted. In many places there was a reversion to the foetal type of epithelium. In the fibrous tissue there was an intense diffuse infiltration with lymphocytes and plasma cells. The bronchial cartilage showed calcification in places. From the microscopic picture it was difficult to imagine how the patient had conducted the normal function of respiration adequately.

Liver : As a whole much diffuse fatty degeneration observed, with a chronic infiltration of the portal ducts.

Kidneys : No significant pathological changes.

Summary of the Pathological Findings.

1. *Macroscopical findings.*—The significant pathological features were the following : Diffuse hyperostosis of the vault of the skull, especially of the frontal and parietal parts of the calvarium with nodular frontal endostoses. The bone was eburnated, the diploe reduced, the frontal dura thickened. There was a flattening and a moderate atrophy of the frontal lobes of the brain. The lungs showed a diffuse fibrosis. There was agranular hypertrophy of the cortex of the adrenals. Three of the four parathyroids were unusually small.

2. *Microscopical findings.—Skull and meninges :* There were no signs of an active process in the hyperostotic bones. The dura mater corresponding to the thickened bones showed proliferation of fibroblasts and slight signs of inflammation. The dura tissue was in some places replaced by fat. The leptomeninges in the same areas were slightly thickened and showed a moderate infiltration. *Brain :* Diffuse degenerative changes, involving all elements of the cortical tissue, throughout the frontal and to a lesser degree in the parietal cortex. The changes were slight in the gyri centrales. In many places the ganglion cells were disorientated. There was dropping out of ganglion cells,

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especially of the third and fifth layers. A great number of ganglion cells showed signs of chronic disease with shrinking, lipoidosis, and neurocytophagia, and there was marked swelling of the myelin sheaths, with signs of disintegration. The associated axis cylinders were swollen. In the frontal and parietal lobes there was a proliferation of all glial elements, but chiefly of the protoplasmatic and fibrillary cells, many of which showed degenerative changes. The basal ganglia did not show any noteworthy pathological condition. In the hypothalamus there were chronic cell changes in the anterior parts of the nuclei supraoptici with a considerable amount of neurocytophagia.

Endocrine glands: In the anterior lobe of the pituitary the number of acidophil cells appeared to be greater than normal. There was a well-defined area within the anterior lobe, differentiated from the surrounding tissue, composed of small acidophil cells with a special arrangement. This cell concentration must be regarded as an adenoma of acidophil elements. The basophil cells were normal. The chromophobe elements formed dense concentrations in the centre of the gland, with amongst them a small number of lymphocytes. There was a marked proliferation of connective tissue without a noticeable reduction of gland tissue. Of the parathyroid glands, three showed an increase of pale oxyphil elements, definitely greater than what is regarded as normal for individuals of the age of the patient. The fourth gland was formed exclusively of large pale oxyphil cells. In the adrenals there was a considerable number of small adenomata consisting of cells of the glomerular and fascicular layers of the cortex. There was a moderate atrophy and fibrosis of the thyroid gland.

Discussion of the Pathological Findings.

With regard to the condition of the brain, it has been regarded hitherto by most authors as a matter of course that the pathological changes of the brain are merely the result of the pressure exerted on the surface of the brain by the thickened internal tabula of the skull. This explanation is only satisfactory in so far as it explains the clinical signs of endocranial pressure and local brain injury, such as might accompany any condition where a bony mass encroaches on the brain, e.g. Paget's disease. It has also been suggested that the action and pressure of the endostoses upon the meninges produce local accumulations of cerebro-spinal fluid, most marked in the frontal regions, and in some measure responsible for the symptoms. In our case there was no evidence to support this hypothesis. The dura showed thickening and a little infiltration which appeared to be secondary to and the result of the growth of the inner bony table. There was no sign of serious reaction in the leptomeninges.

Contrary to what has been suggested, there was no evidence that outgrowth of bone was a response to some dural activity of bone cells. In our case the

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changes of the brain cortex were of the order of a chronic degeneration and seemed to correspond in extent and in severity with the nature and distribution of the hyperostosis, these changes being greatest in the frontal and parietal regions. At first sight it would seem quite obvious to relate the changes of the brain to the changes of the contiguous bone. But it is equally true that the frontal and parietal lobes are the most heavily involved in any of the chronic degenerations of the cortex, so that a similar distribution of degeneration is the rule in many cortical disorders where there is no question at all of an external mechanical or irritating agent. The distribution of the cortical changes is not in itself conclusive proof that pressure of endostoses alone is responsible for these changes, nor were there any special signs of tissue injury characteristic of the results of immediate and direct pressure.

We do not regard these changes as a result of senility. Apart from the fact that the patient showed no clinical symptoms of a senile psychosis, there were no changes in any element of the nervous tissue pathognomonic for senile degeneration. The lipoidosis was only moderate, and the basal ganglia, which in typical senility show marked degeneration corresponding to the cortical damage, were practically unaffected. The dropping out of ganglion cells recalled what is sometimes found in schizophrenia, where, however, the degeneration is not diffuse as in our case. The pathological findings in the brain, therefore, suggest that the changes found in the cerebral cortex might be partially unrelated to the bony interference.

In the deeper regions of the brain there were noteworthy changes only in the nuclei supraoptici. In these nuclei there was evidence of a chronic degeneration of ganglion cells with reduction of the number of cells, especially in the anterior parts of the nuclei. Other nuclei of the hypothalamus appeared unaffected. This finding is of special interest, as the nuclei supraoptici are regarded as having an influence on metabolism, and as it has been shown that nerve fibres arising from these nuclei end in the posterior lobe of the pituitary, which, however, in this case did not show any marked abnormality. Our findings, therefore, seem to confirm the assumption that the infundibulo-hypophyseal system is affected in this disease.

Some authors (Yolton, 1930; Geschickter and Copeland, 1931; Dressler, 1927) took the view that the reduction of the volume of the brain—especially of the frontal lobes—in old age stimulates the growth of the bone. Greig (1928) tried to explain the fact that the frontal bones are the ones chiefly involved by pointing out that in an old and sick person the recumbent posture tends to relax the mechanical approximation of structures, thus favouring the proliferation of bone. Our investigation produced no evidence in support of such a view. The fact that hyperostosis can be found in young people makes this theory untenable, at least in a proportion of cases, and our case material proves convincingly that hyperostosis is not due to senility. Apart from these objections, it is quite obvious that the common forms of brain atrophy do

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not provoke any bony reaction of the nature of cranial hyperostosis. Some proliferation of bone occurs occasionally in the conditions associated with old age. Such bony changes, however, cannot be regarded as part of Morgagni's syndrome.

The diffuse non-specific fibrosis of the lung, with the rarely observed calcification of the small bronchioli, demands special consideration. The origin of the fibrosis is obscure. There was no history of pneumonia and no signs of tuberculosis. The condition of the lungs in Case 2 is all the more interesting, as there were also in Case 1 clinical symptoms of a diffuse fibrosis of the lungs. It is possible that the association of a chronic fibrosis of the lungs with cranial hyperostosis in two of our cases is not merely a coincidence and may reflect some general constitutional or metabolic disturbance responsible for both. It is possible that the tendency to calcium retention and deposition, which favours an increase in the deposition of bone, has produced the calcification of the bronchioli. It is, however, unlikely that this calcification played an important part in the causation of the fibrosis.

Turning to the endocrine glands, changes in the pituitary alone have been recorded in the literature. Stewart (1928) found in one of his cases a marked sclerosis in the anterior lobe, and a deficiency in the chromophil elements. In a second case he found increased connective tissue, the cells of the anterior lobe shrunken and reduced in number. F. Henschen reports reduction of the chromophil cells with increase of the acidophil and basophil elements. Fattovich (1938) found a chronic productive interstitial inflammation of the pituitary. The findings in our case do not correspond with those quoted. It is true that there was in our case a certain degree of proliferation of connective tissue in the anterior lobe, but not enough to justify us in naming it a sclerosis of the anterior lobe. However, there appeared to be some increase of the chromophobe elements in the centre of the gland. A small number of lymphocytes were seen. A similar finding might have induced Fattovich to speak of interstitial hypophysitis. There was certainly no increase in the basophile elements. The eosinophils were very numerous, and there was a small eosinophile adenoma, which did not lead to an enlargement of the gland. We believe that in our case the abnormality of the eosinophile elements alone was sufficiently marked as to be regarded as significant.

Investigation by serial sections of pituitaries taken from a large number of elderly subjects free from any obvious endocrinological disorder shows that there is a great variation in their histological structures. These variations are seen in the distribution and ratios of the different cell types, in the accumulation of fibrous tissue (which is not found in the same degree in younger individuals), and in the number of lymphocytes present. There is hardly any pituitary which does not show some degree of abnormality, and caution must be observed in interpreting these findings. It is, for instance, very difficult to be sure if an increase of one of the cell types is the cause of a certain disorder.

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Rasmussen (1928) has shown that there are very great variations in the percentages of the cells of the anterior lobe in normal individuals. Simonds and Brandes (1925) found lymphocytic infiltration in 21 of 200 cases without clinical signs of endocrine dysfunction, and regard it as a sign accompanying chronic infections of some distant organ or of chronic intoxication. We cannot, therefore, do more than make a guarded assumption that in our case dysfunction of the eosinophile apparatus, indicated by an eosinophile adenoma, has acted in part or entirely as the causative factor of this syndrome. This finding compels us to remember that a thickening of the flat bones of the skull is a regular symptom in acromegaly. One can imagine that a localized hyperostosis as in our case is associated with a comparatively minute disorder of the function of the eosinophile cells. In any case, some such suggestion seems to be more in keeping with the features of Morgagni's syndrome than that such a process could have had an inflammatory origin.

The histological investigation of the parathyroids has apparently been neglected in cranial hyperostosis. Disturbance of the calcium and phosphorus metabolism has been suggested by some authors (Greig, 1928; Sherwood Moore, 1936). There is no doubt that the parathyroids of our case showed pathological changes. Probably the unusually small size of three of the four glands can hardly be regarded as important in the present state of knowledge of parathyroid conditions. There was, however, an unusual increase of oxyphil cells in these three glands, otherwise of normal structure, and the fourth gland consisted entirely of oxyphile cells with signs of disintegration of the protoplasm. These findings doubtless indicate an abnormal functioning of the parathyroid apparatus. Investigation of normal parathyroids by Welsh (1898), Erdheim (1903), and the most recent studies by Gilmour (1939) have shown that no normal parathyroid is composed entirely of oxyphile cells, although these elements are increased with advancing years, especially in females. On the other hand, according to Hunter and Turnbull (1931), where there is a definite hyperplasia of the parathyroids with tumour formation the affected gland is frequently composed of oxyphile cells alone. It has been demonstrated that changes suggestive of hyperplasia are often confined to one or two of the parathyroids, the remainder being normal (Albright, Bloomberg, Castleman and Churchill, 1934). It may therefore be concluded that since in our case one gland consisted entirely of oxyphil cells and in the others the number of these cells was obviously abnormally high, there was a parathyroid hyperfunction at some time during life. We are unable to show whether this hyperfunction had existed for a short period during the patient's life, or was still active at the time of her death. Against this assumption it may be argued that in cases reported with a hyperfunction of the parathyroid, the hyperplasia observed has usually amounted to the formation of a parathyroid tumour many times larger than the normal gland. It seems to be reasonable to assume that unless the evidences of hyperactivity of the parathyroid are great, no great

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increase in the size of the gland need be expected. Reiss has observed certain rare cases in which there was hyperfunction without obvious enlargement of the gland. It might also be argued that if there were a hyperfunction of the parathyroid, the calcium and phosphorus metabolism would be affected. It was not possible to estimate the blood calcium and phosphorus in Case 2. No evidence of recent osteoblastic activity was found at the post-mortem investigation, so that it seems probable that active bone formation was arrested or had come to an end some considerable time before death. In Case 3 there was a very slight increase in the blood calcium. Normal levels of calcium and phosphorus have been reported in the literature. It is by no means certain that the blood calcium level at the time of the investigation, when incidentally the bony changes were well established or possibly stationary, represented the calcium level during the active stages of the disease, and even in some cases of typical osteitis fibrosa cystica the calcium and phosphorus level has been found normal (Cuthbertson, 1927). It is possible that the calcium retention in the tissue prevents a rise of the blood calcium. It is not necessary to postulate a continuously high blood calcium, as the bony changes evidently take place slowly and over a long period, and the actual weight of new bone laid down, although striking in the skull, is not in itself very great.

In cases of established parathyroid hyperplasia, two sorts of bony changes are commonly seen—formation of new bone and destruction. In cranial hyperostosis there is no destruction of bone. This cannot be held as an argument against parathyroid hyperfunction, in view of the work of Selye in Collip's laboratory. He has shown that the prolonged injection of very small doses of parathyroid hormone into rats produces an increased bone formation due to multiplication of osteoblasts, but only if the dose is sufficiently increased is there a multiplication of osteoclasts, resulting in destruction of bone, thus producing the complete picture of osteitis fibrosa cystica. It seems very probable that in cranial hyperostosis there is only a slight degree of parathyroid hyperfunction, sufficient to stimulate the action of osteoblasts, but not great enough to cause osteoclasis.

Erdheim (1903) has put forward the suggestion that hyperplasia of bone of any etiology causes compensatory hyperfunction and hyperplasia of the parathyroids. Since Mandl (1926) and others have demonstrated that in osteitis fibrosa cystica the calcium metabolism returns to normal after the removal of the parathyroid growths, the validity of Erdheim's theory is doubtful. (Hadfield and Rogers, 1932, and others). In cranial hyperostosis the demand of calcium is comparatively small and probably is spread over a long period of life. One could scarcely expect, therefore, that there would be any noticeable compensatory hyperplasia of parathyroids.

There is another mechanism which could be responsible for the pathological changes of the parathyroids, i.e. the action of a parathyrotrophic principle of the pituitary, for which there is some experimental evidence. It must be

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considered that in our case an abnormal function of the pituitary may have influenced the function of the parathyroids. It is of interest that in another pituitary disorder—pituitary basophilism—osteoporosis is a common symptom.

With regard to the changes of the adrenal cortex, it must be admitted that similar changes are not rare in adults without signs of endocrine disorder (Goldzieher, 1929). However, according to Cushing and Davidoff (1927), hypertrophy of the cortex, with or without the formation of adenomas, is found consistently in all the various forms of hyperpituitarism. It is not unlikely that in our case the adrenotrophic hormone (Collip, Anderson and Thompson) is responsible for the hyperplasia of the adrenal cortex, although a primary hyperplasia cannot be excluded, especially as virilism, which is an important part of the complete syndrome, occurs in hyperplasia of the adrenal cortex.

It is possible that the moderate atrophy of the thyroid was part of the polyglandular disorder which existed in our case, although it must be remembered that similar changes are sometimes observed in individuals of this age without special endocrine symptoms. Considering the relationship of the thyroid to other glands, especially to the pituitary, it is highly probable that the changes observed in the thyroid in our case are associated with the abnormal function of the pituitary and other endocrine glands.

The pathological findings can be related to some of the clinical symptoms of the case. It is very likely that the symptoms of meningeal irritation were caused by changes in the meninges which, although not of an acute character, were probably still active until the death of the patient. The diffuse degenerative changes of the brain cortex did not produce dementia. It is hardly possible to explain the character of the psychotic symptoms of the patient by reference to the pathological findings in the brain. We were unable to find a satisfactory explanation for the loss of tendon reflexes of the lower extremities. Possibly the slight irritation in the leptomeninges and around the posterior roots of the spinal cord may have been responsible. It is improbable that the small exostosis found in the body of the seventh dorsal vertebra had any pathological effect on the spinal cord. This loss of tendon reflexes, however, may possibly be attributed to some general toxic process, perhaps connected with the severe physical illness from which the patient suffered in the year before her death. Adie has shown that loss of tendon reflexes sometimes appears in various diseases in which the central nervous system is not primarily involved.

The changes in the endocrine glands are no doubt related to the obesity which was a remarkable feature of this patient for many years. We suggest tentatively that her psychotic attitude towards her husband was influenced originally by abnormal changes in her sexual life. These changes might very well be attributed to dysfunction of the pituitary and perhaps of the adrenals.

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SUMMARY.

Three cases have been described in which there was a hyperostosis of the flat bones of the skull with mental changes and signs of endocrine disorder (Morgagni's syndrome). The first case was a young woman in whom there was a diffuse hyperostosis of the vault of the skull with the mental changes of organic dementia. In the second and third cases the hyperostosis was more localized, being especially marked in the frontal and parietal bones. The psychosis in these cases was of the type of a pure paranoia. Both these cases belonged to a family in which the disease appeared to be due to a dominant Mendelian gene. In Case 3 the syndrome was well developed at the age of 31, and in her daughter there was some evidence of hyperostosis at the age of 10.

Clinical signs of meningeal irritation, causing a general hypersensitivity of the surface of the body, were observed in Cases 1 and 2. They are to be regarded as symptomatic of pathological changes in the meninges resulting from the encroachment of the bone.

A fibrosis of the lungs was found in Cases 1 and 2, and may be related to the whole syndrome.

The pathological investigation in Case 2 revealed diffuse degenerative changes of the brain cortex, affecting mainly the frontal and parietal lobes. It is suggested that these changes are largely due to some primary process correlated to the other symptoms of the disease, and the pressure upon the brain surface only contributes secondarily. A certain amount of cell degeneration was found in the region of the nuclei supraoptici.

Pathological changes were found in the pituitary, the parathyroids, the adrenals and the thyroid. The most marked finding in the pituitary was that of an increase of eosinophil cells with a small eosinophil adenoma. There were definite signs of hyperfunction in the parathyroids. The adrenals showed cortical hyperplasia. There was some atrophy of the thyroid.

The opinion is expressed that the variety of forms of mental disorder seen in Morgagni's syndrome is due to the interaction between the mental constitutions of the individuals, and the disorder of the brain and endocrine glands. The distribution and degree of this disorder is in itself subject to great individual variation.

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Bibliography.

Adie, W. J. (1932), *Brain*, **55**, 98.
Albright, Bloomberg, Castleman and Churchill (1934), *Arch. int. Med.*, **12**, 315.
Albright, Castleman and Mallory (1935), *Amer. Journ. Path.*, **11**, 1.
Van Bogaert, L. (1930), *Journ. de Neur.*, **30**, 502.
Carr, A. D. (1936), *Arch. Neurol.*, **35**, 982.
Cassatti, A. (1936), *Radiol. med.*, **33**.
Collip, Anderson and Thomson, quoted by Rolleston.
Critchley, M. (1931), *Lancet*, **1**, 1120.
Cushing, H., and Davidoff (1927), *Mon. Rockef. Inst.*, No. 22.
Cuthbertson, D. P. (1927), *Glasg. Med. Journ.*, **108**, 218.
Dressler, F. (1927), *Virch. Arch.*, **78**.
Erdheim, J. (1903), *Beitr. z. path. Anat. u. allg. Path.*, **33**, 158.
Fattovich, G. (1938), *Riv. Neur.*, **11**, 444.
Fracassi, T., and Marelli, F. (1936), *Rev. Argent. Neur.*, **2**.
Geschickter, Ch. F., and Copeland, M. M. (1931), *Tumors of the Bone*. New York.
Gilmour, J. R. (1939), *Brit. J. Path. a. Bact.*, **48**, 187.
Goldzieher, M. (1929), *The Adrenals*. New York.
Greig, D. M. (1928), *Edin. Med. Journ.*, **35**, 165.
Hadfield, G., and Rogers, H. (1932), *Brit. Journ. Path. a. Bact.*, **35**, 259.
Henschen, F. (1927), *Morgagni's Syndrome*. Jena.
Hunter, D., and Turnbull, H. M. (1931–32), *Brit. Journ. Surg.*, **19**, 203.
Levirot, P. H. (1937), *Hosp. Aid*.
Mandl, F., quoted by Hadfield and Rogers.
Moniz, E. (1938), *Schizophrenie*, **7**, 223.
Moore, Sherwood (1936), *Arch. Neurol. and Psychiat.*, **35**, 975; (1935), *Surg.*, **61**.
Morel, F. (1931), *L'hyperostose frontale interne*, Paris; (1937), *Schweiz. med. Wochenschr.*, **11**, 1235.
Morgagni (1765), *De sedibus et causis morborum*. Padova.
Pende, N. (1931), *Münch. med. Wochenschr.*, **1**.
Rasmussen, A. T. (1928), *Endocrinol.*, **12**, 129; (1929), *Amer. Journ. Path.*, **5**, 263.
Reiss, M. (1936), *Oppenheimer's Handbuch d. Biochemie*, Jena, 3rd vol., 1872.
Roger, A. (1938), *Can. Med. Assoc. Journ.*, **38**, 120.
Rolleston, H. D. (1936), *The Endocrine Glands*. London.
Schiff, P., and Trelles, J. O. (1931), *L'Encéphale*, **26**, 786.
Selye, quoted by Rolleston.
Simonds, J. P., and Brandes, W. W. (1925), *Amer. Journ. Path.*, **1**, 273.
Stewart, R. M. (1928), *Journ. Neur. a. Psychopath.*, **8**, 321.
Welsh, D. A. (1898), *Journ. Anat. a. Physiol.*, **32**, 292.
Yolton, L. W. (1930), *Arch. Pathol.*, **9**, 432.

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