THE JOURNAL OF NEUROLOGY AND PSYCHOPATHOLOGY.

Vol. IV.

MAY, 1923.

No. 13.

Original Papers.

THE PATHOLOGICAL ANATOMY OF THE DUCTLESS GLANDS IN A SERIES OF DEMENTIA PRÆCOX CASES *

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THE question of the possible relationship of the ductless glands to dementia præcox has been very much in the foreground recently. This is due to the growing realization of the importance of the endocrines both in the normal life of the individual and in various pathological conditions, and more specifically to Mott's¹ studies, on which he has based his theory of a primary regressive atrophy of the gonads in dementia præcox. Considerable work, both clinical and anatomical, has been done on the subject by other investigators, with no clear results. Attention has centred chiefly on the reproductive glands, more especially the testicles, although there have been some isolated studies on the other endocrines. The trend of this work has been rather against any close connection between endocrine disorders and dementia præcox. Nevertheless, statements that such and such a condition has been found in so many cases of dementia præcox and inferences drawn therefrom continue to circulate through the literature. A revision of the subject, in both its clinical and pathological aspects, and in the light of recent researches

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on the functions of the endocrines, is needed to determine just how much evidence there really is of a specific relation of disorders of the ductless glands to dementia præcox. The present study is a contribution to the pathological side of the question.

It is evident that the question must be studied and the actual results interpreted from a broader standpoint than has sometimes been done. Simple tabulation of the conditions found in a series of autopsies on dementia præcox patients is futile. Even if the glands are abnormal, as they very frequently are, it does not prove that there is any connection between the endocrine lesion and the mental disease. The gonads and other ductless glands of a dementia præcox patient may be markedly atrophic owing to causes quite apart from the psychosis.

Aside from the mental disease the main factors which must be considered in evaluating the condition of the glands are the age of the patients, the state of nutrition, and the nature and duration of the terminal disease. Until these forces are allowed for, any abnormalities which may be present cannot be laid to the mental disease *per se*. It would seem that previous studies have not emphasized this point sufficiently. Frequently, too, it is impossible to say whether or not a given histological picture is normal. We have a general idea of what the ductless glands should look like, but no normal standards even approaching exactness for the different glands at different ages, and in varying conditions of bodily nutrition and function, nor for the finer changes produced in them by diseases of the other organs.

In reviewing previous studies on the possible relationship of disorders of the ductless glands to dementia præcox it seems to the writer that the objections to be made to some of them are, in the first place, as has been said, that there has been no allowance for factors other than the mental disease; and, secondly, that the cases have been insufficiently controlled. Either no control observations have been made, or cases suffering from other forms of mental disease or clinical cases of diseases of the ductless glands have been used for controls.

The most logical controls for estimating the possible relationship of disorders of the ductless glands to the psychosis are non-mental—cases of approximately the same ages dying of the same somatic diseases. They are obviously particularly necessary for those cases of dementia præcox in which the glands are inactive or show some pathological condition. In the present study we have made an effort to get such control cases from general hospitals, but it is quite a difficult and laborious task, and we have not yet succeeded in 'matching up' all our cases. It was thought, however, that a small number of cases studied critically and intensively in this way would be of greater value than merely a report of the findings in a larger series.

METHOD.

Cases under forty-five years of age were selected, whose histories were sufficiently characteristic to make the diagnosis reasonably certain. Most of the patients had been in various State hospitals in Massachusetts for periods up to twenty-one years. A few were acute patients who were treated at the Boston Psychopathic Hospital. The autopsies were made by Dr. M. M. Canavan, Pathologist to the Massachusetts Department of Mental Diseases. Only those cases were included which had a negative Wassermann reaction and no disease of the pelvic organs.

The glands studied were the gonads, pituitary, thyroid, and adrenals. Several blocks were made from each testicle and ovary. The pituitary was cut so as to include both anterior and posterior lobes in the sections. One section was made from each adrenal and usually several from the thyroid. The paraffin eosin-methylene-blue or hematoxylin-eosin method was used.

The findings in the ductless glands were studied in connection with the history of the patient, the duration of the mental disease, the degree of mental deterioration, the nature of the terminal disease, the state of nutrition, and any data given in the history on the sex life; also any indications in the physical examinations of anomalies that might be due to endocrine disturbances. Unfortunately information on the last two points was always meagre.

Twenty-seven cases, twelve male and fifteen female, were studied in this way. Summaries of the histories and of the findings in the ductless glands are appended to this article.

I. THE SEX GLANDS.

These were studied first, as discussion centres around them at present, and also because, in the testicle at least, histological changes are more readily detected than in the other ductless glands, and it is easier to exclude adventitious influences. The two functions of the gonads, the production of germ cells and of an internal secretion, must be considered somewhat separately.

The most valuable cases for demonstrating the actual uncomplicated conditions in the glands in dementia præcox are those in which the patient died suddenly without antecedent somatic disease. There were four such in the present series, two men and two women. One man, aged thirty-one (case 1), died from œdema of the glottis, due to knotting a towel around his neck during an excitement. The testicles showed scanty spermatogenesis. The duration of the mental disease had been about a year.

The testicles of a man of thirty-five years (case 2), who died during a katatonic excitement, showed very abundant spermatogenesis, also

numerous interstitial cells. The mental disease had been evident for only a few weeks.

Both the women patients (cases 13 and 14) were forty-three years old. One had been in the hospital eighteen months, the other seven years. The first committed suicide by hanging; the second died of asphyxia from aspiration of vomitus. A corpus hæmorrhagicum was present in each case. Primordial follicles were scarce, as would be expected at that age. No controls to these cases, i.e., sudden deaths in mentally normal persons of these ages, have been obtained. The striking point, however, is that in three out of four of these cases of sudden death in dementia præcox patients the gonads are normally active.

a. The Testicles.—The effects of various influences on the gonads are most complicated. The reaction of the testicle to experimental conditions has been studied more than that of the ovary, as it is a simpler gland, both anatomically and physiologically, than the latter, and its state of functional activity is more easily gauged histologically. A glance at some of the recent work on the subject, both experimental and anato-mo-pathological, will illustrate the complexity of conditions. It is relevant also because similar influences may determine to a greater or less degree the state of the glands in dementia præcox subjects.

The testicle is very sensitive to a variety of pathological influences. Mere cessation of spermatogenesis is not necessarily abnormal, as it occurs when it is necessary for the body to conserve its energy, as in fasting and hibernation; but when it is combined with pathological changes in the germinal epithelium and connective tissue it is significant.

The effects of inanition and vitamin deficiencies have been studied by several authors. Lipperstein² found that acute inanition in adult rats produced stoppage of spermatogenesis and degeneration in scattered tubules, and that re-feeding resulted in re-establishment of spermatogenesis and hypertrophy of interstitial cells. Allen³ fed rats on a diet deficient in water-soluble vitamin and produced in the testicles a total degeneration of all germ cells and a hypertrophy of interstitial cells similar to that caused by the *x*-ray. McCarrison⁴ in his study of the pathology of deficiency disease found in beri-beri pigeons a profound atrophy of the reproductive organs, accompanied by a true hypertrophy of the adrenals, with a proportionate increase of adrenalin. The testicles, ovaries, thymus and spleen atrophied out of all proportion to the other organs. The same changes were associated with inanition. Certainly the effect of inanition in causing degenerative processes in the ductless glands must be considered in those patients with dementia præcox who have been tube-fed for long periods, or who have died of wasting diseases. Minor deficiency conditions also are probably not uncommon among chronic mental patients, although they are not

often diagnosed as such. It is quite well recognized, clinically, that a fairly normal level of nutrition is necessary for the functioning of both testicle and ovary.

Taken as a whole, the results of experimental work on the testicle demonstrate that a similar physiological condition may be produced by widely different means, for example, by the *x*-ray, inanition and vitamin deficiencies, by ligating the vas deferens, and by eliminating the sympathetic supply.

Some interesting work has appeared recently on the reaction of the testicle in acute diseases. Mills⁵ studied MacCallum's material of epidemic pneumonia from the army camps. Although there was no striking gross change, there were marked microscopic lesions, a cessation of activity in the seminiferous tubules, frequent degenerative changes, and in late cases the beginning of fibrous replacement of the degenerated tubules. The severity of the injury corresponded directly with the duration of the pneumonia. Wolbach⁶ notes that severe toxic lesions in influenza seem to be confined to the muscles and the testicles.

Meleney⁷ examined the testicles in thirty-eight cases of acute infections (lobar pneumonia, typhoid, peritonitis, etc.). His results agree well with those of Mills. He found that the proportion of cases showing injury to spermatogenesis increased with the duration of the illness, 18 per cent. showing lesions in the first week, and 100 per cent. in the fourth to seventh weeks. The severity of the lesions also increased with the duration of the disease.

The findings in the male cases in our series, in addition to the two which have already been described, are as follows: Case 3, patient aged forty-two, dying of cerebral hæmorrhage and chronic interstitial nephritis, showed active spermatogenesis. There was thickening of the hyaline membrane and of the arteries. This was a much-deteriorated patient, who had been in the hospital twenty-one years.

A case of the paranoid form (case 4) in a man of thirty-five, dying from septicæmia and acute vegetative endocarditis, presented active spermatogenesis. There were numerous hyaline tubules, but no thickening of connective tissue. The duration of the mental disease had been at least seven years.

A man dying at twenty-two from sepsis (case 5), with a history of mental disease of four and a half years' duration, showed atrophy of the seminal epithelium with scanty spermatogenesis. The patient had extensive cellulitis of the leg, also bedsores and septic pneumonia, and was extremely emaciated at the time of death.

A katatonic of twenty-eight (case 6), dying of miliary tuberculosis, showed extreme atrophy of the tubular epithelium and thickening of the hyaline membrane, connective tissue and vessels. Interstitial cells were present in good numbers. The conditions are in contrast to the control

specimen, in which spermatogenesis was active and the connective tissue was not increased. This would seem to be a clear-cut contrast and in line with Mott's theory, except for the fact that the dementia præcox patient had been in a katatonic stupor for three years, in bed and tube-fed most of the time, and was much emaciated at the time of death, while the control patient was fairly well nourished.

In cases 7 and 8, the patients, aged thirty-five and forty-four, died of pulmonary tuberculosis. There was in the testicles of both cases an absence of spermatogenesis, atrophy of the germinal epithelium, and beginning fibrosis. The control specimen, however, presented even more marked atrophy than the dementia præcox cases. It is well known that tuberculosis can cause a fibrosis of the ductless glands, even when they are not directly affected by the disease. This is true not only for the gonads, but also for the hypophysis, thyroid and adrenal, as is emphasized by the findings in these endocrines in the present series. Cordes⁸ as long ago as 1898 pointed out these changes in the testicles of tuberculous patients.

In one case (case 9) the testicles were undescended, and, as would be expected, were inactive and sclerotic. Moderate numbers of interstitial cells were present.

In three patients the dementia præcox was said to have developed on a basis of feeble-mindedness. The conditions in the gonads of the first case (case 10) were quite striking. The patient was a seventeen-year-old coloured boy, having a mental age of nine and a half. He was well developed and well nourished and showed no obvious signs of endocrine anomaly. He was effeminate in manner, timid and emotional, and inclined to homosexuality. He died of chronic nephritis. The testicles are noted as being small and not threading. Microscopically, the tubular epithelium is poorly differentiated; in some places there are small numbers of spermatocytes, in others only sustentacular cells are present. The hyaline membrane is thickened, and the connective tissue is much increased and is œdematous. The arteries are thickened. There is a mild focal lymphocytic infiltration. Interstitial cells are very numerous. The condition seems to be one of non-development with superimposed chronic inflammatory changes. The control specimen showed a good development of the seminal epithelium, a few spermatozoa, and an absence of fibrous and inflammatory changes.

The second case (case 11) was a young man of eighteen, who died of lobar pneumonia. He was well developed and showed no abnormalities of endocrine origin. There was active spermatogenesis, and motility of the spermatozoa was demonstrated ten hours post-mortem. There was some thickening of connective tissue, and one area of chronic inflammation with lymphocytes, increase of connective tissue and atrophy of tubular epithelium.

The third case was a much-deteriorated patient of forty-three, who had an organic disease of the cord, diagnosed as amyotrophic lateral sclerosis. He died of lobar pneumonia. There was almost no spermatogenesis, some atrophy of the tubular epithelium, and a considerable increase of connective tissue. Interstitial cells were abundant. The control showed moderate spermatogenesis and no increase of connective tissue or interstitial cells.

It is, of course, well recognized that many of the feeble-minded give evidence of endocrine abnormalities. These have been reported clinically, and some descriptions of the gross anatomy of the various glands have been given, but there seems to have been no work done on the histology of the endocrines in a series of mental defectives. It is a subject that would undoubtedly repay study, especially if made in connection with the clinical histories and physical findings.

In regard to the numbers of interstitial cells in this series of cases, it is difficult to make any definite statement. They were abundant in some sections, and in others present in only moderate numbers. It is hard to say whether they are increased unless they are very obviously so, forming large collections between the tubules. This was the case in the feeble-minded coloured boy described above. The numbers of interstitial cells vary not only at different periods of life, but also with the condition of the tubules. Atrophy of the germinal epithelium from any cause is usually accompanied by proliferation of the interstitial cells. It is claimed that they hypertrophy at the beginning of acute infections, and that later they atrophy. As has been said, they increase in inanition. Taking everything into consideration, therefore, it would be extremely hypothetical to ascribe any variations which might be found to the dementia præcox process *per se*.

Mott states that in his cases the degree of atrophy of the sex glands was in proportion to the duration of the mental disease and the degree of psychic deterioration. We have analyzed our own data from this standpoint, with negative results. As stated above, the testicles were active in the much-deteriorated patient who had the longest known duration of the disease in the entire series (twenty-one years), and inactive in the youngest member of the group, the seventeen-year-old boy, whose disease had been evident only a few months. The condition of the glands seems to depend on the nature of the terminal disease, the state of nutrition, and possibly in some instances on whether there is an underlying defect in development which is expressed in feeble-mindedness, rather than on the duration of the mental disease.

b. The Ovaries.—The function of the ovary is extremely complex, and many points concerning it are still in dispute. The considerations which are of immediate importance in the present study are, in barest outline, first, the question of secretion. It is generally recog-

nized that the thecal cells produce a secretion. This is present before puberty as well as during the reproductive life, and there is evidence that it presides over the development of the secondary sexual characteristics. The corpus luteum also produces a secretion which inhibits ovulation, and is responsible for the cyclic changes in the endometrium, the object of which is the embedding of the fertilized ovum. Degeneration of the corpus luteum brings about menstruation, or if the individual is pregnant, abortion.

The second question having a special bearing on both the methods and conclusions of the present investigation is: What are the histological criteria of the functional state of the ovary, and also is it possible with ordinary histological methods to make any statements as to whether the number of ova in any given gland is normal or reduced? It may be said without further discussion that the presence of developing follicles and of corpora lutea, and a non-atrophic genital tract, are sure signs that the ovary is working, and, so far as one can say, normally.

The other point is more difficult. Counting primordial follicles in dementia præcox and control cases would be indecisive unless serial sections were studied. Quantitative analyses of normal ovaries have been made by the serial section method as contributions to normal histology, but for a number of cases such as ours it would be an impossible task. Little can be inferred from examination of a few sections as to the actual or comparative numbers of primordial follicles in the ovaries because their distribution is irregular, some sections containing few, and others from the same case many. It is not known whether they are more abundant in one part of the ovary than in another. The controls to cases 17 and 18 illustrate the great differences in the number of ova seen in sections of normal ovaries. Both patients were young women of normal mental and physical development and active sex life. They were both married, and the first had had one pregnancy, the second patient two pregnancies. Primordial follicles were very numerous in the second case, while in the first they were fewer in number than in some of the dementia præcox patients. This simply demonstrates how fallacious any conclusions as to an abnormal diminution of primordial follicles in the ovaries of dementia præcox patients might be unless they were based on serial sections.

Forster⁹ studied the ovaries in 100 cases of mental disease, including dementia præcox, epilepsy, mental defect, etc. According to the description of the method, which is not very clear, the ovaries were embedded in serial blocks in celloidin, and when the follicles were scanty, serial sections were cut. In other cases, a series was cut only from one block. The author counted the largest number of follicles present at any one level throughout the sections examined. According to the table, there was great variation in the number of ova seen in all the types of

cases, and in some of the control cases there were very few follicles, fewer, in fact, than in the majority of the dementia præcox cases. She concludes, however, that the ovaries of all dementia præcox women who had reached the age of thirty showed signs of early involution, and that even below that age there was a distinct diminution of follicles compared with a normal woman of the same age. The terminal diseases in these cases are not stated. Leaving aside the adequacy of the method, the conclusions do not seem to be borne out by the actual findings.

Mott stresses the degenerative processes found in the follicles in dementia præcox patients. Follicular atresia is, however, a normal process, beginning at or even before birth and continuing until the menopause, causing the destruction of tens of thousands of ova. Out of the enormous numbers of follicles present at birth, only 400 to 600 ever reach maturity. Follicular atresia may, of course, become pathological if it is carried to excess and is combined with other abnormal conditions, as in the 'interstitial oöphoritis' of former gynæcological fame, but this does not come especially into consideration in dementia præcox. There seems, moreover, to be some evidence that excessive atresia is associated with menorrhagia, not with amenorrhœa. The latter would, of course, be more in accord with a premature atrophy of the ovary, such as has been assumed in dementia præcox.

The result of these considerations is that we may conclude from histological data that the ovary is active, but that we cannot say much about the absolute number of follicles present, nor whether there is an abnormal diminution in their number or an excessive atresia.

The third consideration for our purpose is that the ovary is extraordinarily sensitive to various influences. Histological proof of this is less easy to bring than in the case of the testicle, but clinically it is evidenced by the frequency of disorders of menstruation from a wide variety of causes. An illustration on a large scale of the effect of under-nourishment on the ovary was the war amenorrhœa among the women of the Central Powers. Loeb's¹⁰ experiments on guinea pigs show that in conditions of pronounced under-nourishment the follicles cease to develop and begin to retrogress before they have reached medium or large size. The ovary is also affected in infectious diseases, and even by psychic disturbances, perhaps through the medium of the other ductless glands.

Turning to the actual conditions found in our female cases, nine of the fifteen, including the two cases of sudden death, showed corpora lutea and developing follicles. The ages of these patients ranged from twenty-three to forty-three years. The terminal diseases were chronic interstitial nephritis, acute parenchymatous nephritis, bronchopneumonia, septicæmia, influenza, and pulmonary tuberculosis. Examples of these cases are given below.

A paranoid dementia præcox patient (case 15), of at least six years' duration, dying at forty-three from chronic interstitial nephritis, had an active ovary, quite as active, in fact, as the control.

Similarly, the ovaries of case 16, dying at thirty-five from acute parenchymatous nephritis, did not differ essentially from the control. Both contained corpora lutea and numerous primordial follicles.

A woman dying at twenty-four from septicæmia (case 17) showed several corpora lutea and maturing follicles. The control case had equally active ovaries.

A patient with mitral stenosis (case 18), aged thirty-three, in whom the immediate cause of death was influenza, showed a corpus hæmorrhagicum, some recent corpora lutea, and some small follicular cysts. Ova were scarce, and the arteries were much thickened. A control influenza case also had an active ovary, although only a few primordial follicles were seen. A control case of mitral stenosis showed a recent corpus fibrosum, one developing follicle, and rather small numbers of ova.

Five of the six patients whose ovaries contained neither developing follicles nor corpora lutea died of pulmonary tuberculosis. Two were over forty. The atrophic state of the ovaries is not surprising in view of the effect of the tuberculous process on spermatogenesis. In fact, the conditions are analogous.

Two of the women in this last group presented signs of infantilism, both in general make-up and in the genital tract. The first patient (case 26) died of mitral stenosis, at the age of thirty-three. She was under-sized and undeveloped, and the secondary sexual characteristics were poorly differentiated. The breasts were undeveloped, and the external genitalia infantile. Menstruation had begun at fourteen, and had been irregular and painful. The uterus was small and retroflexed. The ovaries contained several corpora fibrosa, very few primordial follicles, and no developing follicles or corpora lutea. The control specimen showed more primordial follicles, although they were not numerous, a developing follicle, and a recent corpus fibrosum.

The other case (case 27) was a woman of twenty-three, in whom the dementia præcox had developed on a basis of feeble-mindedness. Her appearance was immature; the breasts were undeveloped, and the body hair scant. Menstruation had begun at twelve and had been regular, at least before the patient entered the hospital. The ovaries were large and flat. Primordial follicles were rather scarce, and there was an excess of connective tissue in the cortex. Numerous corpora fibrosa were present, and two small follicular cysts, but no developing follicles or corpora lutea. The uterus was small and fibrous.

The frequency of genital infantilism or of some of the manifestations of the hypoplastic constitution in dementia præcox patients has impressed a number of observers. Gibbs¹¹ has very recently studied

the sex development and behaviour of a series of dementia præcox patients, and has noted the frequent absence of "the finishing touches of physical maturity." The presence of a genital infantilism may account for some of the anatomical reports of inactive and fibrous gonads in dementia præcox patients. Nevertheless, this idea should not be generalized too widely, for according to our experience inactivity of the sex glands is far from being the rule in this disease, and when it is present there are usually more immediate causes to account for it.

II. THE HYPOPHYSIS.

A special importance attaches to the examination of the hypophysis in dementia præcox, as its inter-relation with the gonads is closer than with any of the other endocrines. It influences both the development and the function of the sex glands. If a condition of hypopituitarism comes on before puberty, there is a tendency to the persistence of sexual infantilism ; while if it occurs after puberty, there is likely to be atrophy of the gonads and some loss of secondary sexual characteristics.

The hypophysis was available in twenty-one of the twenty-seven cases in this series, nine men and twelve women. There were no signs of hypopituitarism recorded in the physical examinations or autopsies.

The finer histology of the hypophysis in normal conditions is still undetermined, and very little is known of the reaction of the gland to abnormal influences, such as infections. The mutual relationships of the different types of cells are still unsettled. Some investigators believe that the three types, the chromophobes and the two varieties of chromophils (eosinophils and basophils), represent different functional states of one kind of cell. Others consider that the chromophobe is the primary cell and that the acidophils and basophils develop from it in two divergent directions, with perhaps two specific secretions.

The arrangement and numbers of the different kinds of cells vary considerably in different parts of the anterior lobe, so that it is impossible to make any reliable statements as to the predominance of any cell type unless a number of sections are cut from different areas. The exceptions to this are pregnancy and conditions of supposed hyperplasia, in which there is an easily recognizable overgrowth of large chromophobe cells. Doubtless, changes in the relative numbers of the different cells do occur in various conditions, but these finer variations cannot be recognized with any certainty from one or even from several sections of the same gland. No work has been done to determine the general amount of variation in the cell picture among sections from different parts of the anterior lobe. Until some approximate standards have been established on this point it is impossible to say how much can be inferred as to predominance of cell types from examination of a single section. Cushing¹² speaks of the variations in the pars anterior as being so kaleido-

scopic that there seems to be no fixed adult type of 'normal' gland; but apparently a considerable number of generalizations in the literature as to the effects of various conditions on the cell type in the anterior lobe have been made on the basis of comparatively few sections.

For the reason given above we are unable to say anything definite as to the cell picture in the anterior lobe in our dementia præcox cases. A better knowledge of the changes which occur under the influence of various physiological and pathological states is necessary before we can interpret the pictures found in dementia præcox. As a matter of fact, there are considerable differences in the relative proportions of the cell types in sections of the anterior lobes, but they cannot be correlated with any other conditions present.

There are certain other findings, however, which are of interest. In several glands the pars anterior cells were small and closely packed, the nuclei dark staining, and the cell granules inconspicuous, the general picture being one of inactivity. This was accompanied by a mild thickening of the stroma. All the glands showing this condition came from cases of pulmonary tuberculosis, but not all the tuberculous cases showed it. The sex glands were inactive in most of these cases.

Nine of the twenty-one glands showed a degree of fibrosis ranging from moderate to marked. This appeared as a general thickening of the framework, as scattered foci of connective tissue in the interior of the gland, as ingrowths from the capsule, and quite frequently as a radiation from the region of the pars intermedia. There is normally a spot of connective tissue in the centre of the anterior lobe, and some slight spreading of connective tissue into the anterior lobe from the pars intermedia is found so frequently that it can scarcely be called abnormal. These pituitaries showing overgrowth of connective tissue were found in several of the cases of tuberculosis, two cases of chronic nephritis, two cases developing on a basis of feeble-mindedness (one the boy of seventeen referred to above), and the case of sudden death from œdema of the glottis. In all except one of the male cases there was a coincident fibrosis of the testicle. It was more difficult to judge of a similar change in the ovary. Evidently, therefore, the fibrosis found in the testicle in some cases of dementia præcox is not an isolated phenomenon, as a similar condition affects also the hypophysis.

In regard to the functional state of the sex glands in the cases in which the pituitary was examined, five of the nine cases with fibrosis in the pituitary had inactive sex glands (male three, female two), two showed slight activity (male), and two were active (female). Of the twelve cases showing no fibrosis, nine had active sex glands (three males, six females), and two inactive (males). The case of undescended testicles also had no fibrosis in the pituitary. In other words, in cases in which there was some fibrosis in the pituitary, the sex glands were

inactive or only slightly active in 77 per cent. of the cases ; while in those having no fibrosis in the pituitary they were active in 75 per cent. of the cases. Putting the matter in another way, of the seven inactive or slightly active testicles in the series in which the pituitary was examined, five were associated with fibrous pituitaries, and the two cases with inactive ovaries both had fibrous pituitaries. In the three cases presenting active spermatogenesis there was no fibrosis in the pituitary. Of the eight active ovaries, six were associated with no fibrosis in the hypophysis. These results show that there is a tendency for inactive gonads to be associated with some degree of fibrous increase in the pituitary.

In only one patient dying of an acute disease or by accident was there a fibrous pituitary.

In the hypophysis of the patient dying during a katatonic excitement there was intense congestion of the anterior lobe. Numerous acini were filled with a finely granular material staining faintly with eosin, apparently a secretion, which seemed to be continuous with the cytoplasm of the eosinophilic cells which lined the acini.

Several questions arise in connection with these glands. Is the fibrous increase in the pituitary at all characteristic of dementia præcox, or is it found as often in other cases ? Is it connected more closely with the state of the sex glands than with the other endocrines ? If so, is the fibrosis in both organs due to a common cause, and is this one which acts especially in dementia præcox—a primary sclerosis, as has been inferred by Mott—or does it depend rather on chronic somatic conditions ?

For control hypophyses it was necessary to use those in the collection of the pathological laboratory of the Massachusetts Department for Mental Diseases, as the gland is seldom removed at autopsies in general hospitals. There were, however, in this collection a number of cases of epidemic encephalitis and other non-psychotic conditions, a large number from middle-aged, elderly and tuberculous mental patients, other than dementia præcox, and a few from the feeble-minded. In all but one of the non-tuberculous cases under forty years there was no fibrosis in the pituitary, and the sex glands were active. These patients all died of fairly acute diseases. The one case showing increase of connective tissue in the pituitary had a similar condition in the testicle. These findings agree quite well with the results in dementia præcox patients who died of acute diseases. In the middle-aged and elderly individuals there was much variation, some having marked fibrosis, while others, even some elderly persons dying from manifestations of arteriosclerosis, showed none. All the cases of pulmonary tuberculosis had fibrosis, usually of a marked degree. It may come on in young tuberculous subjects, as an advanced fibrosis was found in a sixteen-

year-old girl. This emphasizes once again the sclerosing effect of the tuberculous process which was demonstrated in the reproductive glands. The conditions in the feeble-minded varied, some glands having no fibrosis, and others, even in young people, a marked diffuse overgrowth.

To anticipate the findings in the thyroid and adrenal, it may be said here that fibrosis in the pituitary is more closely linked with a similar process in the gonads than is the case with the other endocrines.

The evidence at hand, therefore, seems to show that fibrosis in the pituitary and the gonads has some special inter-relation, but that this is by no means peculiar to dementia præcox. It seems to depend rather on the nature and duration of the terminal disease and the state of nutrition.

III. THE THYROID.

In the thyroid the situation as to evaluating the histological picture is similar to that in the pituitary. There are considerable differences in histological appearances in various parts of the same gland. In addition to these regional differences, the range of normal histological variation has not been determined. Another difficulty is that ordinarily the whole gland is not removed at autopsy, but only a small specimen is secured from one lobe.

Pieces of the thyroid were available from fifteen cases, eight male and seven female. The considerations given above make any generalized statements as to the conditions found of limited value. Taking the sections as they stand, however, the two facts which are apparent are that pathological conditions are less frequently found in the thyroids of this series than in the gonads, and that a tendency to fibrosis is present in the thyroid as well as in the sex glands and the hypophysis. Considering how sensitive the thyroid is to a variety of conditions, one is rather surprised to find how few signs the glands in this series show of past or present strain.

Sections from seven of the thyroids contained resting colloid tissue only. In six more there were in addition some few acini showing active secretion. Three of these thirteen glands presented some focal fibrosis, which in one was progressing actively. The normal resting or slightly active thyroids came from one of the cases of sudden death, from the case dying during katatonic excitement, from a case of chronic nephritis, one of fibrinous pleuritis, and the remainder were cases of tuberculosis. It is rather interesting that the section from the patient dying in a katatonic excitement showed only very slight signs of activity. The most active specimen was from the feeble-minded coloured boy. The thyroids presenting moderate fibrosis in addition to otherwise normal colloid gland were from cases of tuberculosis, pneumonia and septicæmia.

Sections from two glands showed a moderate hyperplasia with marked focal fibrosis, combined in one instance with collections of lymphocytes. One was from a man dying at thirty-five from tuberculosis; the other from the woman of forty-three who died from asphyxia. Marine¹³ considers that an increase of connective tissue in the thyroid is explained most rationally as a part of a general thyroid reaction during active hyperplasia and its persistence after the epithelial cells have died. According to this interpretation, a fibrosis in the thyroid would signify neither an atrophic nor an inflammatory condition. In three of our cases, however, the usual sign of previous hyperplasia, i.e., a colloid goitrous condition, was absent. In some of the cases, also, with fibrous increase in the thyroid there was a similar condition in the sex glands and the hypophysis. Lymphoid tissue is normally present in the thyroid, and it increases in conditions of hyperplasia of the gland.

Reviewing the condition of the sex glands and the pituitary in the cases in which the thyroid showed fibrosis: In two there was marked fibrosis in the testicles and pituitary. In one case spermatogenesis was active, there was no fibrosis, and the pituitary had only a slight increase of connective tissue. In the two female patients the ovary was active in one, inactive in the other, and the pituitaries were not available. Again we see that the fibrosis in the gonads is not an isolated finding, but it appears also in the other endocrines. We do not wish, however, to over-emphasize the changes in the thyroids, as they were rather mild on the whole, and, as has been said, represent the conditions in only one part of the gland.

IV. THE ADRENALS.

The entire question of the physiological importance of the adrenal is at the present time under revision. From the standpoint of pathological anatomy alone, rather few lesions have been identified. The most important of these are congenital anomalies, tumours, tuberculosis, and the changes which result from acute and chronic infections and intoxications and from inanition. Very little is known of the pathology of the adrenal in relation to the other endocrines, aside from the over-function of the cortex, which is associated in children with sexual precocity, and in adult women with the development of male secondary sexual characteristics. The gland, and more especially the cortex, hypertrophies during pregnancy. The cortical portion is supposed to have a stimulating action on the gonads, but not on the other ductless glands.

The adrenals were examined in twenty-five of the twenty-seven cases in this series. The abnormalities found seem to be sufficiently accounted for by the diseases to which the patients succumbed, as they were such as are usually associated with those diseases, and were of the same general nature in all of a given class of cases.

In the patients dying suddenly from accident, the cortex contained a good amount of lipoid, and the glands were not remarkable in any way. These patients were well nourished and in good physical health. In the septic conditions the lipoid was greatly diminished, the cortical cells showed parenchymatous degeneration, and in one instance there were areas of necrosis in the cortex. The glands were usually markedly injected. In the tuberculous patients the lipoid was small or moderate in amount, the capsule was often thickened, and collections of lymphocytes were frequent. The cases of chronic nephritis had large amounts of lipoid. Degenerative changes and variations in the lipoid content are well recognized in these diseases.

It may be of interest to mention here that the peculiar hyaline or colloid droplets in the adrenal medulla, which are described by Mackenzie¹⁴ as occurring very commonly in influenza, were found in abundance in our one example of the disease. Their origin is unsettled. They are not confined to influenza, but are found also, though infrequently, in other acute infections.

The effects of inanition on the adrenals have been studied by Jackson¹⁵ for the rat, and by Byrne¹⁶ and Meyer¹⁷ for man. In chronic inanition in adult rats there is a variable amount of degenerative change in the cortical cells, combined with simple atrophy, and less marked changes in the medulla, with no decrease in the chromaffin reaction. The lipoid is usually decreased. Byrne noted an enlargement of the adrenals, particularly of the cortex, in autopsies on prisoners in German prison camps. This may have been the result of the quality as well as the quantity of the food, for McCarrison⁴ found that a scorbutic diet produced in guinea pigs a congestion and enlargement of the adrenals, the changes in the glands being present before symptoms appeared. Meyer, in an autopsy on a man who died after fasting for sixty-three days, found extreme disintegration of the cortical cells.

Eleven of our cases were markedly emaciated at the time of death. None were uncomplicated cases of inanition, although several had been tube-fed for considerable periods. Most of them died from tuberculosis or sepsis. The adrenals showed no special peculiarities macroscopically, and were neither markedly increased nor decreased in size. The amount of lipoid was variable, in some instances, especially in the septic cases, being greatly reduced, in others being present in moderate amounts. Foci of lymphocytes, especially in the medulla, were frequent. These were much more common in the emaciated cases, though occasionally present in other conditions. Sometimes they were coincident with collections of lymphocytes in the thyroid, but more frequently not.

The condition of the adrenals in the patient dying in a katatonic excitement is especially interesting from the viewpoint of the reaction of these glands to muscular fatigue. The patient was in the Boston

Psychopathic Hospital for four days preceding death, and was noisy and violent during the entire time. He was entirely sleepless for the first two days, and during the last two he slept only from one to three hours daily. The immediate cause of death was acute cardiac dilatation. The cells of the adrenal cortex were small and stained intensely. Staining with Scharlach R showed that the lipid had disappeared except in small groups of cells in the outer zone. The medulla was extremely congested. As far as could be judged from ordinary Zenker fixation, there was a fair amount of chromaffin material. Laignel-Lavastine¹⁸ reports six cases of mental disease ('mental confusion,' 'acute mania,' Huntington's chorea, and dementia præcox), dying after prolonged and intense motor agitation, in which he found complete absence of lipid in the adrenal cortex. Mulon and Porak¹⁹ had previously noted the absence of lipid in a case of Huntington's chorea.

CONCLUSIONS.

The gonads, pituitary, thyroid, and adrenals have been studied in twelve male and fifteen female cases of dementia præcox dying under forty-five years of age. This has been done as far as practicable in connection with control non-psychotic cases of approximately the same ages dying of the same diseases.

An effort has been made to emphasize the sensitiveness with which the ductless glands react to various influences, and consequently the complexity of the problem of interpretation of the changes which are actually found in them in dementia præcox.

In regard to the gonads, the crude results are that sixteen patients had active glands, using as criteria the presence of spermatogenesis and of maturing follicles and corpora lutea. The patients dying of accident or of acute diseases had active glands, with the exception of one case, in which there was only slight spermatogenesis. In tuberculous cases the gonads were atrophic, and the testicles showed fibrosis. The patients who were emaciated at the time of death also had inactive glands. In two of the patients in whom the dementia præcox developed on a basis of feeble-mindedness the testicles showed abnormalities. Two of the women (one originally feeble-minded) presented signs of a genital infantilism. Further study of the endocrines in the last two groups of dementia præcox patients, i.e., of the mentally inferior and of those who show stigmata of the hypoplastic constitution, is indicated.

When the tuberculous cases, those developing on a feeble-minded or hypoplastic basis, and those dying of wasting diseases are subtracted, the remainder have active gonads.

There was no correlation between atrophy of the sex glands and the duration of the mental disease or the degree of psychic deterioration.

The conditions in the sex glands of the controls were essentially the

same as in the dementia præcox cases for the same terminal diseases, with the exceptions of the feeble-minded, the infantile and the emaciated cases.

The pituitaries in a little less than half of the cases presented a fibrosis, which could be correlated to some extent with a similar condition in the gonads. As demonstrated by controls, this fibrosis in the pituitary is not peculiar to dementia præcox, but depends rather on the nature and duration of the terminal disease and the state of nutrition.

The lesions in the adrenals were such as are usually found in the diseases to which the patients succumbed.

The thyroids showed changes less frequently than the other endocrines. There was occasionally a mild glandular hyperplasia or increase of connective tissue.

The influence of tuberculosis in producing a fibrous increase in the ductless glands, particularly the gonads and pituitary, has been emphasized once more by the study of this series.

From the pathological side there is very little evidence of a primary atrophy of the gonads in dementia præcox, with the possible exception of those cases developing on a basis of mental defect. The fibrosis which is sometimes found in the sex glands is not an isolated change, but is frequently present also in the hypophysis and occasionally in the thyroid. The atrophy, when present, can be accounted for by the somatic diseases from which the patients suffered. This explanation is not only simpler and less hypothetical than that of a primary atrophy, but it is more in accord with the facts if they are critically studied. It agrees also with recent experimental and pathological work on the ductless glands, particularly the gonads.

The condition of the endocrines in dementia præcox requires far more study, both clinical and anatomical, but sufficient work has already been done to demonstrate that the actual state of the glands is very variable. There is no one uniform condition of the gonads or other endocrines in dementia præcox, dependent on the disease process. The main factors which determine the condition of the glands at autopsy are the nature and duration of the terminal disease, the state of the nutrition, and possibly in some instances an underlying defect of development which is expressed in feeble-mindedness or the hypoplastic constitution.

SUMMARIES OF CASES.

1. M. 31. Seclusive make-up. Good student; high school graduate. Economically inefficient. The onset of the disease was with somatic ideas and a religious trend. Emotional reaction shallow. Physical examination not remarkable. Fairly well nourished. The patient passed into an excited

inaccessible state. Death from œdema of the glottis. Known duration of the disease, about one year.

Testicles.—Scanty spermatogenesis. No increase in connective tissue. Interstitial cells present in moderate numbers.

Pituitary.—Considerable diffuse fibrosis in the anterior lobe.

2. M. 35. Jewish. Quiet, industrious, thrifty. Twice married. First wife ran away. Three children. There is an indefinite history of an illness for two months, which prevented patient from working. This was followed by a sudden outbreak of excitement. His dead father was choking him and his brother trying to shoot him. Violent excitement of seven days' duration. Death from acute cardiac dilatation. Well-nourished man.

Testicles.—Very active spermatogenesis. Abundant interstitial cells. Focal increases of connective tissue.

Pituitary.—Intense congestion. Large masses of granular eosinophilic material (secretion ?) in anterior lobe. No fibrosis.

Thyroid.—Mostly resting colloid gland ; occasional signs of activity.

Adrenals.—Practically no lipid. Intense congestion of the medulla.

3. M. 42. Hospital residence of twenty-one years, during the first part of which he was hallucinated, noisy, impulsive, and inaccessible. Later he became extremely deteriorated, apathetic, unoccupied, and untidy. Death from cerebral hæmorrhage and chronic interstitial nephritis.

Testicles.—Active spermatogenesis. Thickening of hyaline membrane and arteries. No increase in connective tissue. Interstitial cells scarce.

Thyroid.—Mostly resting colloid ; a few active follicles.

Adrenals.—A large amount of lipid.

4. M. 35. A long history of auditory hallucinations and ideas of persecution, to which the patient reacted with violence. Poor judgment and no insight. He had been in mental hospitals both in England and in the United States. Well developed and well nourished. Died from septicæmia.

Testicles.—Active spermatogenesis. Abundant interstitial cells. Numerous hyaline tubules. No increase of connective tissue.

Pituitary.—Slight thickening of stroma.

Thyroid.—Mostly normal resting gland. A few foci of young connective tissue overgrowth, associated with collections of lymphocytes.

Adrenals.—Areas of necrosis in cortex. Foci of lymphocytes.

5. M. 22. Jewish. Egoistic, seclusive, precocious. College graduate. The patient had not been normal since eighteen years of age, when he was disappointed in obtaining a teaching position. He became 'nervous' and depressed and developed ideas of reference. Had done no work since his breakdown. In the hospital six months, during which time he was excited and inaccessible, probably hallucinated. His productions were incoherent. He showed mannerisms and was untidy. Died of sepsis. Extremely emaciated at the time of death.

Testicles.—Tubular epithelium thin and spermatogenesis scanty. Interstitial cells numerous. No increase in connective tissue.

Adrenals.—Cloudy swelling of cortical cells. Marked injection. Collections of lymphocytes.

6. M. 28. Seclusive make-up. At twenty-one he became infatuated with a girl. He soon became depressed, had disturbing dreams, and developed ideas of reference. In the hospital he was resistive, mute and untidy. He was in a katatonic stupor during the last three years of life. Much emaciated. Death from miliary tuberculosis.

Testicles.—Extreme atrophy of seminal epithelium. Thickening of hyaline membrane and vessels. Increase of connective tissue and slight lymphocytic infiltration. Interstitial cells numerous.

Pituitary.—Marked fibrosis in anterior lobe.

Thyroid.—Normal resting colloid gland.

Adrenals.—Moderate amount of lipoid.

Control.—M. 26. Died of miliary tuberculosis. Fairly well nourished.

Testicles.—Active spermatogenesis. No fibrosis. Interstitial cells present in moderate numbers.

7. M. 35. Duration of psychosis thirteen years. Died of pulmonary tuberculosis.

Testicles.—Moderate atrophy of seminal epithelium. A few spermatozoa present. Interstitial cells abundant. Moderate fibrosis.

Pituitary.—Considerable fibrosis.

Thyroid.—Slight hyperplasia of gland tissue. Collections of lymphocytes. Marked focal fibrosis.

Adrenals.—Moderate amount of lipoid. Thickening of capsule.

Control.—M. 31. Died of pulmonary tuberculosis.

Testicles.—More atrophy of tubular epithelium than in dementia præcox case. No spermatozoa. No fibrosis. Interstitial cells scarce.

8. M. 44. Married and had one child. He had been in different State hospitals for over fourteen years. Early in his hospital residence he had very active auditory and visual hallucinations and fragmentary delusions, especially of influence. There was progressive dementia, and at the time of death he was much deteriorated. Died of pulmonary tuberculosis.

Testicles.—Resemble those of case 7.

9. M. 39. Hospital residence of eighteen years, in the earlier stages of which the patient showed excitement, impulsive reactions, hallucinations, and expansive delusions. There was progressive deterioration, and for several years before death he was extremely demented. He was fairly well developed and nourished. Beard scanty. Distribution of hair on trunk and extremities abnormal. Genitalia poorly developed. Death from fibrinous pleuritis and hydrothorax, following a fractured rib.

Testicles.—In inguinal canal. Tubular epithelium undifferentiated. Moderate numbers of interstitial cells. Much fibrosis. Arteries hyaline.

Pituitary.—No fibrosis.

Thyroid.—Resting colloid gland.

10. M. 17. Mulatto. Mental age nine and a half. Intelligence quotient 57. The patient had been kept at home and had never worked. He had probably had homosexual experiences, but denied heterosexual relations. He was timid, effeminate and emotional. He had an outbreak of excitement and violence, probably in reaction to auditory hallucinations.

Later he became mute, at times destructive, and showed katatonic rigidity. Well nourished. No anomalies of development recorded. Cause of death, chronic nephritis. Duration of mental disease, eight months.

Testicles.—Tubular epithelium poorly differentiated. Hyaline membrane thickened and wavy. Connective tissue increased and oedematous, with mild lymphocytic infiltration. Arteries thickened. Interstitial cells abundant.

Pituitary.—Moderate fibrosis in the anterior lobe.

Thyroid.—A considerable number of active acini.

Adrenals.—A moderate amount of lipoid.

Control.—M. 16. Died of chronic nephritis.

Testicles.—Complete differentiation of seminal epithelium and a few spermatozoa in numerous tubules. No fibrosis. Interstitial cells present in moderate numbers.

11. M. 18. The patient had been in a school for the feeble-minded. At twelve years he graded at eight and a half. He had shown progressive deterioration since his sixteenth year, becoming noisy, irritable and hyper-religious, and developing auditory hallucinations and somatic ideas. Well developed and well nourished. Developing beard. Genitalia normal. Cause of death, lobar pneumonia.

Testicles.—Active spermatogenesis. Interstitial cells rather scarce. Slight increase of connective tissue and one focus of chronic inflammation with atrophy of tubules.

Pituitary.—Slight increase of stroma in the anterior lobe.

Adrenals.—Not remarkable.

12. M. 43. Originally defective. He had signs of amyotrophic lateral sclerosis. He was in the hospital eight years, and during that time deteriorated markedly. He was actively hallucinated. No endocrine anomalies of development. Death from lobar pneumonia.

Testicles.—Small. Spermatocytes present; no spermatozoa. Interstitial cells abundant. Considerable fibrosis.

Pituitary.—Marked diffuse fibrosis in anterior lobe.

Thyroid.—Resting colloid gland with slight increase in stroma.

Adrenals.—Much lipoid.

Control.—M. 43. Non-alcoholic. Died of lobar pneumonia.

Testicles.—Moderately active spermatogenesis. Interstitial cells abundant. No increase in connective tissue.

13. F. 43. The patient had been in the hospital for seven years, and during the entire time was mute to the physicians, and had been known to speak to the nurse only very rarely, saying a few words each time. She was indifferent to her surroundings and was usually cared for in bed. Fairly well nourished. Suicide by hanging.

Ovaries.—Large. Corpus hæmorrhagicum; receding corpus luteum. Maturing follicles. Primordial follicles scarce.

Pituitary.—No fibrosis.

Thyroid.—Mostly resting colloid gland; some areas of slight hyperplasia.

Adrenals.—Much lipoid.

14. F. 43. At twenty she had 'nervous prostration.' She was

married at twenty-one and had two children. She was in the hospital eighteen months, and during that time was mute, restless and indifferent. She had delusions about water, and also showed stereotypies. Death from asphyxia, due to aspiration of vomitus.

Ovaries.—A fresh corpus luteum present. Few ova seen.

Pituitary.—No fibrosis.

Thyroid.—Considerable hyperplasia. Collections of lymphocytes. Much fibrosis.

Adrenals.—A large amount of lipid.

15. F. 43. Always quiet, seclusive and exceptionally neat. She lived alone, moving frequently because she thought a man was following her. She had auditory and visual hallucinations. Known duration of mental disease, six years. Death from chronic interstitial nephritis.

Ovaries.—A corpus hæmorrhagicum present, also a corpus fibrosum in an early stage. No primordial follicles in section.

Pituitary.—A general thickening of the stroma in the anterior lobe.

Adrenals.—Much lipid.

Control.—F. 43. Died of chronic interstitial nephritis and cerebellar hæmorrhage.

Ovary.—A fresh corpus luteum present. No primordial follicles seen.

16. F. 35. Cause of death, acute parenchymatous nephritis.

Ovaries.—A young corpus luteum present. A few maturing follicles. Numerous primordial follicles.

Pituitary.—No fibrosis.

Adrenals.—Lipoid small in amount.

Control.—F. 27. Died of acute nephritis.

Ovaries.—A corpus luteum present, also numerous maturing and primordial follicles. Corpora fibrosa in various stages.

17. F. 24. Quiet, conscientious and a good worker. An acute onset of the disease seven weeks before death with somatic complaints, fatigue, fear and auditory hallucinations. In the hospital the patient was confused, disoriented, resistive, and hyperactive. Death from staphylococcus aureus septicæmia.

Ovary.—A corpus hæmorrhagicum and several corpora lutea in different stages. A number of maturing follicles.

Pituitary.—No fibrosis.

Adrenals.—Parenchymatous degeneration of cortical cells. Practically no lipid. Congestion.

Control.—F. 28. One child. Therapeutic abortion one month before death on account of chorea. Death from staphylococcus aureus septicæmia. The primary focus was in the antrum, from which the patient had had symptoms for some time before the abortion.

Ovaries.—A receding corpus luteum of pregnancy. Numerous corpora fibrosa in various stages. Three sections contain only a few primordial follicles.

18. F. 33. Always peculiar, high-tempered, stubborn, and seclusive. She was married at twenty-one and had one child. There was a gradual

character change, beginning at twenty-seven years. In the hospital she denied her relatives, gave a fictitious account of her life, called the hospital doctors her father and brothers, and imagined herself pregnant. She had mitral stenosis. Death from influenzal bronchopneumonia.

Ovaries.—Contain a corpus luteum and several recent corpora fibrosa. Moderate numbers of primordial follicles in section. Much arterial thickening.

Adrenals.—A good amount of lipoid present. Hyaline bodies abundant in the medulla. A few lymphocytes.

Control.—F. 28. Died from influenzal pneumonia four weeks after a normal childbirth.

Ovaries.—A receding corpus luteum of pregnancy. Numerous corpora fibrosa in various stages. Primordial follicles very numerous. Some developing follicles. See also control to case 26.

19. F. 31. She was married at twenty-four and had two children. Duration of the psychosis at least six and a half years. Hospital residence of four years, during which the patient showed progressive deterioration. Death from pulmonary tuberculosis.

Ovaries.—One developing follicle. Moderate numbers of primordial follicles in section. Some atretic follicles. Recent corpus fibrosum. Increase of connective tissue in cortex.

Pituitary.—The cells of the anterior lobe are small, closely set, and their granules inconspicuous. Mild diffuse fibrosis.

Thyroid.—Resting colloid gland.

20. F. 31. Coloured. During the first part of her hospital stay of fifteen months she had auditory hallucinations, and was suspicious and inaccessible. She later became violent, resistive, aggressive, and untidy. Cause of death, pulmonary tuberculosis.

Ovaries.—A few primordial follicles in section. No maturing follicles. Cortex fibrous.

Pituitary.—Considerable fibrosis in the anterior lobe.

Adrenals.—An increase of connective tissue in the cortex and medulla. Congestion. Collections of lymphocytes.

21. F. 36. Death from pulmonary tuberculosis.

Ovaries.—A corpus luteum present. A few maturing follicles and many atretic follicles. Small numbers of ova.

Pituitary.—Slight focal increases of connective tissue.

Adrenals.—Very little lipoid.

22. F. 43. Always 'nervous.' She was married at thirty and had two children. The onset of the disease was at thirty-five, when she thought people were trying to shoot her, became excited and noisy, and wandered away from home. In the hospital she gave evidence at first of auditory hallucinations and ideas of persecution, but soon became mute, resistive, inaccessible and slovenly, with peculiar mannerisms. Death from pulmonary tuberculosis.

Ovaries.—Appear large, due to increase of connective tissue in the cortex. Very few primordial follicles. Some atretic follicles. No corpora lutea. Vessels much thickened.

Pituitary.—Marked focal fibrosis in the anterior lobe.

Thyroid.—A tendency to the colloid goitre type of gland (no gross enlargement). No signs of activity.

Adrenals.—Lipoid scanty. Thickening of capsule. A few lymphocytes.

23. F. 33. Portuguese. The patient was married, and had had two children and several miscarriages. The second child was born three years before the patient's death, while she was in the hospital. She was committed at twenty-nine years on account of auditory hallucinations, and ideas of reference, jealousy and poisoning, which gave rise to homicidal and suicidal attempts. She had a period of katatonic stupor of two months' duration following her last confinement. Death from pulmonary tuberculosis.

Ovaries.—No corpora lutea present. Numerous corpora fibrosa. Moderate numbers of ova and one developing follicle.

Thyroid.—Inactive. Considerable fibrosis in one section.

Adrenals.—A small amount of lipoid. A few lymphocytes.

24. F. 41. The patient was married and had one child. At thirty-four years she had an outbreak of excitement and violence, with auditory hallucinations and ideas of reference and persecution. She was in the hospital seven years, during which time she steadily deteriorated. She died of pulmonary tuberculosis.

Ovaries.—No corpora lutea or primordial follicles. Several atretic follicles.

Pituitary.—Focal fibrosis in the anterior lobe.

Thyroid.—Resting colloid gland with a few signs of activity.

Adrenals.—A good amount of lipoid. Numerous collections of lymphocytes.

25. F. 23. Polish. Past history unobtainable. She had been in two State hospitals, residing in the last one eighteen months. Here she was noisy and violent at first, probably in reaction to hallucinations. Later she was inactive, solitary and uninterested, with poor grasp on her surroundings. Poorly developed and nourished. Height, 4 ft. 8 in.; weight, 81 lb. Death from bronchopneumonia.

Ovaries.—One mature follicle present. Small numbers of ova. Atretic follicles frequent. Cortex thick and fibrous. Moderate thickening of arteries.

Pituitary.—Slight focal fibrosis in the anterior lobe.

Adrenals.—A small amount of lipoid.

26. F. 33. The patient held numerous positions only a short time, giving as the reason that "all the men fell in love with her." There was a marked change in the patient after she had influenza in 1918. She lost ambition, had 'dazed' periods, and was irritable. At the hospital she admitted auditory and visual hallucinations and ideas of influence. She thought that she was threatened by a man who dominated her. She had two periods of stupor. Physical examination showed a small, poorly developed girl. Weight, 89 lb. Signs of mitral stenosis. Breasts undeveloped. External genitalia infantile. Uterus small and retroflexed. Menstruation began at fourteen; irregular, accompanied by dysmenorrhœa. Death from the cardiac condition three years after the onset of the mental disease.

Ovaries.—Large and elongated, due to the overgrowth of connective tissue. Very few ova. Some atretic follicles. No developing follicles or corpora lutea.

Adrenals.—A moderate amount of lipid. Much congestion.

Control.—F. 36. Died of mitral stenosis.

Ovary.—Contains a recent corpus fibrosum. One developing follicle seen. More ova than in case 26, although they are not numerous.

27. F. 23. Always defective. At twenty years she began to deteriorate. She heard voices which frightened her, was unoccupied, untidy, and occasionally irritable. Menstruation at twelve; regular. Physical examination: poorly developed and nourished. Breasts undeveloped. Body hair scant. Cause of death, pulmonary tuberculosis.

Ovaries.—No corpora lutea present. Numerous corpora fibrosa. A few ova and some atretic follicles.

Pituitary.—The cells of the anterior lobe are small and closely packed, and their granules inconspicuous. Slight thickening of stroma.

Thyroid.—Chiefly resting colloid gland. Activity in a few acini.

Adrenals.—Only a small amount of lipid. Congestion. Thickening of capsule.

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