while there was no growth from the distal epiphysis, the growing plate having been destroyed. The grafted part had somewhat increased in length and also markedly in thickness during ensuing years. While originally the grafted portion was in the centre of the arm, it was pushed toward the distal portion owing to the more vigorous growth from the proximal epiphysis. The arm is shorter than its neighbour, and no one would take it for an artist's model, but it has been of great service to its owner. Since manhood he has been able to maintain himself and his family by his own efforts—first as a joiner, then as laboratory attendant—and also, he has been able to go to the front and do his bit for King and country during the great war.

For the restoration of the lower jaw, grafting and transplanting of bone has been frequently successfully employed by many surgeons (especially in Frogna), restoring thereby the symmetry of the face, and, with the help of the dentist, the function of the lower jaw. In two such cases, operated on over eighteen years ago, the mandible has increased in size and strength commensurate with the rate of growth of the face, leaving little trace of the hideous deformities from which the patients would otherwise have been doomed to suffer.

One has endeavoured to give a glimpse into some phases of the comparative anatomy of the antler of the deer. Were one able to extend one's vision into other spheres of animal life, not only would they prove of absorbing interest intrinsically, broadening one's views, but they would shed fresh light on human structure in evolution and repair.

As to Nature as a whole, we are still in deepest darkness. Isn't there within each of us a mystery which has never yet been fathomed—a mystery which man shares in common with the minutest speck of primordial protoplasm of the wayside pool? The further we penetrate into the depths of Nature, the more numerous are the paths which are revealed for our searching, and to our finite eyes seem illimitable. Yet, in our search there are at least two things which we may find—one, not the extent, but a measure, of our abysmal ignorance; the other, that if we pursue our quest with a single purpose in search of truth for truth's sake only, we may get a glimpse of the spirit of Nature and feel the touch of The Hand that weaves the woof.

NORMAL AND MORBID CONDITIONS OF THE ADRENALS IN 100 HOSPITAL AND ASYLUM CASES;

WITH SPECIAL REFERENCE TO DEMENTIA PRAECOX.*

(With Special Plate.)

BY

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INTRODUCTION.

In making *post-mortem* examinations at the London County Asylums I (F. W. M.) had long been struck with the frequency with which I found small suprarenal capsules in cases of dementia praecox as compared with general paralysis. I have already shown a regressive atrophy of the testes and ovaries in dementia praecox, and compared the conditions found in one hundred cases of each dying in hospitals and asylums.⁵ There are many physiological and pathological facts showing the correlation of the reproductive organs with the cortex of the suprarenal gland, therefore it would not be surprising to find a diminution in weight of these glands.† There are certain clinical symptoms in

dementia praecox which show the probability of the correlation of a morbid change in the medullary portion of the gland—namely, low blood pressure, feeble pulse, cold extremities, acrocyanosis, shallow breathing, low oxygen consumption, and katatonia. Dr. G. H. Rae Gibson,¹⁶ working at Claybury at my suggestion, investigated the blood pressure in various types of insanity, especially in relation to the above clinical signs of dementia praecox.

Table of Average Blood Pressure in 143 Cases.

	Males.		Females.	
	Average Blood Pressure.	Average Age.	Average Blood Pressure.	Average Age.
Dementia praecox katatonia ...	113	28	111	28
Dementia praecox hebephrenia	118	30	114	27
Dementia praecox paranoia ...	113	35	125	43
Epilepsy	120	36	123	39.5
General paralysis	138	45	123	44.5
Congenital imbecility	115	21	109	34.5

I should not attach much importance to the results of the average blood pressure in these various groups, for where the difference is great—for example, dementia praecox and general paralysis—the age factor might be cited as the causal relationship of the difference. But on examining the tables in which the blood pressure of each of the 143 cases is given, one finds that in 10 of the cases of katatonic dementia praecox, and in 4 of the 27 cases of hebephrenic dementia praecox, the blood pressure is under 100; whereas in the 12 cases of epilepsy, in the 15 cases of general paralysis, and in 9 of the 10 cases of congenital imbecility, there is not a single case in which the blood pressure is under 100; moreover, in 5 out of the 10 cases of katatonia, and 2 out of the 4 cases of hebephrenia, the blood pressure was very low—under 90. In not one of the cases of general paralysis was it under 120. These observations were made before I undertook the investigation of the reproductive endocrine system of glands.

Dr. Dawson, assistant medical officer at the Maudsley Hospital, undertook last year, while assistant medical officer at Hanwell Mental Hospital, an investigation regarding the blood pressure and Goetsch reaction in dementia praecox. The following is a summary of Dr. Dawson's results.

The Blood Pressure and Goetsch Reaction in Dementia Praecox.

In a series of 50 cases the blood pressure was as follows:

	No. of Cases.	Systolic Blood Pressure.		
		Average.	Minimum.	Maximum.
Katatonic	27	116 mm.	93 mm.	135 mm.
Simple dementia praecox ...	14	117 mm.	104 mm.	126 mm.
Paranoid dementia praecox ..	7	120 mm.	115 mm.	136 mm.
Hebephrenic dementia praecox	2	115 & 122		

The diastolic reading was between 55 and 65 mm. in all cases.

Goetsch Reaction.—A subcuticular injection of 0.05 c.cm. of 1 in 2,000 Parke, Davis and Co. adrenaline solution was made in all cases. Two cases only gave a normal reaction; these had a systolic blood pressure of 122 and 128 respectively. One was a katatonic and the other a simple dementia praecox case with congenital defect. Eighteen cases gave a moderate reaction: in 13 of these the blood pressure was 120 or under (minimum 104); in 5 it was over 120 (maximum 130). Thirty cases reacted only faintly: in 25 the blood pressure was 120 or under (minimum 98); in 5 it was over 120 (maximum 136).

The test was repeated in cases with a high blood pressure which gave a faint reaction, and the same result was obtained. In several cases it was found that a faint reaction might be intensified by administration of thyroid extract, but without material alteration in the blood pressure.

Katatonic Stupor.—Nine cases of this variety of dementia praecox were included in the series. One case had a blood pressure of 135, but reacted faintly to the Goetsch test. In the other 8 cases

* This research was carried out with the aid of a grant from the Board of Control.

† Dr. Langdon Brown, in his interesting Croonian Lectures on the sympathetic nervous system in disease, says: "It is both interesting and suggestive to note that an important group of endocrine glands—the adrenals, the thyroid, and the pituitary—have three features in common: the secretion of each is stimulated by the sympathetic, they all lower carbohydrate tolerance, and they all act and react with the reproductive organs."

the blood pressure was below normal. The reaction to the Goetsch test was faint in all cases except one, in which it was moderate but less than normal.

So far, then, as the Goetsch reaction and the blood pressure are any indication, cases of dementia praecox, especially of the katatonic variety, appear to suffer from adrenal inadequacy.

Some years ago, in conjunction with Professor Halliburton, I undertook¹⁷ a histological examination of the suprarenal gland of patients dying in Claybury Asylum, and we correlated the same with the chemical and physiological investigation of the adrenaline content of the gland. No definite results were obtainable, but this is not surprising, because the amount depends upon the cause of death and the time lapsing between death and the *post-mortem* examination. For this reason I did not think that comparative results by chemical and physiological investigations would be of value. I therefore resolved to pursue an investigation of the gland by the same histological methods as I adopted in the case of the reproductive organs. This work has been largely carried out under my direction by Dr. Emslie Hutton.

HISTOLOGICAL EXAMINATION OF THE ADRENAL GLANDS IN 100 CASES.

The material dealt with in this article was collected from patients who died in the London mental hospitals, and also hospitals for consumption and various military and general hospitals.* In the majority of the mental cases the reproductive organs have already been examined, and work is going on at present on the thyroid and pituitary of these cases. So far as we have been able to ascertain from a search of the bibliography, there has been no complete systematic investigation of a similar nature.

One hundred cases were examined and classified, and the numbers in each group are tabulated below. The number in the class dementia praecox is large, the principal reason for carrying out the work being to afford an opportunity for determining if there is a change in the adrenal in this disease, the great importance of which is obvious from the fact that the bulk of incurable cases in mental hospitals belong to this group of the insanities. Moreover, many of the symptoms of this disease, as already indicated, point to an affection of the medulla of the adrenal gland. The number of hospital cases (which includes thirteen cases of death due to severe accident) is also large, for it is necessary to have a good picture of the normal. A comparatively large number of cases of tuberculosis in young adults were examined; these were required for comparison with cases of dementia praecox, the majority of whom die eventually from tuberculous affections. It has, indeed, been stated that 75 per cent. of the dementia praecox cases die of tuberculosis, and the hypothesis that tuberculosis stands in causal relation to dementia praecox might therefore be justified. Against this, however, is the fact that if this were so similar clinical symptoms and morbid histological changes to those found in dementia praecox should occur in cases dying of tuberculosis without mental symptoms. Moreover, some of the cases of dementia praecox died from pneumonia, dysentery, and suicide. These cases presented no signs of tuberculosis *post mortem*, although the histological changes in the reproductive organs and the brain were similar.

Classification of Cases.

Mental Hospitals :				
Dementia praecox	...	...	...	26
Other psychoses	...	...	...	8
General paralysis of the insane	...	...	...	22
Hospitals for Consumption :				
Tuberculosis	...	...	...	12
General and Military Hospitals :				
Death as result of severe accident	...	...	...	13
Death from various general causes	...	...	...	19

100 cases.

Method of Examination.

It was impossible to arrange that the glands should be removed by the same person, but they were taken out care-

* We wish to thank the superintendents and medical officers of the London County mental hospitals for kindly forwarding material and notes of the cases, also the pathologists to the general hospitals and hospitals for consumption who have assisted us by providing the material for this investigation. We are especially indebted to Dr. Roodhouse Gloyne of the City of London Hospital for Diseases of the Chest, Victoria Park, E.2, for material.

fully, and in most cases arrived in a satisfactory condition. They were thoroughly freed of extraneous tissue in the laboratory, each being weighed separately, and then hardened for two months in formol. Each was cut across in the same way, and as nearly as possible through the thickest parts of each gland. Sections were cut by the freezing method and were of approximately equal thickness; various stains were used, the chief of which were haematoxylin and eosin, Scharlach R. alone and with haematoxylin counter-stain. Most of the details of the fibrous and nuclear changes were observed in sections stained by the Del Rio Hortega* method, or by that method counter-stained by eosin. The sections so stained were examined systematically. Their outline, magnified by means of an Edinger projection apparatus, was made; this showed very clearly the relative thickness of the cortex and medulla, and the general size of the organ. Means were also taken for obtaining an approximate idea of the relative amounts of cortex and medulla. The section was then microscopically examined and a full account of the appearances was recorded. The nuclear ratio in the medulla (to be explained later) was taken in each case.

Before proceeding to describe the morbid histological changes met with it is desirable to give a brief account of the weight and microscopic appearances presented by the normal human gland.

The Normal Adrenal Gland.

Each organ weighs from 6.5 to 7.5 grams, some, however, as will be shown later, weigh slightly more; the body weight must be taken into account when judging whether a case is lighter or heavier than the normal. According, however, to the very careful records of Kojima, body weight does not seem to have much influence.¹⁴ The medulla is at least as wide as the cortex, and more often exceeds it in width at the thickest part of the gland. The cortex is composed of well defined polygonal cells, arranged in columns (zona fasciculata). Near the surface of the organ the columns have a more open arrangement (zona glomerulosa); near the medulla the arrangement is much more open (zona reticularis), and for convenience of description these terms will be used throughout this paper. The cells are well defined, and contain one, and sometimes two, darkly stained nuclei. They are packed with a glistening refractile lipid substance; this is, as a rule, present in all the cells of the cortex, but is sometimes absent from its innermost layers. In these latter layers are often seen brown pigmented granules tightly packed in the cell; their significance is not yet known.³ The cortical adenomata, such as are described by Elliot⁷ and Vasilescu,⁸ have never been observed in this series of cases. The fibrous tissue of the cortex continuous with that of the capsule is well defined, but of delicate structure, and runs down in a septa-like fashion between the cells carrying the blood vessels and lymphatics. The medulla will now be described fully, as it is here that most of the more definite microscopic changes, especially in dementia praecox, have been observed. There is a light fibrous groundwork with fine offshoots surrounding groups of cells; there is no pericellular arrangement of the fibres. The cells have a different arrangement and differ in form from those of the cortex. They are arranged more loosely in irregular columns with large interspersed blood sinuses; a striking feature is the appearance of the large vessels with very thick muscular coats; generally speaking, the medullary cells are arranged around and in contact with these vessels. Sometimes, however, the sections show the cells of the zona reticularis arranged around and in close contact with them. The cells are polygonal and larger than those of the cortex;

* **Nuclear Staining: Del Rio Hortega Method.**—Sections cut by the freezing method are taken from distilled water, placed into the silver solution (see below), and warmed at a temperature of 50° to 55° C. until slightly yellow in colour. They are then placed direct into a 2 per cent. solution of formol (neutralized by calcium carbonate) until the section becomes black; washed in distilled water for about one minute, and then placed into gold chloride solution (1 in 500) until the section becomes grey, usually about half a minute; then into a 3 per cent. solution of sodium hyposulphite for five minutes—in this it becomes a rose colour. Wash in water, fix section to slide, blot off excess of water, and dehydrate with a cresote-carbolic-xylol mixture (cresote 10 c.cm., carbolic acid 10 grams, xylol 60 c.cm.), and mount in Canada balsam.

Silver Solution.—5 c.cm. of a 10 per cent. solution of AgNO₃, precipitated by 20 c.cm. of a 5 per cent. solution of sodium carbonate; dissolve precipitate by a few drops of ammonia, and add water to 55 c.cm.

they may be also very irregular, and even ragged in outline, in this respect differing greatly from those of the cortex, which are sharply defined and compact. Many of the cells contain very fine droplets of lipid. Sections treated with chrome show brown granules in many of the medullary cells, and most workers are of opinion that these chromaffin granules are limited to the medulla, though Cramer⁴ shows very convincingly that they are also to be found in the zona reticularis. We have also noted this in cases, and apparently these granules occur in greater abundance in the zona reticularis than in the medulla; at any rate, this applies to the human subject, according to our experience. The cytoplasm of the cells stains well with eosin, and there is but little vacuolation; with the oil-immersion lens numbers of fine eosin-stained granules can be seen—?mitochondria.

The nucleus is small in comparison to the cell; it is round, stains deeply, and contains numerous chromatin granules, some intensely black and coarse when stained by Del Rio Hcrttega method, and others of dust-like fineness; a distinct and fairly complicated chromatic skein is present. The cell nuclei are for the most part of uniform size and shape. In normal glands there are very few nuclei without surrounding cytoplasm, and those are paler and contain fewer granules than the nuclei contained in the cells. Moreover, instead of being round, they are generally oval or fusiform in shape. Some of these may be fibroblastic.

Mitosis has been observed in the cells of the medulla of many glands and also in the zona reticularis. Graham⁵ has found mitosis in the medulla, but much less frequently than in the cortex. In many cases groups of sympathetic ganglion cells were found in the medulla or just between the cortex and medulla, and occasionally bundles of non-medullated fibres. Cortex and medulla react as a whole in a different way to stains, for whereas the medulla takes up the basic, the cortex takes the acid stain.

Size and Weight of Adrenal Glands in One Hundred Cases.

Size.—The adrenals are glands so small and light that slight differences in their size and weight may have a certain significance. These differences may sometimes be marked and obvious even at the *post-mortem* examination; they can be still more clearly observed upon studying a stained section through the gland in its thickest part. It can be noted, on the one hand, without the aid of the microscope that the adrenal glands of a case of dementia praecox are, as a general rule, smaller than in cases belonging to any other class; and, on the other hand, the adrenal glands of a case of general paralysis are usually larger. It was also noted that a section of the gland in a case of tuberculosis did not differ, as a general rule, from that of the section of the gland of a normal hospital case dying of injury.

Weight.—The average weight for each group of cases was taken. Many of the glands in dementia praecox only weighed from 2.8 to 4 grams; the average weight, however, in this class was higher than might have been expected. Several factors contributed to the raising of this average, of which the following were the principal.

One case with heavy adrenals had been clinically diagnosed as dementia praecox and is included in the list, but its history showed that it was doubtful whether it was a case of dementia praecox.

Four were puerperal cases, which would probably account for some increase of the weight owing to the enlargement of the cortex¹¹ connected with the puerperal condition.

A few adrenals were heavier than normal, owing to the great fibrosis of their medulla.

The average weight of adrenals in dementia praecox cases = 6.326 grams (women = 6.548 grams, men = 5.327 grams).

Average weights were as follows:

Dementia praecox	6.32 grams
Other psychoses	6.60 "
General paralysis	7.35 "
Tuberculous cases	6.28 "
Hospital cases	7.21 "

The weights in the different classes are probably more clearly shown in the following table. The sum of the right and left adrenal is taken in each case, and the percentage of cases between certain weights is given.

	5 to 10 grams.	10.1 to 15 grams.	15.1 to 20 grams.	20.1 to 25 grams.
Dementia praecox (21 cases) ...	Per cent. 43	Per cent. 29	Per cent. 28	—
General paralysis of the insane (21 cases)	9	43	43	5
Various psychoses (8 cases) ...	25	50	25	—
Tuberculosis (10 cases)	20	70	10	—
Hospital cases (23)	16	42	37	5

Note the high percentage of dementia praecox cases between 5 and 10 grams, and of cases of general paralysis of the insane between 15 and 25 grams.

The average for the normal gland of this series is 7.21 grams—a much higher average than Elliot's, which was between 4 and 5 grams. Testut¹¹ gives 6 to 7 grams as the average weight, and Vierordt¹² working from a very large number of cases, gives 7.3 grams as his average.

Ratio of the Area of Cortex to that of the Medulla.

So striking were the differences in the width of the medulla in the different cases that it was thought advisable to find means of arriving at some idea of the relative area of the cortex and medulla. This was at first done by actual comparative microscopic measurements through the thickest portion of the medulla, but it was felt that this method was open to many fallacies, so the following method was adopted. It has been previously explained how the glands were cut as nearly as possible through the thickest portion of the gland. The magnified outline of the section was drawn on paper of equal thickness by means of an Edinger projection apparatus. The medulla was also outlined, and this is a very simple matter, for, owing to the fact that their staining reactions are so different, the cortex and medulla stand out quite clearly from each other. The medulla and cortex having been delineated upon the paper were then separately cut out and each accurately weighed; thus a representation of the area in terms of weight was obtained. It was found that the normal glands showed an average ratio of 2.7—that is, the cortex covered 2.7 times as much area as the medulla. Tuberculosis cases showed an average ratio of 3.7, and general paralytics one of 3.2. The average for the dementia praecox cases was, however, a much higher one, and showed that the cortex covered 8.6 times more area than that of the medulla. If this fact be coupled with the fact that the average dementia praecox adrenal is relatively a smaller organ, it is probable that the deficiency in weight in most of the cases was, in great measure, due to deficiency in medulla. In fact, in some of these cases the medulla is a mere narrow strip of tissue; in a few cases, however, the medulla is as extensive as in normal cases because of great substitutive fibrous hyperplasia. The cases investigated by Dr. Dawson (referred to in the earlier part of this communication) have for the most part not died, therefore we have no precise data regarding the correlation of blood pressure, Goetsch reaction, acrocyanosis, katatonia, and anergic stupor with the degree of atrophic change in the medulla of the adrenal gland.

I am at present instituting an intensive research on the relation of the histological changes in the reproductive organs, the whole endocrine system, and the vegetative nervous system, to carefully recorded clinical investigations, including basic metabolism in individual selected cases of dementia praecox. (F. W. M.)

There does not seem to be any literature in which accurate figures can be found to compare with those of this series; Elliot and Tuckett,¹³ however, have worked out this ratio in animals, and from the figures obtained have deduced the proportions of cortex and medulla in man. The proportion of cortex to medulla which they give is somewhat higher than that which we have found in this series. A graph shows well the ratio of the cortex to the medulla in the different classes of case.

Histological Changes in the Cortex.

(a) *Lipoid.*—It was found that in most of the cases of dementia praecox, in all cases of general paralysis and the other psychoses, as in the normal cases, it was apparent to

The following are drawings of sections through that part of the adrenal gland where the medulla is thickest. They are drawn from the slide preparation by aid of an Edinger apparatus with a magnification of 2.5.

FIG. A.—Section of adrenal gland of a male, aged 20, who died from suppurative encephalitis two months after a severe bullet wound of the head. Note the extensive medullary portion.

FIG. B.—Section of adrenal gland of a case of general paralysis of the insane of two years' duration. Note the extensive medullary portion.

FIG. C.—Section of adrenal gland of a case of epilepsy who was for three years before death in a mental hospital, where she died of tuberculosis, aged 38 years. Note the extensive medullary portion.

FIG. D.—Section of adrenal gland of a case of dementia praecox who was for five years in a mental hospital, where he died of dysentery, aged 30 years. Note the extensive area of the medulla, which stains black because it is composed almost entirely of thick strands of fibrous tissue.

FIG. E.—Section of adrenal gland of a case of dementia praecox who was for two years in a mental hospital, where he died of pneumonia at the age of 25 years. Note the narrow strip of medulla, which is deeply stained because of the fibrous tissue which largely composes it.

FIG. F.—Section of adrenal gland of a case of dementia praecox who was for sixteen years in a mental hospital, where she died, aged 33 years. Note the narrow strip of medullary tissue, which, however, is not deeply stained, as there is no marked fibrosis present.

FIG. G.—Section of the adrenal gland of a case of dementia praecox who was for two years in a mental hospital, where she died, aged 29 years. Note the narrow strip of medullary tissue.

the naked eye that there was abundance of lipid present throughout the cortex; the cortical cells in the three zones were filled with coarse to fine droplets of this refractile substance. In a few of the dementia praecox cases dying of tuberculosis lipid was entirely absent, and in many it was reduced in amount to a variable degree. In one case who died of dysentery it was entirely absent. It was absent also in two cases of head wound where death was caused by septicaemia. It was also absent or much reduced in amount in cases of young adults dying from tuberculosis.

It may be said that the lipid was absent or diminished where acute or chronic septic conditions were present. This is in agreement with what other workers, among whom are Elliot⁷ and Mott, have found, and supports the view that it is an important source of antitoxins. It cannot be said that the lipid content seems to have any kind of relationship to the mental condition of the patient. It has, probably, as Mott⁵ has shown, an important relation to the function of reproduction. In one of the cases of dementia praecox of this series, the testis was absent on one side and on that side the adrenal gland was one-half the size of the other. A full account of this case was given in a previous communication.¹⁸

(b) *Fibrous Septa*.—Several of the cases showed thickening of the septa, but this did not seem to have any relation to the different classes of case. A fair number of general paralytics, and also a proportion of the normal cases, showed this appearance. When this was present in the cortex there was not always a corresponding fibrosis in the medulla.

(c) *Cells*.—It was not observed that these showed any definite changes. In the zona reticularis in some cases of dementia praecox active mitosis was seen, but it was not generally present; here, too, chromaffin granules were observed in some of the cases.

(d) *Lymphocytic Infiltration*.—In many of the general paralytic cases it was observed that along the lines of the fibrous septa there was an infiltration of small lymphocytes. In some cases there were definite clumps of these small lymphocytes near the outer part of the cortex, but more often the appearance was simply one of infiltration along the fibrous septa. In one of the hospital cases this appearance was present, but in no other case was it observed.

Changes in the Medulla.

It was in the medulla that the striking changes were seen; the first of these—namely, the differences in the amount of medulla present in the gland—has already been dealt with, and the microscopic changes will now be discussed.

(a) *Cells*.—In dementia praecox, even in very early cases, there were distinct cellular changes. Sometimes these changes were only found in some of the cells and many normal cells were present. The cells were as a rule smaller than the normal, and their cytoplasm was much vacuolated. The cell nuclei varied much in shape and size, and were generally smaller than the normal nucleus, though they were larger in proportion to the cell; they were not always round and many tended to be oval. They also stained poorly and showed fewer and finer granules than the normal nucleus, and many exhibited a very faint and simple chromatin network. Syncytia containing numerous polymorphic nuclei were frequently seen. There were a great number of nuclei present which were not surrounded by cytoplasm; these either occurred in patches or were diffused throughout the medulla. These nuclei were nearly round, but tended to be oval or fusiform, and many were larger, paler, and contained fewer chromatin granules than the nuclei seen in cells. In various psychoses, such as manic-depressive cases, somewhat similar changes were found, but never to such a marked

degree as in cases of dementia praecox. Syncytia were sometimes seen and the cells showed in some cases a certain amount of atrophy and vacuolation; slight nuclear proliferation was present in a few of these cases. A few cases of tuberculosis showed atrophy of the cells and vacuolation of their cytoplasm, but most of the specimens presented a normal appearance. A few of the hospital cases showed slight atrophy of the cells and vacuolation of their cytoplasm, but in most of them no definite cell changes were observed comparable with those seen in dementia praecox.

(b) *Fibrosis*.—There seemed to be a certain amount of fibrosis in all the dementia praecox cases, and this was also seen, though to a slighter extent, in some of the other psychoses. This fibrous hyperplasia was sometimes coarse and consisted of heavy wavy bundles which extended round groups of cells. On the other hand, it was in many cases a very fine fibrosis and delicate strands of fibrous tissue ramified between individual cells. In one dementia praecox case there were such thick bands of organized fibrous tissue that they could even be seen in sections by the aid of a hand lens. In a few of these cases the medulla consisted of little else but fibrous tissue, and the amount of cellular tissue was very small. It could not be said it was this fibrosis alone that caused the cell change, for in some adrenals that showed a marked fibrosis the cells were fairly normal. General paralytic cases showed a fair amount of fibrosis, but there was no pericellular arrangement of the fibres. The majority of the hospital and tuberculosis cases showed no fibrous hyperplasia, though there were a few specimens in which this was present.

(c) *Nuclear Ratio*.—It was thought that as there were in some cases such numbers of nuclei and so few cells, it might be instructive to count the numbers of nuclei and of cells in a given area. This was done, the area used being 0.25 mm. The numbers of nuclei and of cells were separately counted in three such areas and the averages taken. The number of nuclei was divided by the number of cells and a ratio of nuclei to cells was obtained. The averages of the nuclear ratio in the different classes of case were as follows:

Dementia praecox	...	...	...	6.37 to a cell
Other psychoses	...	...	...	3.82 " "
General paralysis	...	...	...	1.85 " "
Hospital cases	...	...	...	1.94 " "
Tuberculosis	...	...	...	1.84 " "

A glance at the above figures shows that the hospital, the tuberculosis, and the general paralytic cases have an almost identical average ratio. The dementia praecox cases show by far the highest ratio of all. The other psychoses occupy a place midway between the others, and it would seem as though this were possibly a stage of the process towards what is found in the dementia praecox cases.

(d) *Lymphocytosis*.—In many of the general paralytic cases a lymphocytosis was present along the line of the fibrous septa of the medulla and the cortex. This was very marked in some of the cases where the lymphocytes formed clumps which could be well seen even under a low power magnification. Some of the adrenals showed this much more markedly than others, and even in those cases where it was very marked the glands seemed to be otherwise practically normal.

(e) *Lipoid*.—In the great majority of cases this was present in small amounts in the medulla. It was distributed in fine droplets and was never present in all the cells, and very often in quite a small proportion of them. It was absent, as in the cortex, in cases where there was an acute or chronic septic condition.

SUMMARY OF DISTINCTIVE CHANGES WHICH CHARACTERIZE THE DIFFERENT CLASSES OF CASE.

Dementia Praecox.

Much more striking changes were found in this class of case than in any other, and these will now be given seriatim.

(a) *Size*.—The organs were smaller than the normal; this was quite apparent to the naked eye, and very marked in the slide preparation. They generally had a thin and shrunken appearance which was as a rule quite typical.

(b) *Weight*.—As a rule the organs were much lighter than the normal and many of them weighed only from 2.8 to

5 grams. The average weight was somewhat higher than this, but it has been already shown why this was so.

(c) *Medulla as a Whole*.—This was distinctly narrowed and in some cases was a mere narrow strip of tissue. In a few cases the medulla was as wide or wider than the normal, but this may be accounted for by the fact that in these cases there was marked fibrous hyperplasia and only comparatively few normal medullary cells. In one of the cases the fibrous bands were so thick that they could just be seen by the naked eye.

(d) *Medullary Cells and Nuclei*.—The cells were smaller than the normal and their cytoplasm much vacuolated. In some cases even atrophous cells were very few in number. The nuclei were, relatively to the normal, smaller and paler, the chromatin granules were fewer and finer, and the chromatin skein was simple or indefinite. They varied much in shape and size, and were usually out of proportion to the size of the cell. There were many nuclei present which were not surrounded by cytoplasm, and these were pale and larger than those which were surrounded by cytoplasm; they were generally oval or fusiform in shape, and the granules were scanty and fine. The ratio of nuclei to each cell (this had previously been explained) was 6.37, while the normal was 1.94.

(e) *Fibrous Tissue*.—Medullary hyperplasia has already been very fully described; it varied enormously. It was in some cases slight, and in others there was great coarsening of the fibrous framework; it may be a very fine pericellular ramification, or there may be thick organized strands of fibrous tissue.

(f) *Cortex*.—Here little or no change was observed, except that in some cases the fibrous septa were much thickened. Where there was fibrosis in the medullary portion it was not observed that there was always a corresponding thickening of the fibrous septa of the cortex. Lipoid was absent only in cases dying of acute or chronic septic conditions.

Other Psychoses.

In manic-depressive cases changes very similar to those in early cases of dementia praecox were seen in some of the cases. The cells were in some cases smaller, the nuclei immature, the cytoplasm was vacuolated, and a slight fibrosis was sometimes present. In no cases were the changes very advanced. The ratio of nuclei in the medulla was high—3.82 to a cell—which is midway between the ratio of the normal and dementia praecox cases.

General Paralysis.

The adrenals of these cases were larger than the normal, and there were few exceptions to this; this was very noticeable even on naked-eye examination of the slide preparation, and the average weight was greater. The medulla in all cases was large and wide, and here fibrosis was occasionally present, but never to any great extent. The cells were normal or practically normal throughout, and contained a great number of granules and a complicated chromatin skein. In some cases there was slight vacuolation of the cytoplasm, and in a few of the cases syncytia were present. The nuclear ratio corresponded with that of the normal adrenals.

The most marked feature was the presence of lymphocytosis, and this was seen along the line of the fibrous tissue septa in both cortex and medulla. In many of the glands there were such large collections of lymphocytes that well marked clumps were present, and these could be well seen even under the low power of the microscope. This lymphocytic infiltration may to some extent account for the weight of the adrenals in this disease even exceeding the average normal. But we are quite sure that this does not wholly account for the large adrenal glands in general paralysis. More probable is it that the large glands are connected with a strong sexual instinct. Spirochaetes were not seen; the Horta method would probably have shown them had they been present. It is probable that these lymphocytes came from the cerebro-spinal fluid.

Tuberculosis Cases.

There was nothing remarkable to note about most of these cases, as they did not differ from the normal except in their cortical lipid content. Sometimes the

medullary cells showed atrophy and vacuolation of the cytoplasm, but the nuclei showed but little deviation from the normal and there was little or no fibrosis. The medullary nuclear ratio was the same as in normal cases. In many of the cases the lipid was entirely absent, and in nearly all of the remainder it was diminished in amount.

It will thus be seen that the histological appearances were different from those in dementia praecox. It might have been suggested that the changes in the adrenals of the dementia praecox cases were due to the tuberculosis from which they so often die. But this is not a fact, for twelve cases of tuberculosis occurring in young sane adults were examined with the above negative results. It may be observed that no lymphocytosis was observed in these twelve cases. There were, however, three cases, which were not used, as they showed tuberculous foci in the medulla. None of the many cases of dementia praecox that died of tuberculosis showed tuberculous foci in the adrenal glands. Another argument against the change in the medullary cells being due to tuberculosis is that some of the cases of dementia praecox died of dysentery and pneumonia after a short illness, and these presented no signs of tuberculosis at the *post-mortem* examination.

Extracts from Cases.

Space does not permit of extracts from all the cases, so eleven have been selected, and very brief notes appended. Two are hospital cases, four are cases of dementia praecox, two are cases of psychoses, one is a case of general paralysis, and two are cases of tuberculosis.

CASE I.

Case of duodenal ulcer; death occurring after operation. Adrenals weigh 10 grams and 9.5 grams respectively. The cortex and medulla are in normal proportion to each other; abundant lipid is present in the cortex in all its layers, and there is no evidence of fibrosis. The medullary cells are of the normal shape and size, they stain well and show little or no vacuolation. The nuclei are round and of a uniform size and shape; they stain deeply and show many chromatin granules, some coarse and darkly stained, and others of dust-like fineness. The nuclear ratio is 1.2 per cell.

CASE II.

McK., aged 19 years. Admitted to Charing Cross Hospital ten days after accident. The wound was in the mid-dorsal region, and was foul and septic; there was complete paraplegia, and death occurred seven days later of septicaemia. Adrenals weigh 9.7 and 12.5 grams respectively. The medulla is large and wide and in normal proportion to the cortex; lipid is entirely absent throughout. There is no fibrosis, and the medullary cells show a typically normal appearance. Nuclear ratio is 1.1.

CASE III.

W. F. S.; dementia praecox. Male, aged 18 years at death. He was for two years in a mental hospital, where he died, and before admission was said to have been ill for only four months. He was fairly intelligent, but childish mentally and physically for his age. He was hallucinated for general sensation and had curious feelings in his legs, upon which he based various delusions. He was quiet and depressed and was distinctly anergic, and on admission was certified as adolescent melancholia. For six months after admission he improved slightly, but then began to deteriorate and became apathetic, untidy, and anergic. He rapidly became more demented

and developed tuberculosis, from which he died. Adrenals were small and weighed 3.9 and 4.3 grams respectively. The medulla showed marked pericellular fibrosis, and there was scarcely a normal cell present. The nuclear ratio is high.

CASE IV.

P.; dementia praecox. Female, aged 29 years at death. She was for two years in a mental hospital, where she died. Before admission there was several months' history of strange behaviour, moodiness, solitariness, and abstraction; she had one child. On admission she was restless, excited, impulsive, and disoriented. She was emotional, wept for no apparent reason, then laughed in a senseless fashion, grimaced and rolled her eyes. Six months after admission she showed negativism, and stereotypy of manner and speech. Six months before death her health began to be very poor and she became anaemic, cyanosed, and the extremities were oedematous. The Goetsch reaction was faint. She was stuporose and the breathing was shallow and slow. Tuberculosis was suspected, though physical signs were negative, and there was no rise of temperature. Gradual emaciation occurred and death. *Post-mortem* examination showed extensive pulmonary and intestinal tuberculosis. Adrenals: The medulla of this organ is a mere strip of tissue, and in this few normal cells can be seen. The cells are small and atrophied, there is considerable fibrosis, and the marked nuclear changes already described are found. The nuclear ratio is high.

CASE V.

G. T.; dementia praecox. Male, aged 37 years at death. He was for four years in a mental hospital, where he died from pulmonary tuberculosis. He was a typical case of dementia praecox of the type where progressive dementia is the most marked symptom. The adrenals weighed only 2.8 and 3.9 grams respectively and are small and shrunken in appearance. The medulla shows a pericellular fibrosis, and many of the cells are atrophied. There are, however, a fair number of almost normal cells. There are advanced nuclear changes and the nuclear ratio is high.

CASE VI.

R. M. W.; dementia praecox. Male, aged 19 years at death. He was for eight months in a mental hospital, where he died of exhaustion; there was nothing else to note in the *post-mortem* examination. He was a typical case of dementia praecox. There was a bad family history: his mother and father were aged 20 and 21 years respectively at their marriage, and have been separated for eighteen years. The mother was violent and drank heavily; the maternal grandmother died in a mental hospital; a maternal uncle and an elder sister were in a mental hospital at the same time as the patient. On admission he was sullen and depressed, but subject to attacks of acute excitement, when he was most impulsive and resistant. He steadily deteriorated mentally and physically. Adrenals: The organs are of normal size, and the medulla is not diminished in extent. The medullary cells vary to a considerable extent, some being normal and others being atrophied and showing much vacuolation of the cytoplasm. There are nuclear changes, but these are not very advanced and the nuclear ratio is low.

CASE VII.

E. B.; mental defective with polyglandular insufficiency. Female, aged 18 years. She died four days after admission to hospital, and at the *post-mortem* examination military tuberculosis was found. Little was known of her history as she was brought in by the police as a lost child at the age of 4 years and was at a special school. The adrenals weighed 2.5 and 4 grams respectively. The medulla shows fibrous hyperplasia and the cells vary greatly; some are normal and others show atrophy and vacuolation. The nuclei vary greatly in size, and there is a high nuclear ratio.

CASE VIII.

C. B., male, aged 50 years; melancholia. He was in a mental hospital for three years, where he died of pulmonary tuberculosis.

DESCRIPTION OF SPECIAL PLATE.

Fig. 1.—Drawing of a section of medullary portion of the adrenal gland of a male, aged 20 years, who died as a result of a bullet wound of the head; stained Del Rio Hortega method. (A macroscopic drawing of this gland is Fig. A.) Note the light fibrous groundwork, the abundant cytoplasm of the cells, the nuclei, which vary little in size or staining, and which contain abundant chromatin granules, both coarse and fine. (Magnification 800.)

Fig. 2.—Drawing of a section of medullary portion of the adrenal gland; stained Del Rio Hortega method. A case of dementia praecox who was for two years in a mental hospital, where he died of pneumonia at the age of 25 years. (A macroscopic drawing of this gland is Fig. B.) Note the fibrous groundwork, which tends to be pericellular and somewhat coarse. The cells show scanty cytoplasm, and some of the nuclei have no surrounding cell body. The nuclei are irregular in shape and show great variation in size and in intensity of staining; they contain fewer and on the whole finer chromatin granules than the nuclei in Fig. 1. (Magnification 800.)

Fig. 3.—Photomicrograph of a section of the medullary portion of the adrenal of the same case as Fig. 1, but the magnification is much less; stained Del Rio Hortega method. (Magnification 450.)

Fig. 4.—Photomicrograph of a section of adrenal gland of a case of chronic pulmonary tuberculosis in a man who died at the age of 32 years. Stained Del Rio Hortega method. The fibrous groundwork is light; the cells show exhaustion of the cytoplasm, which is small in amount and shows vacuolation. The nuclei, however, are of equal size, and show abundant chromatin granules, both coarse and fine. (Magnification 450.)

Fig. 5.—Photomicrograph of the medullary portion of the adrenal gland of a case of general paralysis of the insane, to show the infiltration with small lymphocytes that occurs here and there throughout the gland. A few cells are seen at the corner of the photograph, and these contain abundant cytoplasm and nuclei, which are regular in form and staining, and which contain abundant chromatin granules. (Magnification 350.)

Fig. 6.—Photomicrograph of a section of the medullary portion of the adrenal gland of a case of dementia praecox who was for eighteen months in a mental hospital, where he died of pneumonia following influenza at the age of 21 years. The cells in this case vary much. In parts, as at the top of the photograph, can be seen cells which approach the normal in appearance. Throughout the specimen small cells are seen, the cytoplasm shows vacuolation, and the nuclei show variation in size. (Magnification 450.)

Fig. 7.—Photomicrograph of a section of the medullary portion of the adrenal gland of a case of dementia praecox who was for sixteen years in a mental hospital, where she died, aged 33 years. (Fig. F is a macroscopic drawing of the whole gland.) Note that the fibrous background is slightly thickened, that the cells are small, and that the nuclei are surrounded in some cases by a very small amount of cytoplasm, and in some cases none is present. The nuclei vary in size and in staining. (Magnification 450.)

Fig. 8.—Photomicrograph of a section of the medullary portion of the adrenal gland of a case of dementia praecox who was for two years in a mental hospital, where he died, aged 29 years, of tuberculosis. (A macroscopic drawing of this gland is Fig. G.) Note the coarse fibrosis and the cells, which are atrophied. Some of the nuclei have no surrounding cytoplasm. The nuclei show variation in size. (Magnification 450.)

SIR FREDERICK MOTT: NORMAL AND MORBID CONDITIONS OF THE ADRENALS IN HOSPITAL AND ASYLUM CASES.

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 4.

FIG. 5.

FIG. 6.

FIG. 7.

FIG. 8.

For many years before admission he was very abnormal mentally. The adrenals weigh 8.02 and 6.52 grams respectively. There is little contraction of the medulla, and here there is coarse fibrosis with a pericellular arrangement of the fibres. There is scarcely a cell to be seen, and not one that could be called normal. The nuclear changes are very advanced and the nuclear ratio in the medulla is high.

CASE IX.

C.; general paralysis of the insane. Male, aged 48 years at death, which occurred in a mental hospital where he had been for two years. The adrenals were markedly large and weighed 9.8 and 10 grams respectively. The medulla is not constricted and lipid is present throughout. The medullary cells are normal in appearance and there is no fibrosis. The nuclei are normal and the nuclear ratio is low. Lymphocytic infiltration is present along the fibrous septa, and here and there are small clumps of lymphocytes.

CASE X.

Chronic tuberculosis. Female, aged 22 years at death. The adrenals weigh 6 and 5.5 grams respectively. There is no lipid present except for a few droplets in the outermost layer of the zona granulosa. The medulla is not contracted and the cells are normal in appearance; the nuclear ratio is low. There is no fibrosis present nor any appearance of lymphocyte infiltration.

CASE XI.

V. B., single, aged 18 on June 12th, 1920, was charged with being drunk and disorderly, was sent to Holloway, and was certified insane on June 21st. She was admitted to the Manor on June 25th, and transferred to Horton on October 26th, 1920. Her mother stated that, as far as she knew, the girl was mentally sound up to about a week before certification. She was accustomed to take beer, generally on Saturday, and was described as a flower seller and afterwards a wardrobe dealer. She reached the sixth standard at school; one uncle was at Cane Hill, and another uncle died at Horton some years ago. In other respects the history was defective. On admission she was diagnosed as a case of adolescent insanity. She was very noisy, irrational, excited, rambling, and resistive; was strange in manner and became emotional and abusive; was violent and impulsive at times, and needed much supervision. Her physique and general health were good apart from a mitral murmur. On admission to Horton she was katatonic, destructive, and dirty. On December 11th, 1920, she had a profuse offensive vaginal discharge, but no gonococci were found. On January 10th, 1921, she had frequently relaxed stools containing blood and mucus, followed by obstinate constipation, and her general condition caused phthisis to be suspected. During 1921 she became progressively demented—dull, apathetic, with impulsive outbursts, and the symptoms of impairment of volition (negativism) continued. She was considered a typical case of dementia praecox. Her health again got worse, and on September 12th, 1922, she had pyrexia and relaxed offensive stools. The diagnosis of pulmonary tuberculosis had by this time been confirmed, and after becoming very emaciated she died on October 19th, 1922. *Post-mortem* examination showed pulmonary tuberculosis of both lungs with caseation and cavity formation. The ovaries weighed 3.4 and 3.2 grams; thyroid 8.3 grams; suprarenals 7 grams each. The most striking endocrine deficiency was in the thyroid gland. The suprarenal glands were of normal weight, and there was no obvious diminution of the medulla. Microscopic examination showed abundance of well formed cells; in many places there was a nuclear excess and polymorphism associated with deficiency of cytoplasm. Throughout the medulla there was a pretty general pericellular fibrosis. In this case—which was, relatively to most of the other cases of dementia praecox, of short duration—there was not much histological change in the medulla.

CORRELATION OF ATROPHOUS CHANGES IN THE INTERSTITIAL CELLS OF THE TESTIS AND THE ATROPHOUS CHANGES IN THE ADRENAL MEDULLA.

In a paper on "Further Pathological Studies in Dementia Praecox, especially in relation to the Interstitial Cells of Leydig" (Mott and Prados y Such) regressive atrophic changes were shown in the interstitial cells of twenty-seven cases of dementia praecox, the degree of atrophic change corresponding as a general rule to the length of time elapsing from onset of symptoms and death. Duration of asylum treatment does not strictly connote the length of duration of symptoms.

In nine cases of psychoses other than dementia praecox, death occurring in post-adolescence, similar appearances of regressive atrophy of the testes were found in those cases in which the psychosis was biogenetic in origin and terminated in dementia. Three cases of manic-depressive insanity without symptoms of dementia showed active spermatogenesis, but apparently a diminution of normal interstitial cells.

As a contrast to these regressive atrophic changes occurring in the biogenetic psychoses are the changes in the testes in cases of general paralysis due to local inflamma-

tory lesions. The interstitial cells in this disease do not undergo the same regressive atrophic changes.

There is considerable similarity in the findings of the medullary cells of the adrenal glands and the interstitial cells of the testes. The normal medullary cells of the adrenals, like the normal interstitial cells, are polygonal in shape with a round nucleus; the cytoplasm in both is stained with eosin and presents a fine granular appearance. In the regressive atrophy of dementia praecox that occurs in both these tissues the cells lose their discrete outline, are smaller, have irregular crumbling edges, and tend to form a nucleated syncytium. The nuclei, instead of being a fairly uniform round shape and size, are more or less irregular in size and shape, and increased in numbers, and there is a lack of chromatin in many; especially the large pale irregularly oval shape nuclei appear to be deficient in chromatin. In both tissues there is a fibrosis and increase of fibroblastic nuclei.

Microscopic appearances indicate the continuous development of new interstitial cells of the testes, and new medullary cells of the adrenal, as in both instances mitosis was observable.

In both the atrophic interstitial cells and the atrophic medullary adrenal cells the failure of development of cytoplasm points to a probable failure of the mitochondria to develop. This failure of development may be correlated with a failure of secretion of the specific autacoid of these two glands.

In an acquired disease, general paralysis, the adrenal medullary cells do not as a rule show a deficiency of cytoplasm. In tuberculosis, another acquired disease, there is not any deficiency in the majority of cases dying in an advanced stage in consumption hospitals.

There is, therefore, a certain degree of correlation probable between the symptoms and their duration in dementia and the regressive atrophy of the reproductive organs, and the medulla of the adrenal gland. An investigation on similar lines, of the pituitary glands (shortly to be published), shows that there is a similar regressive atrophy of the cytoplasm, and nuclear changes of the cells of the anterior portion of the gland. An investigation of the thyroid gland is in progress on similar lines. But what is required now is an intensive clinical and laboratory investigation of the whole reproductive endocrine glands and sympathetic system in the various types of mental disease. These generalized researches on a large number of cases should be followed by an intensive study of individual cases, to correlate if possible clinical signs and symptoms with pathological findings. (F. W. M.)

Conclusion.

The most constant change which is found in the medulla adrenalis in dementia praecox is, then, the increased number of nuclei, irregularity of their size and form, and deficiency of chromatin. There is, moreover, an increase of fibrous tissue which often takes a pericellular arrangement and an increase of fibroblastic nuclei. In tuberculosis there may be a great diminution of cytoplasm, but these nuclear changes are not seen. In general paralysis the nuclear change is not observed and the cytoplasm as a rule is not affected to any extent.

We wish to express our great indebtedness to Mr. Chas. Geary for his skilled assistance in making the microscopic sections and the photomicrographs.

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