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Part I.—Original Articles.

A STUDY OF THE HISTOLOGY OF THE TESTIS IN SCHIZOPHRENIA AND OTHER MENTAL DISORDERS.

By R. E. HEMPHILL, M.A., M.D., D.P.M.,
Medical Superintendent, Bristol Mental Hospital;

M. REISS, M.D., D.Sc.Prague,
Director of the Endocrinological Department, Burden Neurological Institute; and

A. L. TAYLOR, M.D.,
Hon. Pathologist and Director of Clinical Laboratories, Bristol General Hospital.

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SYMPTOMS attributed to dysfunction of the ductless glands have long been noticed in the group of mental disorders formerly known as dementia praecox, now included in the wider designation schizophrenia. A variety of such abnormalities has been described, but without sufficient consistency or clarity to help in formulating a pathology of the disorder. From the first, the usual onset in adolescence or early adulthood, and the symptomatology, prompted investigation of the gonads. Papers have been published by Fränkel (1919), Mott (1919), Pézard (1920), Tiffany (1921), Lewis (1923), Morse (1923), Geller (1923), Münzer (1926), McCartney (1929), in which histological changes in the testis in schizophrenia are cited and discussed. The contributions of Mott, Lewis and Morse are the most important, for their material and histology are more accurately controlled and described. It appeared as if the very extensive work done by Mott had succeeded in establishing a direct relationship between gonadal failure and dementia praecox. Subsequently his findings were heavily criticised and the conclusions to a great extent rejected, for, like others, he had obtained material at post mortem, mostly from patients who had died of tuberculosis or other diseases liable to produce the very changes he regarded as specific; very few were young adults in the early phases of the mental disease. These objections constituted an apparently insuperable difficulty, and the whole question has remained virtually in abeyance ever since.

Testicular biopsy, employed by Lane Roberts *et al.* (1939), Charny (1940), in urology, allowed a new approach. By this simple operation, small pieces of testis adequate for histological examination can be obtained from patients selected for good bodily health, and in characteristic forms, phases and durations of the mental illness. Bioptic examinations were made by us in a representative series from various psychoses as well as schizophrenia. Except in special examples referred to in the text, all patients were well nourished and in good bodily health, diets were standard, there was little possibility of avitaminosis. The histological investigations will be described here; clinical correlations and implications will be presented in a subsequent paper.

METHOD.

The following technique was adopted as standard: After the usual pre-operative preparation, the skin of the scrotum over the middle of the lateral aspect of the larger testis is infiltrated with percaine (Ciba) for about 2 cm. An assistant supports the testis, being careful not to exert pressure sufficient to cause venous obstruction. The skin is incised and the various layers of the tunica vaginalis divided between forceps. The escape of a small quantity of fluid signifies that the sac has been opened. The shining tunica albuginea is incised for about 0·5 cm., at right angles to the long axis of the globe, avoiding visible vessels. Slight pressure on the testis at this moment causes a knuckle of tissue to protrude. This is snipped off with very sharp iridectomy scissors and transferred on the point, so as to avoid squeezing with a forceps, directly into Bouin's solution. The skin is closed with one catgut suture and sealed with collodion. The patient wears a suspensory bandage and, if convenient, remains in bed for two or three days. Morphia, gr. ¼, and paraldehyde, drm. ij, by mouth are routine premedication in mental patients. The operation is only possible under local anaesthetic if patients do not resist, and consequently must be conducted very gently. The testis clamp advocated by Schlossmann (1943) must cause venous and lymphatic congestion, and so may alter the histological picture.

The tissue removed is fixed for two days in Bouin's solution—Zenker's solution and 10 per cent. formalin are both inferior—and after careful washing, blocked in paraffin. Sections are cut at 5μ and stained with standard Delafield's haematoxylin and eosin; Mallory's orange G, Masson's trichrome and Van Gieson's stains are used for examination of fibrous and connective tissues and vessels. Formalin fixed frozen sections stained for lipoids proved quite unsatisfactory and, after an initial trial, were not used subsequently. With this technique and precautions uniform sections were obtained, so that the normal and pathological features could be compared in the whole series. In a few cases biopsies were performed on both testes, similar pictures being observed in each. We have found in agreement with Charny (1942) that the bioptic method gives specimens fairly representative of the condition of the whole testis; it has been reliably used experimentally in larger animals (Smith, 1938). Cellular and structural detail are much better preserved in fresh than post-mortem tissue, in which there is a tendency to shrink so that the inter-tubular spaces are exaggerated and the tubules may look smaller (Fig. 1).

MATERIAL.

The specimens were obtained from 90 cases of schizophrenia and 25 others, namely, mania 3, depression 3, involutional melancholia 2, neuroses 4, alcoholism 4, syphilis 2, mental defect 6, organic brain disease 1. There are comparatively few cases of mania or depression, for most of these improve rapidly, and it was felt unjustifiable to seek consent for operation in patients likely to recover quickly unless testis changes could be anticipated and a sufficient number of young subjects in good bodily health could be obtained for study. These conditions cannot be easily fulfilled in the manic-depressive psychosis and other mental illnesses commoner in middle or late life.

As will be seen, the indications are that causally related pathological changes in the testis do not occur in mental disease other than schizophrenia, in the absence of organic disorder. This is in keeping with the findings of Mott, who noted that the testes obtained at post mortem from about 70 non-schizophrenic cases, excluding syphilis and senile states, were comparatively normal. Of the schizophrenic group in our material, apart from three, no cases have been included in which there was evidence at the time of operation of malnutrition, active physical illness or history of tuberculosis, and no patient has been accepted with gross gonadal defects, such as obvious hydrocele or incompletely descended testis. The pathological specimens were numbered and studied without knowledge of their source, in order to avoid possible prejudice. An objective report was made from each in which the histology in general and the state of particular components were described irrespective of the age or clinical diagnosis, which as far as possible were not known at the time.

When specimens from 50 different patients had been examined it was seen that severe pathological changes were present in many; others were less or not at all

affected. The reports were then classified in five groups according to the degree of departure from what was regarded as normal. Some slight adjustment was made later in the light of further experience, and less emphasis laid on certain features, such as intertubular oedema, which had appeared to be of significance in the earlier stages of the investigation.

As a basis for any classification it is essential to establish criteria for what constitutes the normal testis. This is fairly constant for individuals of similar species, age and endocrine state in lower animals. But in man this is not the case. The so-called normal testis is obtained at post-mortem or operation and, apart from the effects of the morbid process, may contain areas of destroyed or damaged elements that are possibly attributable to old age, trauma or intercurrent disease. Nevertheless, in other respects it may be functionally active.

The literature relating to the anatomy and pathology of the human testis prior to 1930 has been well discussed by Stieve (1930). Up to this date there was a tendency to regard what may be called the " textbook " testis as what was commonly to be expected at post mortem in adults free from tumour or local disease. The later investigation of Sand and Okkels (1936, 1937) and others on testes obtained by legal castration or accidental death have shown that the absolute normal is very rarely encountered in mature adult life.

In the normal " classical " testis of adults, tubules whose walls are formed of layers of connective tissue, of which the innermost supports the basement membrane, enclose the regularly arranged seminiferous epithelium and the less obvious Sertoli cells and their processes. The tubules are tightly packed, and where maturation is complete may show lumina containing mature spermatozoa. Elsewhere less mature but actively developing cells fill the tubules, which are seen cut in cross- or oblique section in a relatively loose stroma. In the stroma are various interstitial cells and vessels with groups of Leydig's cells close, but not necessarily related (Rasmussen, 1928) (Figs. 1 and 2).

This picture is rarely seen to perfection in post-mortem tissues. Kyrle (1920) in 1,000 cases saw not one entirely normal testis; Branca (1911), Schinz and Slotopolsky (1924), Romeis (1926) found much the same. Stieve (1930) agreed, but noticed no sign of degeneration in men between 16 and 25 who had suffered accidental death, although spermatogenesis was often unequal in the tubules. Maximow and Bloom (1942) consider that small areas of atrophic tubules are not uncommon after 35 in the normally functioning testis. Koopman (1936) examined testes from castrated sex criminals. Like many other authors, he made no allowance for age or psychiatric diagnosis. Of 69 cases all testes were within a " normal " range and none were non-functioning. He supposed that the small areas of atrophy found in some may have been related to inflammatory or vascular processes, and were more extensive and more frequently seen with increasing age. Testes from 125 sex criminals of another series were " normal " (Rossle, 1935). According to Teem (1935), studying 504 post-mortem cases, a remarkably active state of spermatogenesis is frequently seen as late in life as 40 and 69 years. Sand and Okkels (1936) found 8 completely and 12 nearly normal testes in a selected group of 34 between 20 and 71 years; the remainder were outside normal range. Somewhat similar findings were noted in castrated sex criminals between 20 and 66 years, of average age 39. In a further paper Sand and Okkels (1937) describe an entirely normal histology in 17 out of 72 castrated and sudden death specimens, mostly in the fourth decade.

A fair summary of all these important papers would suggest that up to 25 years of age, with normal bodily health free from endocrine abnormality, the testis should be functionally active and without atrophic processes. From 25 to 35 atrophic areas may be encountered, and from 35 to 66 these will be seen more frequently; there should be fairly active spermatogenesis in most tubules, decreasing with advancing years.

In assessing the degree of normality of the testis the state of spermatogenesis as well as the presence of pathological processes must be evaluated. The former, irrespective of age, must be considered the more important, for the value of a testis as an organ depends on its functional possibilities; these need not be significantly impaired by local areas of atrophy. Pathological changes in a study of the sort undertaken here must be regarded as of secondary importance, unless they produce widespread interference with the organ and are characteristic of the state of the

testis tissue as a whole. Too little is known about the regulation of the internal secretion of the human testis to allow conclusions to be drawn from the histological inspection of a small piece. So although the state of the Leydig cells has been recorded, no attempt has been made to estimate their functional value.

To meet the difficulties and requirements the material was classified as follows: *Group I:* Entirely normal, or free from pathological changes and showing active spermatogenesis (Fig. 2). *Group II:* Active spermatogenesis in the majority of tubules with small and apparently unimportant pathological areas (Fig. 3). *Groups III* and *IV:* Showing increasingly severe degrees of impairment, with defective spermatogenesis and other important pathological features shortly to be detailed (Figs. 4, 5). *Group V:* The severest grade of defect, includes the entirely functionless testes in which no normal spermatozoa were seen in any tubule and in which widespread atrophic areas were apparent (Fig. 6). Thus in certain cases in Group IV almost no normal spermatogenesis was seen, but pathological changes were not extreme (Fig. 5); in others, in Group III, while pathological features were marked, spermatogenesis was moderate in some tubules (Fig. 6). In every case the functional importance of the testis has been emphasized, and if anything the significance of pathological change has been underrated. It is probable that Group II contains examples which are abnormal for the age, if under 25 years, but, on the whole, Groups I and II may be considered to be within normal limits. Although a proportion of Group III would be probably within the normal range if allowance were made for the greater age, it is not possible to regard any case of Group IV or V as approaching normality. The distribution of the case-material among the types of mental disorders will be seen in the table, which shows that the great majority of cases making up Groups IV and V are of schizophrenia. In general these are younger than the other mental types. Their extremes of age being between 15 and 43, all the youngest subjects of any mental illness in Groups IV and V suffered from schizophrenia. The other psychoses ranged in age between 18 and 56 years, and the oldest of all patients are to be found in Group III. If adjustment were made for increasing years it would operate more favourably for the non-schizophrenic psychoses.

When it is seen that apart from one chronic alcoholic and two cases of syphilis, the remaining 22 out of 25 specimens from non-schizophrenic patients are in Grades I, II and III, and that more than half of those from schizophrenics are in IV and V, a considerable difference in the pathology of the testis in these two mental groups will be anticipated. This is, in fact, so, and there are marked differences between the schizophrenic testis and those of other conditions. It will be convenient to consider first the changes in the component parts, and later piece them together to obtain as far as possible a picture of the whole pathological process.

Histological Criteria.

(1) *Changes in Intra-tubular Epithelium.*

Abnormal spermatogenesis may occur with or without noticeable alteration of the tubular capsule. Although both coexist in many of the specimens from schizophrenics, capsular changes were exceptional in the non-schizophrenic group. These appearances may be considered as:

(a) *Breaking up of intra-tubular elements.*—Fragility of the contents of the tubules, with, in the lumina, debris and fragmented cell tissue which tended to stain poorly, was commonly seen in many cases of all groups. According to Maximow and Bloom (1942) this should not be regarded as abnormal unless extensive. Clumps and "balls" of debris and shedding of immature cells into the lumen is always pathological according to Stieve (1930). This picture was regarded as indicating a local condition unless many tubules were affected, and in such cases there were usually evidences of more serious damage elsewhere.

(b) *Falling out of tubular centres.*—A complete arrest of spermatogenesis at any stage of maturation produces an appearance as if the centres of the tubules have dropped out, so that all cellular elements and Sertoli network are lost. The intra-tubular structures seem to become fragile, break away and pass into the lumina. Although frequently observed in a few tubules it was extreme in only two cases (Figs. 7, 8). Both suffered from schizophrenia, but in addition one developed acute miliary tuberculosis and died shortly after biopsy, while the other had been

refusing food and was undernourished. A photomicrograph almost identical with Fig. 7 of a single case published by Stieve (1930) represents changes in the testis of a healthy adult who committed suicide after 16 days' privation when pursued by the police. The tendency to disintegration of all elements is not characteristic of the usual causes of atrophy, e.g. heat, X-ray, etc., where the more resistant Sertoli network is well preserved, and it gives the impression of being an acute process, for shrinkage or collapse such as occurs when hyalinized tubules lose their contents has not taken place. The view that this is an artefact, the intratubular material having dropped out in fixation, may be set aside, for, as seen in Figs. 8 and 9, the lumina may contain a colloid-like substance, which stains pinkish violet with Mallory's orange G. This form of degeneration is probably the result of an acute change in intratubular elements and not secondary to affection of the tubular capsule. Both these special cases have been included in the series, because in some of their tubules the more characteristic changes associated with schizophrenia were seen.

(c) *Reduced spermatogenesis.*—A relative inactivity of sperm formation was the chief defect in non-schizophrenic and non-organic cases. This could be judged only by comparison with the most active specimens, and by itself did not condemn any to a lower grade than II. In older patients, over 40, there was as a rule a noticeable quantitative reduction of seminiferous epithelium, although what was seen appeared to be in adequate activity. The Sertoli cells were better preserved and with some disappearance of seminiferous epithelium became more obvious. The testis of a chronic alcoholic in the sixth decade was well equipped and appeared remarkably active (Fig. 10).

(2) *Tubular Changes Associated with Alterations of the Tubule Capsules.*

(a) *"Cart-wheels."*—This appearance is produced by the combination of severe loss of seminiferous cells and prominence of Sertoli cells and their processes. The Sertoli processes radiate from a hub composed of poorly staining degenerate or immature cells in the centre of a tubule that is without patent lumen (Figs. 11, 12). They are prominent and seem often to be thickened, and in a state of activity in contrast with the seminiferous cells (Fig. 12).

Peripherally they are in close relation with the basement membrane. Between the " spokes " of the wheel are seminiferous cells, relatively few in number and inactive. No mature forms are seen, and even the spermatogonia may be defective in number and show few mitoses. This picture resembles the atrophy that has been demonstrated in animals as the result of heat, malposition of the testis and noxious agents, and in certain human cases, in which the more mature germinal forms suffer most but the hardier Sertoli cells survive. The vacuole formation described by Charny (1942) is similar, and produced by gaps in the syncitial background due to loss of cells.

It was noted that the capsule was usually thicker than normal in the " cart-wheel " tubule and consisted of layers, somewhat separated and split; it often presented a wavy appearance. In the great majority of specimens showing this form, damaged tubules with hyalinized capsules were also present. Although the basement membrane was usually thicker than normal, the hyaline change, now to be described, was not seen in the well developed " cart-wheels."

(b) *Tubular atrophy with hyalinization of the capsule.*—In almost all the more seriously damaged testes, as well as in some of class 2 of the schizophrenic group a characteristic finding regardless of age was hyaline degeneration of the capsule. It was observed that inside tubules so affected the cells, seminiferous and Sertoli alike, lost their distinct morphology and tended to become one mass of indeterminate structure that stained rather heavily but without any clear definition. Although mitotic figures were observed, mature sperm forms were not seen, and the appearance was that of degenerating cells (Fig. 13). Many specimens showed tubules affected in varying degree, and it was therefore possible to study the development of the germinal atrophy and the process of hyalinization.

All the evidence is that the intratubular change is secondary to the hyalinization. Some tubules were seen in which nearly normal spermatogenesis was proceeding in spite of a little alteration of the capsule, but in every tubule in which the hyalinization reached a certain extent, the germinal cell degeneration occurred. Thereafter the result seemed to be always the same. The thickened layer of the

capsule encroached on the interior of the tubule; normal spermatogenesis ceased, and as soon as the basement membrane reached a certain thickness the contained cell mass became detached and passed freely into the interior of the tubule. The hyaline shell later collapsed, and the tubule was represented by a slit or a mass of hyaline material between the surviving tubules. The site of primary change can be stated with certainty to be the basement membrane. This structure is barely visible in the normal active testis of early adult life. It becomes thicker and somewhat more obvious at 40 to 45 years (Stieve, 1930). That it is not necessarily affected by malnutrition and by the usual causes of testis atrophy is well demonstrated by Case A. F— (Fig. 14). Here it may be seen as a thin band in close relation to the seminiferous epithelium and Sertoli cells, lying internal to the flattened nuclei of the lamellated connective tissue that forms the outer supporting wall of the tubule. This patient died of terminal broncho-pneumonia, superimposed on Alzheimer's pre-senile cerebral atrophy. His illness had been protracted, and for some months before death he was grossly emaciated.

We have found it convenient for purposes of classification to assess the course of the morbid process in five grades of increasing severity:

First stage.—In Fig. 15, depicting a normal tubule in active spermatogenesis, the basement membrane can only just be discerned. In the first stage of change it becomes more clearly defined; for a while spermatogenesis may proceed satisfactorily (Fig. 16).

Second stage.—The basement membrane appears definitely thickened by comparison with the normally thicker outer layer; spermatogenesis is affected, the intra-tubular elements lose their clarity and fuse into a rather amorphous mass in which some cells are still in mitosis. By contrast with the tubular atrophy of testis injury or bodily disease all elements are disorganized, the primitive germ cells and Sertoli cells are not specially preserved, the seminiferous epithelium losing its architectural arrangement (Fig. 17).

Third stage.—With further thickening, now well marked even at low magnifications, the degeneration proceeds and the tubule shrinks in size (Fig. 18). At this third stage the contents break away from the basement membrane, and the tubule collapses as the walls approximate (Fig. 19). In Fig. 20 (the same case as Fig. 15) at high magnification the epithelium can be seen closely related and attached to the basement membrane. By contrast, in Fig. 21 (same case as Fig. 18) the enormously thickened hyalinized membrane projects into the lumen of a tubule in folds to which the degenerated epithelium is no longer attached. The hyalinized portion has already exceeded in width the outer layers of the capsule. Detachment of the epithelium precedes collapse, as empty but patent tubules often occur; shrinkage is not entirely responsible, for tubules which would be of normal size if full are frequently seen in process of emptying.

Fourth stage.—The empty tubules may remain as incompletely closed slits, empty or containing a little debris (Fig. 22). Spermatozoa and other cells from unaffected parts of the tubule distal to the destroyed area are never seen, so it appears as if the lumen is blocked or spermatogenesis has ceased beyond this point.

Fifth stage.—In the last stage the hyalinized walls tend to fuse, and all that is left is a mass in which the faint outlines of the original tubule can sometimes be recognized (Fig. 23). The outer layers of the capsule never become hyalinized, and there is no hyperplasia or fibrosis of the interstitial stroma. The end-result in advanced cases is a destroyed testis containing tubules in every stage of atrophy in a non-fibrous stroma with, in places, areas of amorphous hyaline material (Fig. 24).

The hyalinization has certain peculiarities. It is patchy and not necessarily continuous throughout the entire length of the tubule. This is well seen in Fig. 25, showing a tubule in the first stage; one portion in the wall shows the grey line of change, but elsewhere the capsule is healthy. In spite of the small size of the biopsy material serial sections tend to confirm that the process is patchy. The degeneration is progressive, for in severe or long-standing cases longitudinal sections show it throughout (Fig. 24). It cannot be ascertained how many tubules are similarly affected without investigating the whole testis, for no doubt several sections of the same tubule cut through different loops are seen in the biopsy specimen. In many specimens cross-sections showing the greatest damage are grouped together so that they probably represent extensive change for a great length of the same tubule. No reason for the local predilection was apparent.

The hyalinized membrane stains silvery grey with haematoxylin-eosin, dense blue with Mallory's orange G, pinkish red with Van Gieson's. Externally it is in the main smooth, being limited by the unaffected outer layer, but centrally it has a wavy form and projects towards the centre of the tubule. Yet, even in destroyed tubules, the boundaries of the membrane, both external and central, are retained, and the internal outline can always be identified by a thin dark line (Fig. 21). Detached portions of hyaline material are never seen in the lumina. When the hyalinizing process has reached a certain development it is arrested, for there is an apparent limit to the size the basement membrane can attain, which was much the same for all tubules, and fusion of the walls only takes place long after complete tubular collapse. This suggests that the pathological process invariably attacks a basement membrane of normal size which has not been subjected to some earlier disturbance or fibrosis.

The hyalinization, in effect only a histological appearance, must represent chemical changes occurring in the basement membrane. As grave degeneration of all intra-tubular contents is seen in the second stage of hyalinization, before encroachment on the internal volume of the tubule can be great, it will be noted that a much better state of spermatogenesis often exists in more contracted tubules where Sertoli cells are better presented. These changes must be due not to the mechanical effect of pressure, but to interference with the nutrition of the epithelium, an effect which, if prolonged, is fatal to all elements, Sertoli cells included. It is felt justifiable to regard the affection of the basement membrane as the primary tubular factor in this form of atrophy, and characteristic of the degenerated testis of schizophrenia.

This degeneration is not an isolated phenomenon seen in an otherwise healthy testis. In most of the schizophrenic material hyalinized tubules were accompanied by the other forms of atrophy in varying degree, but more especially the cart-wheel type, and no really active and seemingly normal specimen of any group contained many severely hyalinized areas. This suggests either that one pathological process affects tubules in different ways, that the non-hyalinized atrophy is secondary to, or primary for, the hyaline type, or that independent pathological processes coexist. The second, or a combination of the first and second, suggestions are the most feasible. It has been shown that the hyaline change does not necessarily involve the entire length of any one tubule, rather that it is patchy and distributed irregularly. Considering the great length and many loops of each tubule, a patchy change which leads to obstruction of the lumen with degenerated cell material and eventual collapse and obliteration must, where it is on the proximal side of areas as yet unaffected, cause blocking of their outlet, with back-pressure. Any one field might show sections of loops on the proximal side of affected areas possibly in normal condition and activity, as well as those hyalinized, and others distal with obstructed outlet. It seems likely that atrophy of seminiferous epithelium, with preservation of the Sertoli network, can result from obstruction of this sort as, according to some workers, follows tying the vas deferens. But an additional factor, possibly endocrine, may have to operate as well as back-pressure, to prevent the regeneration of seminiferous epithelium which occurs after experimental closure of the excurrent ducts in animals (Moore, 1938). This explanation is consistent with the observed facts.

(c) *Other changes of the capsule.*—Thickening of the outer layers of the capsule amounting to peritubular fibrosis, in which these layers blend with the connective tissue of the interstitial spaces, was not uncommon in the older patients and where the atrophy was of some years' duration. On the whole, however, it was not in proportion to the degree of atrophy, and in many cases the end-result was a shrunken mass of tubules in every stage of atrophy surrounded by a loose or oedematous stroma, with little increase in intra-tubular connective tissue. In the syphilitic and in one of the alcoholic cases there was a marked increase of peritubular fibrosis, so that the capsules blended with a dense fibrous stroma that bound them together. In all atrophic testes, irrespective of the cause, the average size of the tubules was small.

Capsules split into layers with a wavy outline, which we have called "crenellation," are not necessarily pathological. This appearance is caused by irregular shrinkage of the circular coats so that the layers become separated and distorted. It is more marked when for any reason, such as normal emptying or loss of cells,

the contents of the tubules are reduced. It is therefore not seen where hyalinization of basement membrane encroaches on the internal volume and presumably increases the intra-tubular pressure.

(3) *Interstitial Tissues.*

(a) *Stroma.*—A colloid-like material, which stained with eosin and pinkish violet with Mallory's orange G, was commonly found between the tubules in many cases, irrespective of the grade of testis or clinical diagnosis. This has been described by other observers as oedema, a name that has therefore been retained in this paper. At first in agreement with them it was regarded as pathological, but it appeared so frequently even in testes of the highest grade that this is evidently an overstatement. It was however most noticeable where tubules were small and where atrophy without peri-tubular fibrosis had taken place. Here it appeared to be compensatory to the reduced tubular volume.

Many papers have described a compensatory increase in interstitial cells, and even hyperplasia of Leydig's cells in areas of tubular atrophy. This was not seen in the majority of the schizophrenic testes and is therefore a point of difference, especially as in non-schizophrenic organic atrophy, e.g. from syphilis or alcoholism of long standing, there was a marked interstitial reaction. In many chronic testes of Grade V the interstitial as well as the tubular tissue was much shrunken, and neither fibrosis nor oedema were much in evidence. It is probably safe to regard the interstitial oedema as space-filling in response to immediate changes in tubule volume, physiological or atrophic, but temporary, and apt to disappear as the testis shrinks or becomes fibrosed, or conceivably if the tubules regain size. It is certainly not due to trauma as suggested by Wangensteen (1927).

(b) *Leydig's cells.*—Their presence has been noted. It was felt unjustified to try to estimate their functional state from the histology. Masses of these cells are found scattered in the interstitial tissue of the normal testis, and their absence from a small biopsy specimen is not evidence that they are reduced in the slightest. No deprivation results follow unilateral castration, and probably the internal secretion is adequately supplied in adults so long as a fraction of the total secreting cells persists. Even examining the whole testis Sand and Okkels (1936) were unable to find quantitative measurements of Leydig's cells of value. Estimation of the excretion of androgens as 17-ketosteroids, which in healthy male adults are derived from adrenal cortex and gonads, at least 9 and 5 mgm. respectively from each (Fraser *et al.*, 1941) showed that a very high or very low output was not necessarily associated with presence or absence of Leydig's cells in the biopsy specimens in our cases, irrespective of the morphology. Thus it is clear that histological examination of Leydig's cells by the ordinary staining methods used in this study can tell nothing of their functional state. Secondary sex characteristics were not abnormal in any of the patients, so presumably their maintenance was supplied by an adequate internal secretion.

(c) *Vessels.*—In a high proportion of the schizophrenic material there was a marked thickening of the blood vessels, particularly those of smaller size. The lumina were much reduced, and the walls stained a dense blue with Mallory's orange G and red with Van Gieson's stain (Figs. 26, 27). No bodily disorder was found to be responsible in any case; hypertension and urinary disturbances were not present. This type of vascular sclerosis was found in many schizophrenics of all ages, including some of the youngest, but not in other cases of uncomplicated mental illness. The possibility that the tubular atrophy was secondary to vascular sclerosis was considered and rejected, as in some specimens the two processes did not co-exist, for healthy tubules were occasionally associated with sclerosed vessels, and satisfactory tubular conditions were found in several of the older non-schizophrenic testes in spite of vascular changes. This abnormality is to be regarded as part of the pathology of some forms of schizophrenia, and in keeping with the vascular anomalies commonly observed in this disease.

Macroscopic Features.

It is of interest to note here the varying macroscopic features met with at biopsy. They corresponded significantly with the microscopic picture subsequently portrayed.

The testes of many patients when the scrotum was opened were found to be

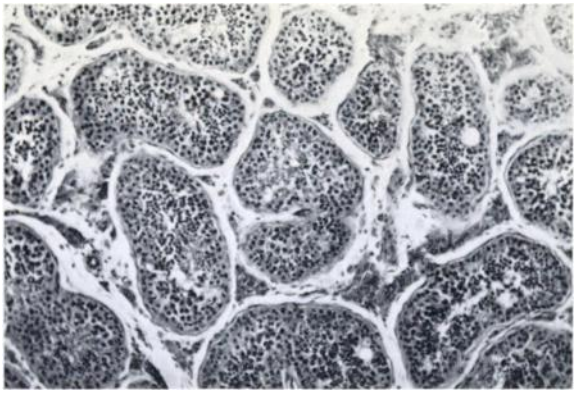

FIG. 1.—Non-mental, aged 39. Post-mortem normal. Well filled tubules; thin capsules; normal Leydig's cells. × 100.

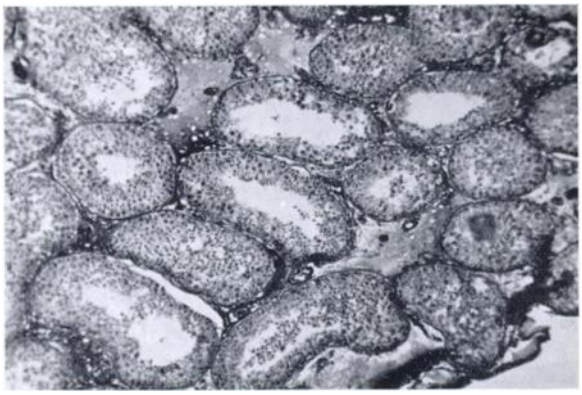

FIG. 2.—Early paranoid, aged 25. No. 110. Normal active spermatogenesis; thin capsule; intertubular oedema. × 80.

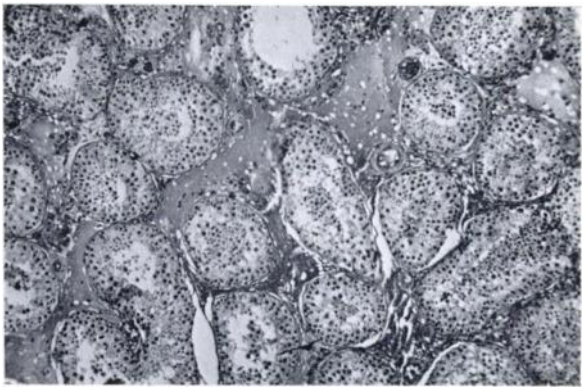

FIG. 3.—Paranoid, aged 32. No. 39. Grade II. × 80.

Note.—The arrow on certain figures indicates the basement membrane.

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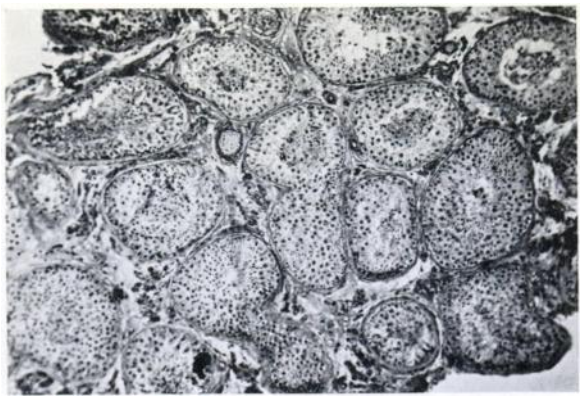

FIG. 4.—Early schizophrenic, aged 24. No. 96. Grade III. Capsular thickening; some "cart-wheels"; fair spermatogenesis. × 80.

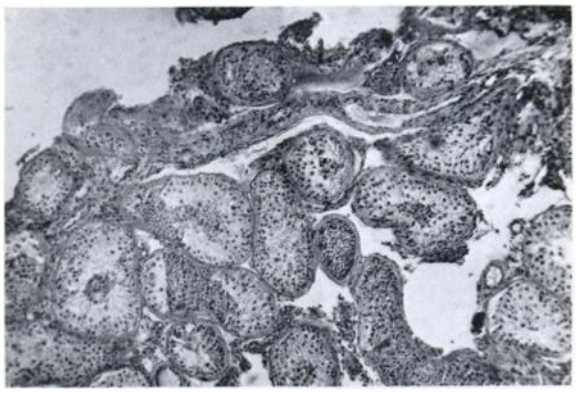

FIG. 5.—Chronic deteriorated schizophrenic, aged 36. No. 12. Grade IV. Capsular thickening showing hyalinized tubules, a few well filled. × 80.

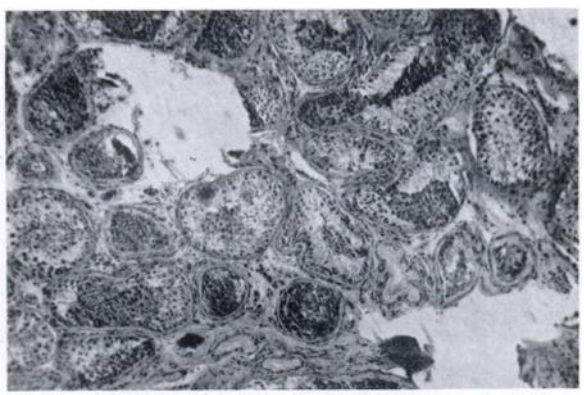

FIG. 6.—Chronic deteriorated schizophrenic, aged 17. No. 15. Grade V. Shrunken atrophied tubules. Hyalinized masses. Hyaline changes basement membrane. × 80.

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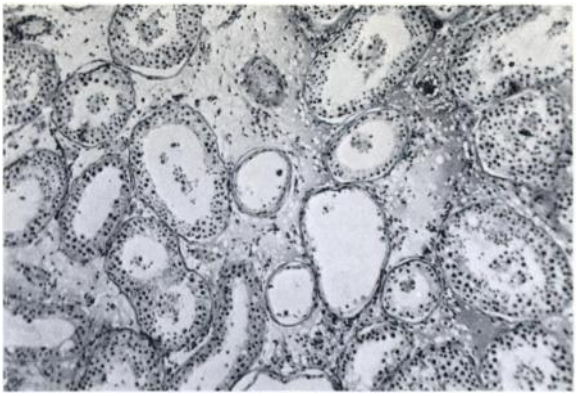

FIG. 7.—Early acute catatonic schizophrenic, aged 25. No. 32. Grade V. Showing "falling-out" of centres; all types of cells breaking away; fragility of epithelium. × 80.

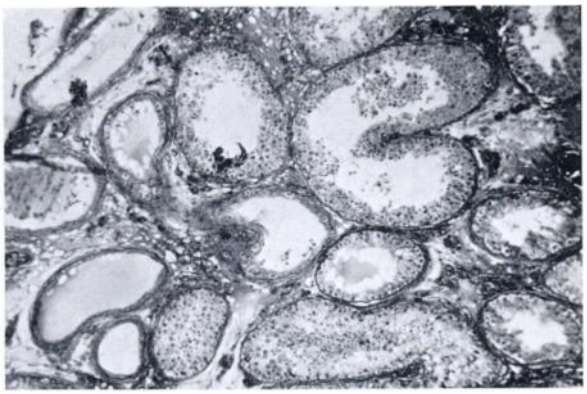

FIG. 8.—Mixed schizophrenic, early, aged 19. No. 104. Grade III. Showing "falling-out" of centres. Note colloid in empty lumina; stained Mallory's orange G. × 80.

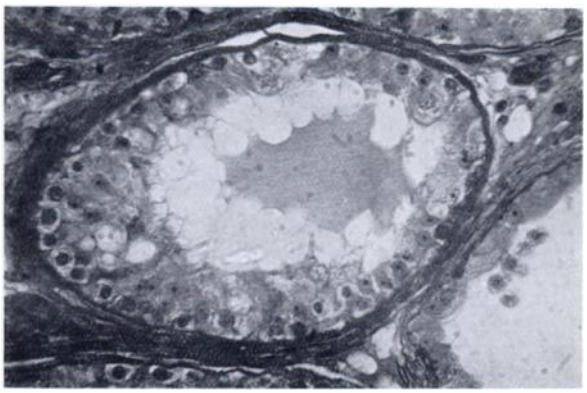

FIG. 9.—Tubule from Fig. 8. No. 104. Stained Mallory's orange G. × 330.

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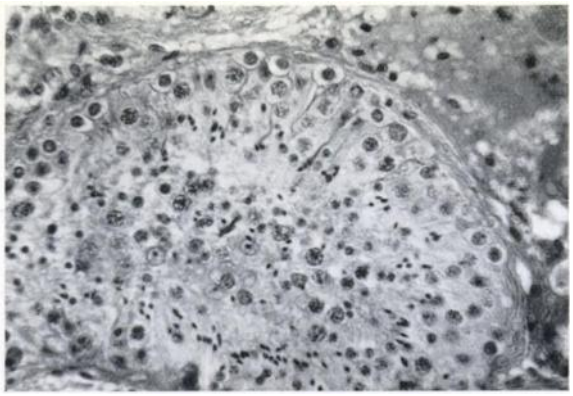

FIG. 10.—Tubule from chronic alcoholic, aged 56. Note regular architecture of epithelium with thin basement membrane. × 420.

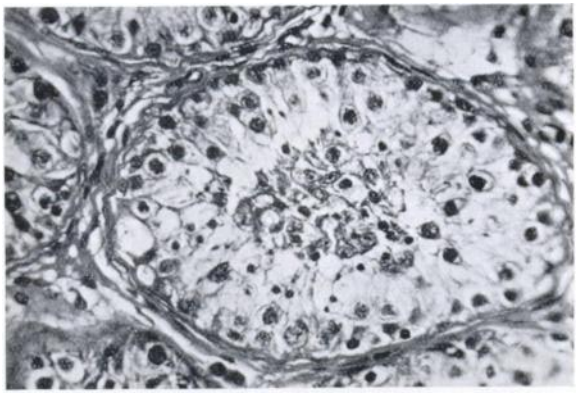

FIG. 11.—Chronic catatonic schizophrenic, aged 29. No. 43. Grade V. "Cartwheels." Note loss of spermatogenetic cells with preservation of Sertoli structure; slightly thickened basement membrane. × 330.

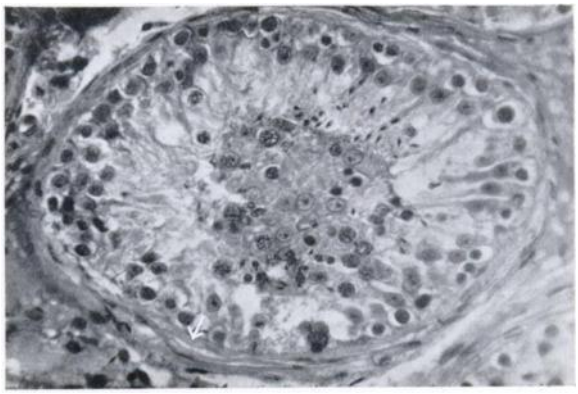

FIG. 12.—Early schizophrenic, aged 24. No. 98. Grade V. "Cartwheel." Note debris in centre, prominent Sertoli structure, some activity and stage 2 thickening of basement membrane. × 330.

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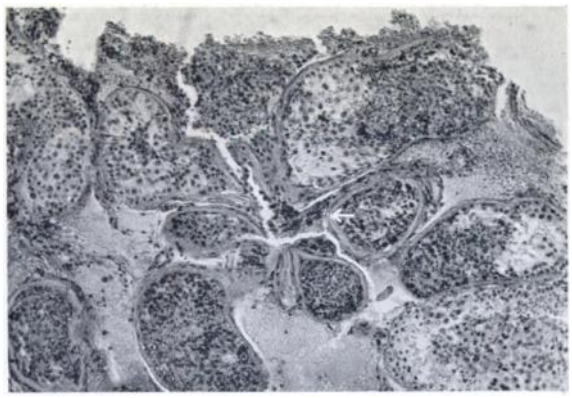

FIG. 13.—Mild chronic schizophrenic, aged 34. No. 54. Grade III. Showing shrinkage of tubules and atrophy with hyalinization of basement membrane, mostly third stage. × 80.

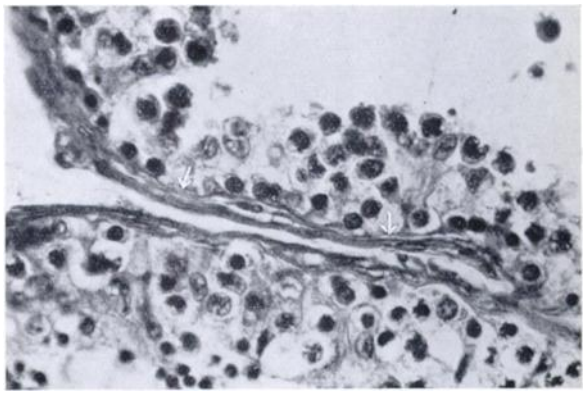

FIG. 14.—Post-mortem specimen from emaciated non-schizophrenic, aged 49, showing slightly thickened basement membrane narrower than lamellated outer capsular layer. Note well preserved architecture of seminiferous epithelium. × 420.

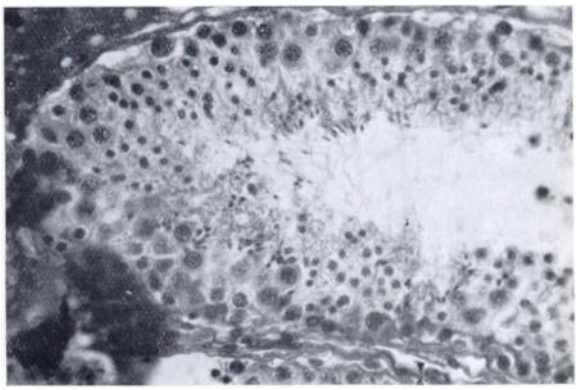

FIG. 15.—Early paranoid, aged 25. No. 110. Grade I. Note thin basement membrane, regular architecture, very active spermatogenesis. × 330.

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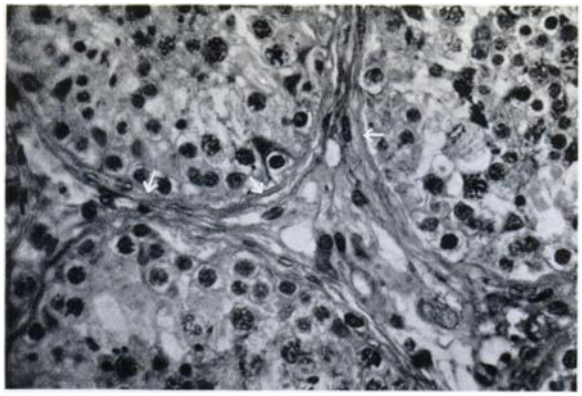

FIG. 16.—Early schizophrenic, aged 20. No. 90. Grade III. *First stage* of change; basement membrane is becoming thick and obvious. × 420.

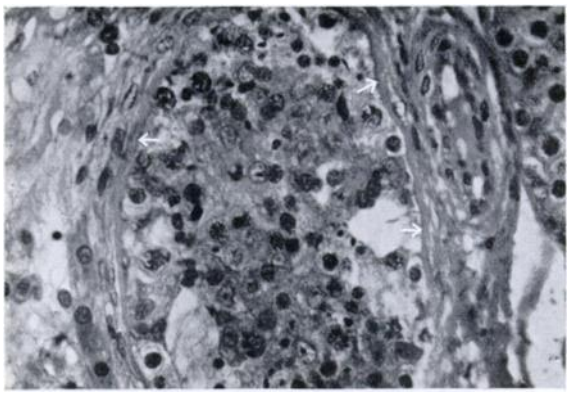

FIG. 17.—Same case as Fig. 20. *Second stage.* Basement membrane thicker, becoming hyalinized. Contents of tubule losing clarity, beginning to break up. × 420.

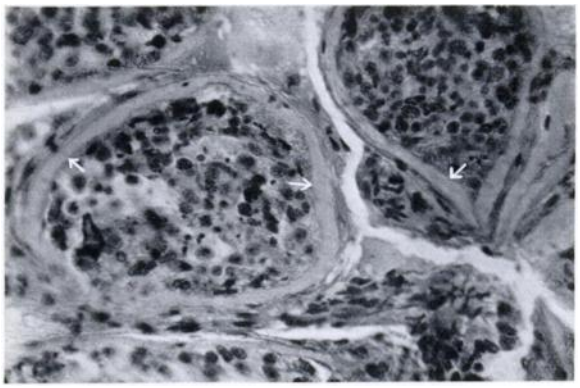

FIG. 18.—Mild chronic schizophrenic, aged 34. No. 54. Grade III. *Third stage* of change: Basement membrane hyalinized, thick and grey, tubular contents degenerating, tubules on left beginning to collapse. × 330.

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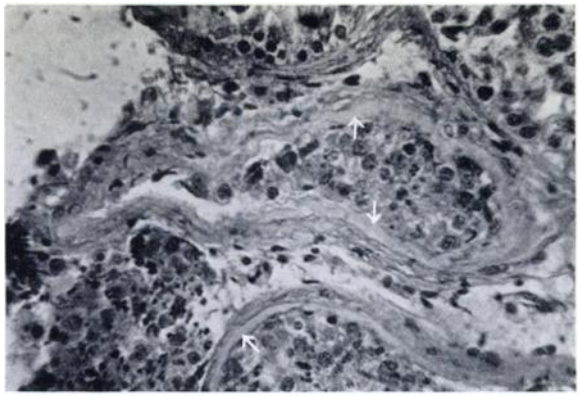

FIG. 19.—Chronic catatonic schizophrenic, aged 34. No. 60. *Third stage.* Note amorphous cell material breaking away from collapsing tubule. Grade V. × 330.

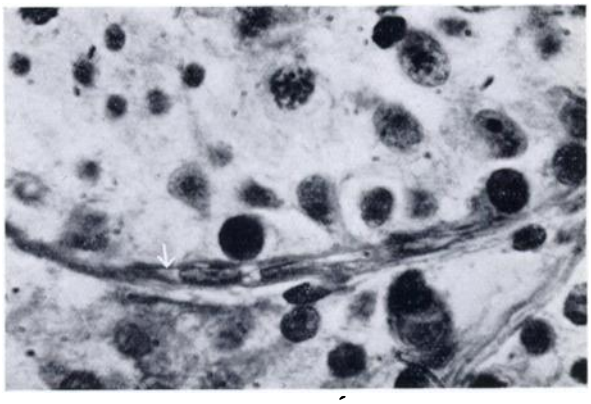

FIG. 20.—Normal tubule, same as Fig. 15. Note thin basement membrane, with seminiferous epithelium closely related and well preserved. Lamellated outer layer of capsule external to its nuclei; thicker than basement membrane. × 960.

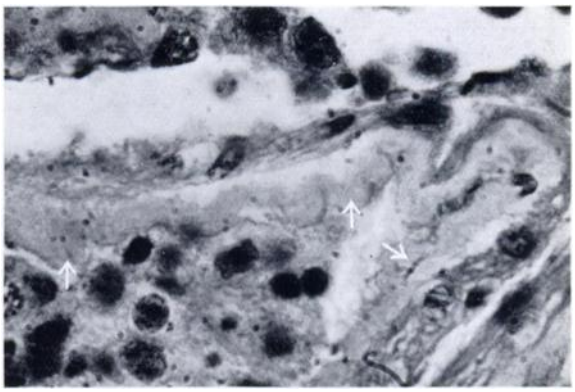

FIG. 21.—Same case as Fig. 13. Grade III. Note thick hyalinized basement membrane extending with folds towards centre of tubule and degeneration epithelium detached from it. Compare with Fig. 24. × 960.

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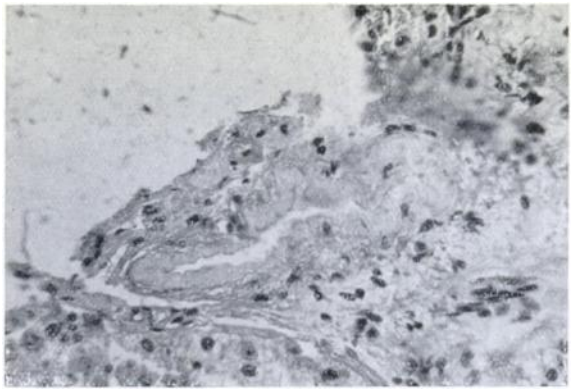

FIG. 22.—Early schizophrenic, aged 15. No. 108. *Fourth stage.* Empty hyalinized tubule. × 330.

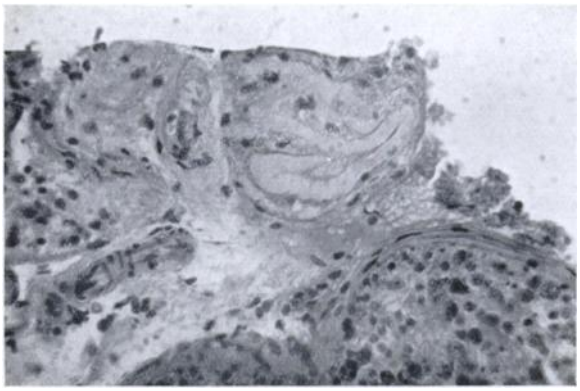

FIG. 23.—No. 60. Same case as Fig. 19. *Fifth stage.* Hyalinized masses of fused tubules. × 330.

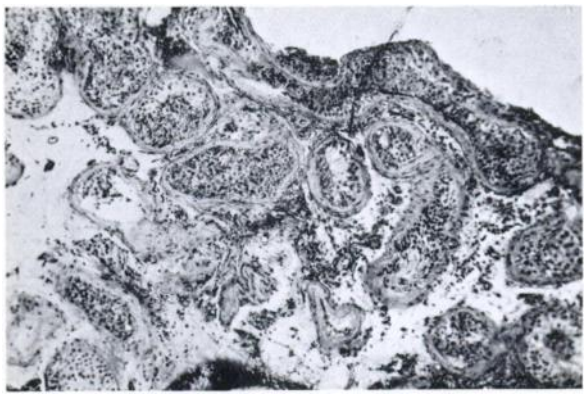

FIG. 24.—Chronic deteriorated schizophrenic, aged 43. No. 63. Highly damaged testis; no normal tubules; end result of atrophic process. × 80.

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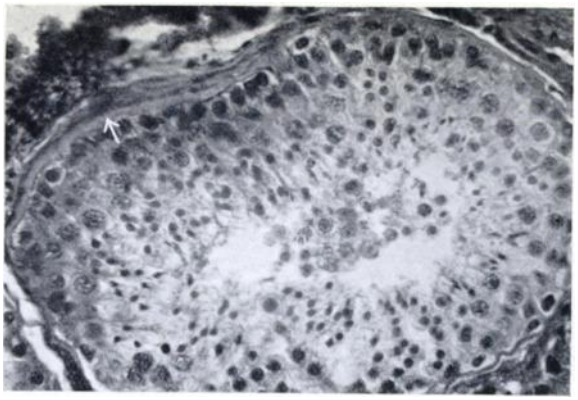

FIG. 25.—No. 54. Same case as Fig. 13, showing patchy hyaline change in one part of tubule. × 330.

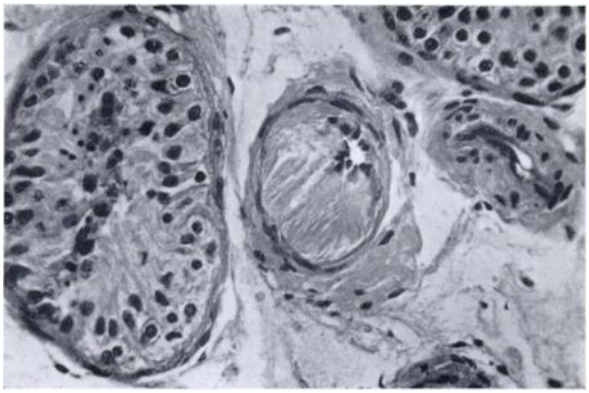

FIG. 26.—Chronic schizophrenic, aged 27. No. 5. Sclerosed vessels in atrophied testis. Grade V. Vessel in centre cut obliquely. × 330.

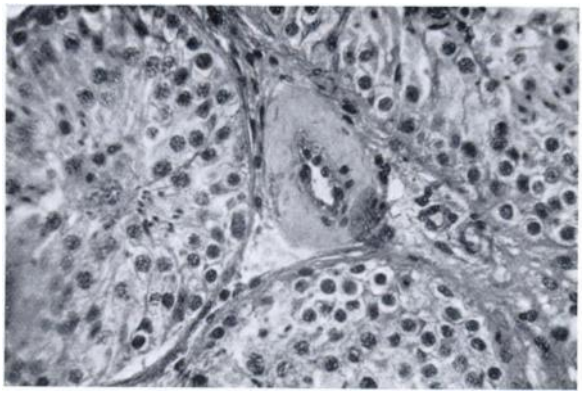

FIG. 27.—Early schizophrenic, aged 19. No. 97. Grade III. Fair tubules besides sclerosed vessel. × 330.

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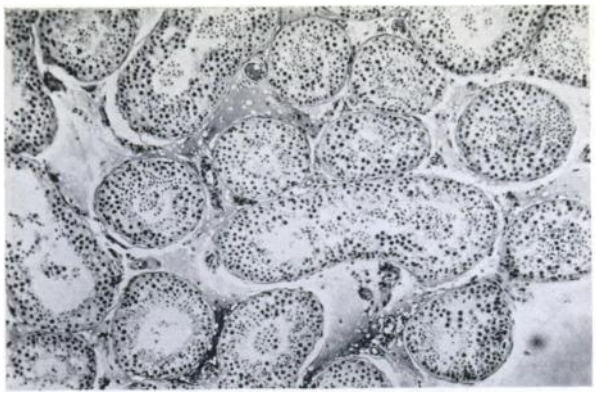

FIG. 28.—Mania, aged 35. No. 34. Normal. Grade I. × 80.

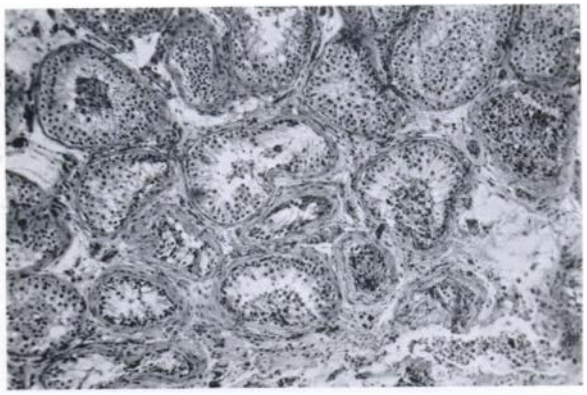

FIG. 29.—Chronic deteriorated schizophrenic, aged 33. No. 21. Peri-tubular fibrosis in shrunken testis. Grade V. × 80.

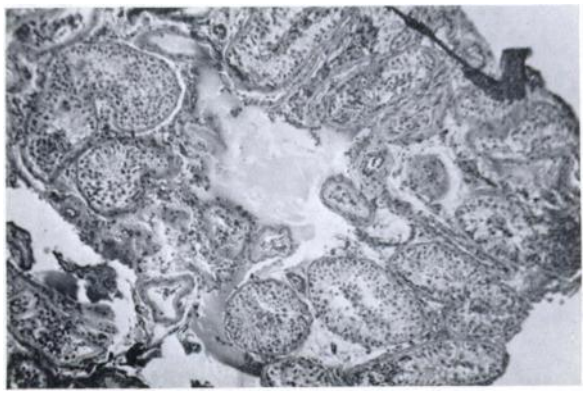

FIG. 30.—Chronic deteriorated schizophrenic, aged 34. No. 46. Grade V. Showing numerous hyalinized and shrunk tubules. × 80.

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small and soft. External examination was of little value, for small hydroceles or masses of adipose tissue in and around the tunica vaginalis were not uncommon. In non-atrophic testes the globe felt firm or resilient, and very slight pressure, as soon as the tunica albuginea was incised, caused tubular tissue to extrude. This cut easily and made good histological preparations. The atrophied testes looked shrunken. It was always difficult to open the tunica albuginea cleanly against the reduced resistance, and pressure on the globe failed to extrude the contents. The pieces obtained were friable and broke up in the fixing solution. The nature of the tissue could usually be judged at operation, and it will be noticed that in the low-power photographs the lowest grade specimens are often ragged and small. The apparent preponderance of hyalinized tubules at the periphery is explained by the tissue breaking off in fixation at this fragile place. Awkward haemorrhage from the interior of the testis caused haematocele in three cases and bleeding was often troublesome in atrophic testes, no doubt due to the vascular changes.

There was a noticeable difference in sensitivity in various patients. The tunica albuginea cannot be anaesthetized, and in normals (non-mental) a severe " testis " type of pain is often experienced as it is being incised. This was sometimes sufficient to cause a state of reflex shock and temporary collapse. The shrunken testis of schizophrenia was appreciably more difficult to open quickly, as its softer surface recedes from the knife, and when open the tissue will not extrude without pressure —conditions that should materially increase pain and likelihood of shock. On the contrary, most of these patients ignored this stage of the operation, irrespective of whether they had opposed the earlier manipulation. Severe reflex shock was not seen.

Histological Classification.

The histo-pathological criteria described above may now be applied for the classification of all the biopsy material. It is at once evident that the vast majority of atrophied testes belonged to cases of schizophrenic psychosis, while a fair proportion of those from other mental types were within normal limits or damaged to an extent commensurate only with the age or co-existent physical illness. The table summarizes the distribution of the grades of testis defect according to the mental diagnosis, and records the ages of the non-schizophrenic subjects concerned. Apart from four cases complicated by chronic alcoholism and two syphilitics, the grading of the non-schizophrenic material varied between complete normality (Grade I) seen in cases of mania (Fig. 28), and only moderate loss of germinal epithelium and reduction of spermatogenesis in the older subjects (Grade III). None of these changes is beyond expectation, for if allowance were made for age, all may be regarded as being within normal limits; of the ten cases in Grade III eight were in the fifth or sixth decade.

The statement that chronic alcoholism always causes testis damage irrespective of the age, frequently quoted from Weichselbaum and Kyrle (1910), is obviously not true. Only one of the four cases in this series showed the changes described by him—thickening of the capsules, increase of interstitial tissue, cessation of spermatogenesis and obliteration of tubules. Case 56 (Figs. 9, 10), a former publican suffering from Korsakoff's psychosis and chronic alcoholism, at 56 the oldest patient investigated, had a highly active testis, with no hyaline change, only mild thickening of the outer capsule layers, and considerable vascular sclerosis. In spite of the greatest abuse of alcohol, this testis and that of Case 58 (also alcoholic) are well up to the normal for the age.

In the two neuro-syphilitics without gummatous orchitis spermatogenesis was almost absent and a dense interstitial fibrosis bound up the tubules, features similar to those described by Mott (1919) in G.P.I. and to the non-gummatous areas of chronic fibrous orchitis of syphilis (MacCallum, 1940).

By contrast with the relatively mild changes in the non-schizophrenic specimens, the preponderance of grossly defective testes in the schizophrenic series is highly significant. Out of a total of 90 only 2 show a normal histology, and no fewer than 71 fall into Grades III, IV, V; 26, or more than one-third, present extreme atrophic change. It is unnecessary to record individual ages for, unlike the non-schizophrenic group, the vast majority were in the second and third decades, so that in no cases can age be held a contributory factor. For this reason Grade III

defect in schizophrenia is certainly significant, and cannot here be regarded as being within normal limits for the age.

It is justifiable to conclude that the atrophic changes of the testis described in this paper are a specific feature of many cases of schizophrenia; they have not been found in the commoner forms of other mental illness and mental defect, and therefore it is suggested that they are an integral part of some forms, at least, of the schizophrenic reaction group. Clinical evidence in support will be presented in a subsequent paper.

Discussion.

The biopsy material reviewed in this study resolves itself into normal histology, damaged testes with interstitial fibrosis, and the hyalinized testis seen in schizophrenia.

Interstitial fibrosis accompanied by degenerative atrophy of the seminiferous epithelium is a usual result of chronic systemic affections, local trauma, and a variety of toxic processes. It has been regarded as such by Hansemann (1895), Lubarsch (1896), Cordes (1898), Oberdorfer (1930), Charny (1942), and many others. With them we are in agreement. When found in the chronic schizophrenic testis it indicates a superimposed fibrosing process. Case 21 (Fig. 29), who suffered from chronic pulmonary tuberculosis is an example. There is no proof as to whether the atrophy of germinal elements is secondary to capsular fibrosis or not, but it is generally recognized that infections, even of short duration, may cause a cessation of spermatogenesis, in which the later and more mature cells suffer first and the spermatogonia, Sertoli and tubular walls survive longest (Metz, 1938). Five stages of atrophy in unselected post-mortem testes, mainly senile, are described by Schinz and Slotopolsky (1924). The first three cover the stages of degeneration of spermia, spermatids and spermatocytes; in the fourth only a few cells are left, and this state "endures" until succeeded by the stage of hyaline degeneration of the wall of the tubule. This concept, with which Stieve (1930) agrees, assumes that this form of hyalinization of the tubular wall is a late stage of intra-tubular atrophy, and if these authors are correct, constitutes an important point of difference between the atrophied testis of schizophrenia and that due to other causes. In the non-schizophrenic material the abnormalities, therefore, were what might have been anticipated for the age and state of bodily health.

As we have shown, the changes in schizophrenia varied between a slight reduction in spermatogenesis and gross atrophy. A striking and constant feature in the more severely damaged testes is hyaline degeneration of the basement membrane, associated with atrophy of the seminiferous epithelium of the tubules so affected. In some instances the process seems to have been progressive, so that the worst grade of testis is a shrunken organ with few active tubules, many hyalinized in varying degree, and hyaline masses representing the remnants of others (Fig. 30). This state does not depend on the age of the patient, and typical examples were seen in young and old irrespectively. The germinal atrophy succeeds the hyalinization and is dependent on it. In the most damaged specimens spermatogenesis is never completely normal, even in the better preserved tubules, and where there is no severe hyalinization the cart-wheel formation is usually evident. Sclerosis of testicular smaller vessels is common, and there is relatively little interstitial fibrosis. The tubules are mostly of small size, but there is no compensatory hyperplasia of the interstitial substance, as is usually found in other forms of tubular atrophy. Oedema is frequently present; Leydig's cells are inconstant in quantity. As a general rule testicular sensation is much reduced and the tunica albuginea in particular is surprisingly insensitive. These histological and clinical features were found in so many cases of schizophrenia that they must be regarded as characteristic of the state of the testis in this disorder. The correlation of atrophy with clinical forms of schizophrenia will be discussed in a later paper.

The little that is known about atrophy of the testis in humans throws no certain light on the origin of this special form. Conditions that have been accepted as responsible for testis atrophy are: disturbances in food intake—over- or underfeeding; avitaminosis; errors in metabolism; alcohol, nicotine, caffeine and other poisons; acute illnesses; chronic illnesses, such as cancer, tubercle, syphilis; psychic influences (Stieve, 1930). Apart from the few cases specifically mentioned, none of these, psychic excepted, operated in this case-material. The psychic

influences mentioned by Stieve need not be considered, for they refer to the effects of captivity on animals.

The histological changes in the testis of animals (there is so far nothing known about the human) due to deprivation of vitamins A, B group, C, D, E, have been summarized by Mason (1938). They do not resemble what has been described above, and hyalinization of the capsule is not mentioned. Cancer, chronic ill-health, and malnutrition are the commonest causes of tubular atrophy and fibrosis, which are nearly always associated with interstitial hyperplasia (Collins, 1936), although the converse is not true (Bothe and Robinson, 1933). Hyalinization was not observed by these writers. The senile testis shows an inconstant atrophy, and sometimes may be well preserved. Spangarro (1902) has described capsular hyalinization as being a terminal state of atrophy in senility, following cessation of spermatogenesis. It was not observed by Jemerin (1937) in seniles; he commonly noted hypertrophy of the interstitial tissues in proportion to the reduction in tubular size.

Sand and Okkels (1937) found capsular hyalinization in a number of testes of castrated sex criminals. They believed it was in proportion to an earlier atrophy of the underlying epithelium provoking in some way thickening of the basement membrane; this caused impaired nutrition and a vicious circle was established. They do not disclose what were the mental and physical conditions before operation. Sex offences are usually the result of disordered mental states, among them schizophrenia, as seen in some of this case material, and it is possible that the hyalinized specimens were provided by this group. The same applies to other similar work, for no allowance has ever been made for mental illness, and no histologist seems to have suspected its importance in pathological material that was not specifically supplied from mental hospitals.

It might be suggested that the damaged tubules in the schizophrenic testis are due to imperfect development, and represent degenerative changes in infantile and immature structures. The small size of many of the tubules and the youth of some of the patients in the worst grades might seem to support this. Charny (1942) assumes that "failure of tubular development is indicated histologically by the presence of small tubules filled with undifferentiated cell forms. Peritubular fibrosis was not present," The statement is not supported by evidence. Hypoplastic testes are found frequently in children under 11 years, but in less than 6 per cent. between 12 and 20 (Voss, 1913), and are usually normal by puberty (Diamantopoulos, 1921; Wangensteen, 1927). It would be exceptional to find a high proportion of hypoplastic testes in schizophrenia unless there were some reason to associate errors of development with this illness, and no such reason exists. Moreover, the thick tunica albuginea, normally fully mature between 15 and 17 years (Stieve, 1930), and the characteristics of most tubules, indicates complete pubertal development. Some degree of hyaline degeneration may be seen in tubules of the largest adult size which still produce adult spermia, although the more severely damaged tubules are usually small. We can therefore assume that the hyalinized tubules seen in pubertal and early adolescent cases are not necessarily immature, and that the pathological process shows no predilection for tissues in retarded development.

The only reason that might be suggested for regarding the vascular sclerosis as of primary importance is the experimental evidence that section of the internal spermatic artery in dogs is followed by reduction in size of the testis and scattered areas of degeneration (Wangensteen, 1927). It is noteworthy that hyalinization of the basement membrane was not described in his experiments. In our cases the association of vessel and testis change was not invariable, and in the non-schizophrenic material considerable vascular sclerosis did not produce tubular atrophy.

It is less easy to exclude impairment of nerve supply as the causative factor. Ablation of the inferior mesenteric ganglion and nerves of the right spermatic artery in dogs is followed by extensive germinal degeneration (Kuntz, 1919; Takahashi, 1922). Autonomic abnormalities are common in schizophrenia, and it was noted that at operation many patients showed no appreciation of pain or severe reflex shock when the tunica albuginea was opened. But the whole problem of the nerve supply of the testis and its component parts is still obscure, and much more corroborative evidence of local nerve impairment would be necessary to establish a

neural origin for the tubular atrophy, for obviously the relative anaesthesia of the tunica albuginea might be explained on different grounds.

Cryptorchidism has been more extensively studied than any other abnormality of the testis in the human, and there are points of similarity between the cryptorchid and the schizophrenic testis. The evidence is that both local and endocrine factors operate. In experimental cryptorchidism the Sertoli cells usually persist (Moore, 1924), but atrophy and hyalinization of the basement membrane may occur (Dick, 1936). Up to puberty the testis may be normal, but thereafter there is a progressive atrophy corresponding to the age, although spermatozoa have been found in the semen at 24, and a fairly well-preserved germinal epithelium occasionally in the sixth and seventh decade (MacCallum, 1935; Rea, 1942). There is thus a proportion of tubules capable of functioning even years after puberty. Capsular fibrosis with hyalinization may occur which precludes any chance of regeneration (Pace and Cabot, 1936). Most modern authors remark on the notable absence of hyperplasia of the interstitium. In the patchy progressive atrophy, with local hyaline changes, the persistence of some co-existent germinal activity, the presence of some tubules containing only Sertoli cells ("cart-wheels"), the lack of an interstitial hyperplasia and the preservation of an internal secretion, the resemblance to the schizophrenic testis is close. In both conditions some interference with the normal development and health of the seminiferous epithelium is apparent. In cryptorchidism local heat is the principal agent (Moore, 1924), but interference with the normal hormonal control could achieve a similar result. In schizophrenia there is no local factor, and as the pathology is not that of changes due to noxious agents, an endocrine cause is the most probable.

Almost nothing is known of the hormonal control of the adult testis in the human or of the changes that follow its modification or withdrawal. Destructive conditions of the anterior pituitary may cause gonadal atrophy, and extensive tubular degeneration with hyalinization of the capsules may result from hypothalamic tumours (personal observation).

In one case of endocrinopathy, where only a fragment of thyroid remained, there were reduced spermatogenesis, wide oedematous interstitial spaces and no interstitial hyperplasia (Wegelin *et al.*, 1926); in a case of myxoedema with a pituitary adenoma Marine (1939) noticed small testes, with small widely spaced tubules; there was no spermatogenesis, the Sertoli cells were intact, the interstitial cells much reduced. It appears that in general, atrophy of the testes associated with endocrine disorder is not accompanied by the interstitial hyperplasia usually seen in other conditions. Degeneration of the human testis can be produced by administration of oestrogen, which depresses the activity of the anterior pituitary (Zondek, 1936). Biopsy studies were made on two patients before and after treatment with stilboestrol by Dunn (1941). There was marked degeneration of the seminiferous epithelium, reduction in size of the tubules and number of interstitial cells. The published photomicrographs show "cart-wheels," and in one case what appears to be moderate hyalinization of the basement membrane. Regeneration is said to have occurred some time after cessation of treatment.

Although more is known of pre-pubertal pituitary insufficiency, the exact histology is still to be presented, and it has still to be shown how far lack of gonadotrophic hormone in adults is responsible for mild degrees of germinal atrophy, oligospermia and the contradictions of senility. Atrophied tubules and hyalinized capsules without interstitial fibrosis have been attributed to endocrine causes (Charny, 1940, 1942; Hotchkiss, 1942); but they supply insufficient proof, and the published results of gonadotrophic hormone therapy are neither convincing nor satisfactory. Hypophysectomy causes gonadal atrophy in animals; the changes are not similar in different species. Reduction in tubular size, thickening of the capsule and cessation of spermatogenesis with appearance of immature cells is usual in rats and monkeys (Smith, 1938). We have examined a large number of testes of rats at various periods after complete and partial hypophysectomy. The sudden arrest of spermatogenesis produced the "punched-out" effect described before (Figs. 7, 8); the resemblance was greatest a week or less after operation and after incomplete hypophysectomy; slight interstitial oedema was observed as the tubules shrank but only before interstitial fibrosis had replaced it. Capsular thickening, not indisputably of the innermost layer, was always an accompaniment of atrophy; hyalinization was not seen. Although frequently described in humans,

hyalinization does not seem to have been noticed in animals, and to our knowledge it appears in neither the accounts nor the photomicrographs of animal experiments. The comparative histology can be taken no farther, and it may be fairly claimed only that some of the pathological features of the schizophrenic testis are also seen in testis atrophy after hypophysectomy in lower animals. We have attached some importance to the relatively small interstitial amount of interstitium and the poor interstitial response to tubular atrophy. If, as we believe, the form of atrophy we have described in schizophrenia has an endocrine origin, this might be due to a failing pituitary regulation, whereby the so-called interstitial cell stimulating hormone is no longer produced as a compensatory process. It has still to be shown how far the histological changes might be due, if this assumption be accepted, to the inability of the anterior lobe of the pituitary to maintain an adequate output of gonadotrophic hormone under physiological conditions, or to increase its production in response to necessity. Although outside the scope of this histological paper, we felt obliged to remark that while none of our schizophrenic patients were clinical hypogonads, abnormalities of the distribution of hair, especially of the growth of the beard, were common, in spite of obviously well-developed external genitals—an effect in keeping with a condition of partial, or qualitative, gonadotrophic hypofunction. We hope at some future date to be able to investigate the ratio of androgen to oestrogen in some of these cases, with a view to clarifying this point.

The foregoing account covers most of what is known or has been described of the histology of atrophic changes in the human testis, not the result of local trauma, tumour or orchitis. It is evident that there is much more to be learned, and in this respect testicular biopsy offers the only useful method of obtaining reliable histological material. Such material should be evaluated with regard to all clinical aspects, mental as well as physical and endocrine.

In the detailed descriptions of Mott (1919), Lewis (1923), " parenchymatous " tubular degeneration appears. Great importance was attached by Mott to interstitial hyperplasia. This, as has been shown, is characteristic only of physical disorders, and was in all probability due to the morbid processes that brought the patients to autopsy. It was therefore a pathological contamination, and probably in most cases superimposed on the more specific type of atrophy. Hyaline degeneration of the basement membrane was often seen.

Original preparations made available for study by the kindness of Prof. Nevin, Prof. Golla and Dr. A. Meyer, and photomicrographs of Mott show many examples similar to some of those reproduced here. The cytological investigations (McCartney, 1929) have made little contribution to the histology of the human testis.

Although this study confirms the contention that testis atrophy in schizophrenia does occur, it disagrees in the main with what Mott and his contemporaries regarded as characteristic of the histology, its causation and significance in pathogenesis of the disorder. Tiffany (1929) alone seems to have commented on the lack of interstitial cells and poor interstitial reaction compensatory to tubular atrophy in schizophrenia. Sclerosis of testis vessels has not been described before in this condition. Lewis (1923) endeavoured to show that hypoplasia of the cardiovascular system was a constitutional defect in schizophrenia, but almost certainly he was describing the results of bodily wasting in chronic tuberculosis, from which most of his younger patients died.

Summary.

Histological examinations were made of biopsy specimens from the testes of 90 cases of schizophrenia and 25 cases of other mental disorders. Pathological changes of varying severity were observed in many specimens; these changes have been classified in grades according to the intensity of the degenerative process.

The non-schizophrenic specimens were within normal limits, due allowance being made for age and organic disease.

A special form of atrophy involving chiefly the tubules and their contents was found in many cases of schizophrenia, but not in other mental disorders. This atrophy is characterized by changes in the basement membrane leading to its hyalinization, with arrest of spermatogenesis, progressive degeneration of epithelial elements, and eventual destruction of the tubule. The course and development of

this atrophy have been described and analysed. It differs in essential features from atrophy due to systemic affections and to the familiar causes of testis degeneration. Interstitial hyperplasia is rare, and when present in schizophrenic subjects is due to some superimposed organic process.

The work of Mott and others has been discussed in the light of this study. Although they reported pathological changes which they regarded as specific for schizophrenia (dementia praecox), the histology differed significantly from what is described in this paper. It is clear that as autopsy was the only source of their material, serious contaminating factors, such as advanced age and intercurrent infections, were introduced, and would inevitably tend to obscure the histological picture.

The importance of a normal basement membrane for preservation of Sertoli cells and seminiferous epithelium has been demonstrated, and it has been shown that hyaline change in the basement membrane in atrophy of the testis is a cause and not a result of degeneration of the epithelium as other writers have suggested.

GRADES OF DEFECT.

Diagnosis.	1.	2.	3.	4.	5.	Total.
Mania	(39), (33) = 2	(39) = 1	—	—	—	3
Depression	—	(45), (18) = 2	(44) = 1	—	—	3
Involutional melancholia	—	—	(51), (55) = 2	—	—	2
Neuroses	(41) = 1	(43) = 1	(47), (38) = 2	—	—	4
Chronic alcoholism*	—	—	*(50), *(55), *(42) = 3	—	*(45) = 1	4
Syphilis*	—	—	—	*(49), *(20) = 2	—	2
Organic brain disease	—	(41) = 1	—	—	—	1
Mental defect	—	(40), (25), (38), (38) = 4	(28), (41) = 2	—	—	6
Total	3	9	10	2	1	25
Schizophrenia	2	17	24	21	26	90

N.B.—Patient's age is in parentheses.

* = Known organic or endocrine condition associated with mental illness.

Hormone estimations were made at the Burden Neurological Institute, Bristol, under the direction of Dr. Max Reiss.

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