

Epilepsy and the Ductless Glands. By GUY P. U. PRIOR, M.R.C.S., L.R.C.P., Medical Superintendent, Mental Hospital, Rydalmere; and S. EVAN JONES, M.B., Medical Officer, Mental Hospital, Callan Park, New South Wales.

THE actions of the ductless glands are very complex, and become greatly complicated when one of them is either under or over acting, because of its stimulating or inhibitory effect upon some other endocrine organ. To help in the difficulty of understanding their action, as an aid in diagnosing abnormalities in their secretion and in administering extracts of these glands, we drew up the following tables. So as to do no injustice to the authors upon whose works we have taken the liberty to base these tables, we should like to repeat that in many cases, the author to whom we attribute a statement, is himself frequently quoting someone else, and often does not support the view we have credited to him. It is only by reference to the original work that the author's meaning can be appreciated. Accepting as probably correct Gower's theory, that epilepsy is due to some chemical affecting the nerve-cells (1), and considering the great influence the endocrine glands have on chemical changes of the body, we have endeavoured to study these glands in their relation to epilepsy, and to discover if there is any evidence of their abnormal action in this disease.

EXPLANATION AND ABBREVIATIONS IN TABLES.

The statements as to the action of the glands have been taken from books or papers of various authors. In many cases the author to whom a statement is attributed is himself quoting some other authority, and does not of necessity support that statement. It is only by reference to the original work that the author's meaning can be fully appreciated.

The authority for any given remark is indicated by an initial, as:

S	= Schäfer, <i>The Endocrine Organs.</i>
B	= Bell, Blair, <i>The Sex Complex.</i>
P	= Paton, Noel, <i>Regulators of Metabolism.</i>
F	= Falta, <i>The Ductless Glandular Diseases.</i>
Sajous	= Sajous, paper in <i>Practitioner</i> , Feb., 1915.
L. Pr.	= Leopold-Levi, paper in <i>Practitioner</i> , Feb., 1915.
B. Pr.	= Bell, Blair, " " " "
W. Pr.	= Waller, H. E., " " " "
W. L. Pr.	= Williams, L., " " " Jan., 1915.
H. Pr.	= Hertoghe, E., " " " "
Herty, Pr.	= Herty, Pr., " " " "
E. Pr.	= Elliott, T. R., " " " "
V. Pr.	= Vincent, Swale " " " "
E1 & E2	= statement is to be found in <i>Endocrinology</i> , vol. 1 or vol. 2.
+	= increases.
-	= diminishes.
O	= ovarian.
T	= testicular.

Epileptiform convulsions may occur after removal of the thyroid parathyroid system (2), in extreme cases of Addison's disease (3), in hypopituitarism (4); also in cases with minus parathyroid action, as when associated with tetany (9). In two young epileptics, who died suddenly, we found considerable enlargement of the thymus gland and small heart and aorta; in both these cases the aorta would only admit one finger, and in both these cases the suprarenal glands microscopically showed a large extent of vacuolation. These cases, in their mode of death and in their *post-mortem* findings, much resemble status lymphaticus.

Is there usually, in epilepsy, any change in the ductless glandular system, and can treatment with these glands in any way influence the disease for better or worse? We think that we can show that both these questions can be answered in the affirmative.

Pituitary.

Schafer says that in conditions of hypopituitarism a tendency to epilepsy has occasionally been described (4). Several authors have recorded cases of epilepsy making great improvement with anterior pituitary extract. Spears (5) relates a case of a man, *æt.* 28, an epileptic since 6 years of age, with an average of three or four fits weekly, who, after four months' treatment with anterior pituitary, had no fit, and has continued without for eight months. Tucker (6) records a number of cases that improved with the same treatment; and Joughin (7) the case of a girl, *æt.* 16, who improved within two weeks of taking anterior pituitary extract, and has been without major seizures for two years. This case was clinically one of hypopituitarism.

G. C. Johnston (8) claims that there are often changes about the pituitary in cases of epilepsy unattended by gross evidence of pituitary disorder, and advises the use of radiography in these cases. We have under our care eighty male epileptics, of whom four are clinically unmistakable cases of hypopituitarism. They all have abundance of adipose tissue, and have no hair on the body except pubic hair, two have no hair in the axilla, and the other very little. Three have but a scanty amount of hair on the face, one case has rather an abundant beard. All four have large mammary glands. They all have a low blood-pressure, their highest record being 115 mm. Hg., which was reached once in one case in the recumbent position; the majority of their blood-pressure readings were higher lying down than standing.

Although these cases, from their general appearance and clinical signs, may be taken to be typically apituitary, the improvement they have made on treatment with whole gland pituitary has been but slight. We have used the whole gland pituitary in preference to the

anterior gland, as one case in which we used this latter was so much worse while taking this that we had to discontinue the treatment, when improvement immediately followed.

At the time of treating these cases we were unaware of the success that others had obtained with the anterior gland, and intend to give this a more extended trial.

Case 43, without any medicinal treatment, has an average of 7 fits a month, varying from 2 to 14. For four months he was taking pituitary extract, gr. $2\frac{1}{2}$ t.i.d.; for these months he averaged 10 fits a month, ranging from 8 to 14.

Case 8 has been treated over a longer period; without treatment for a period of twelve months he averaged 13 attacks monthly, ranging from 7 to 15; for four months he was taking pituitary extract, for which time he averaged 10 fits a month, being a slight reduction from his former average. For a second period of four months, he received calcium chloride, gr. x, every four hours, with a resulting average of 10 fits monthly. For three months he has been taking potass. brom., g. vii 4 tis horis, with an average of 5 fits a month. This patient appears to have received slight benefit from pituitary gland, but to have received more from bromide.

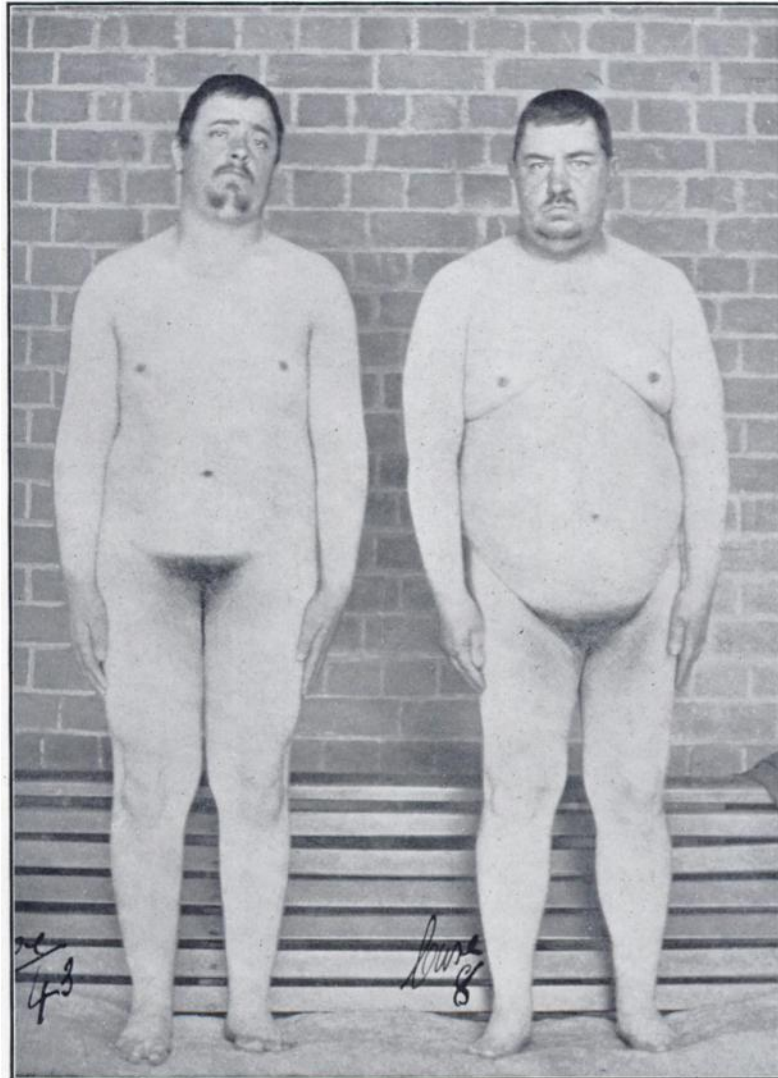
CASE 38.—For nine months, while being treated with pot. brom., gr. xx t.i.d., averages 18 attacks a month; for two months he takes pituitary gland in addition to the bromide, when the average rises to 22 monthly. With suprarenal gland for three months in place of the pituitary, the average number of attacks monthly drops to 18. For three months didymin, gr. xv, daily is given, and the average rises to 20.

If, in any way, the epileptic attacks in this type of patient are directly associated with or due to insufficient pituitary action, an increased number of fits is to be expected with didymin, as the gonads are stated to inhibit the action of pituitary (10).

Parathyroid.

Falta (9) states that epileptic attacks in tetany are not rare, and that Redlich collected seventy-two cases where these diseases have been associated. He also states that in parathyroprivic individuals unilateral or bilateral epileptiform convulsions with loss of consciousness have been observed. Blair Bell (2) says that animals from which he removed both the thyroid and parathyroid glands died of convulsions. Know (11) records cases of epilepsy which improved with parathyroid and calcium lactate. One of our cases on admission presented many signs that might be accounted for by parathyroid insufficiency.

CASE 39.—A male, æt. 21, had an insane inheritance, and had suffered from epilepsy since he was two years old.



Apituitary.

To illustrate paper by Drs. PRIOR and JONES.

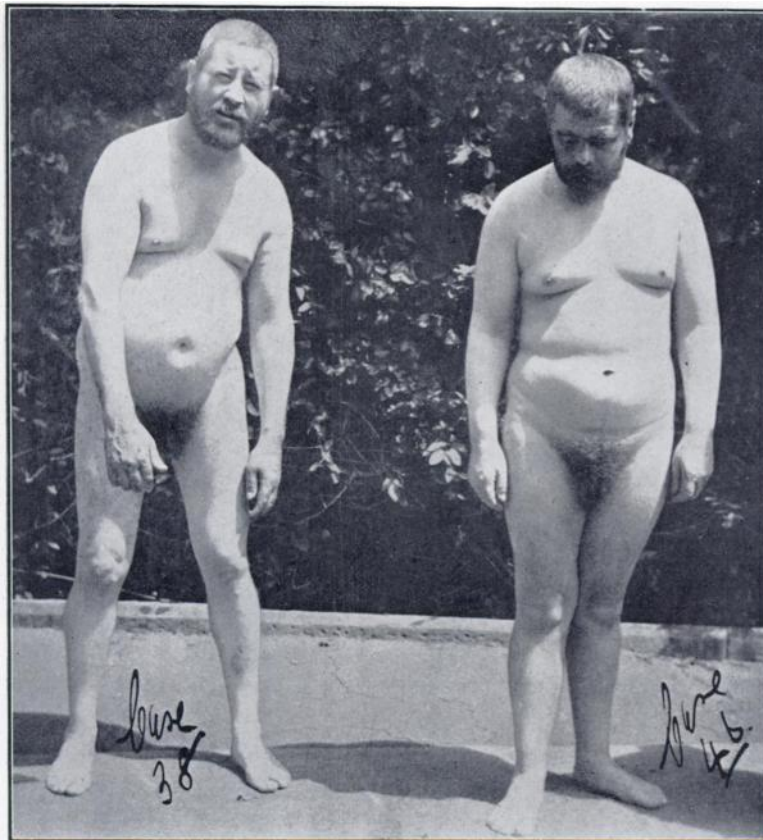
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Apituitary.

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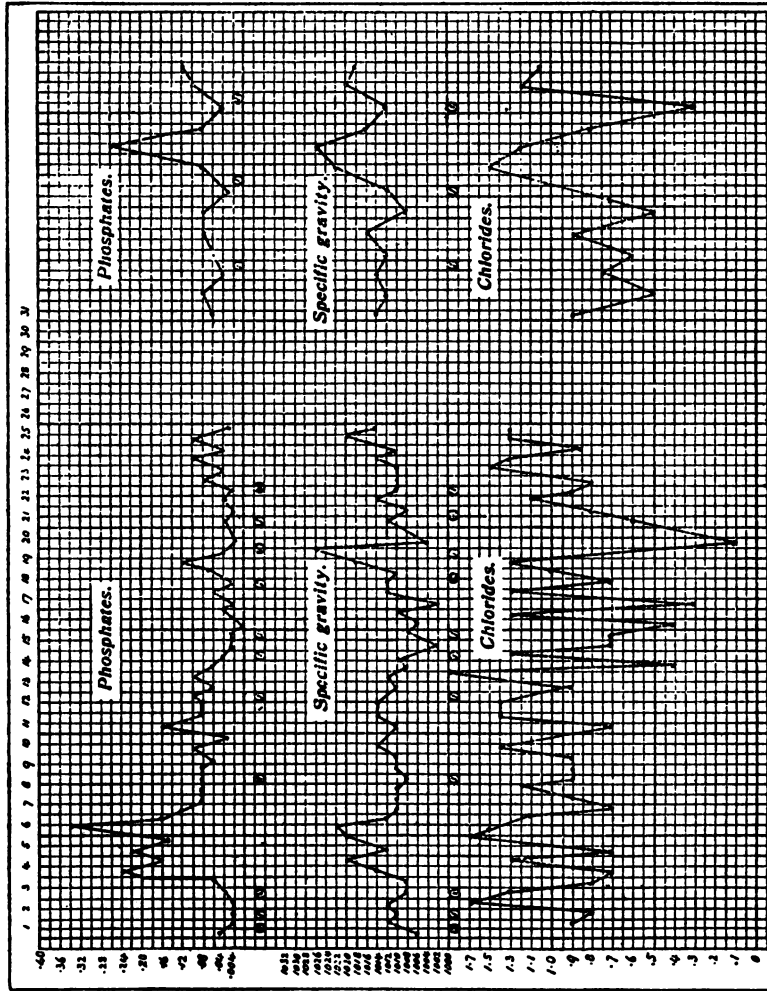
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Apituitary.

To illustrate paper by Drs. **PRIOR** and **JONES**.

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CASE NO. 18.

CASE NO. 26.

Charts showing the specific gravity and the amount of phosphates and chlorides in grammes *per cent.* in 12-hourly in Case No. 26, and in 24-hourly in Case No. 18, specimens of urine and their relations to epileptic attacks. Fits thus O. Equivalents in form of tremors thus ———.

On admission he was extremely thin and wasted, of light build, and with small bones, saliva flowed from his mouth in one constant stream, his teeth were carious, nails badly developed, he had but little appetite, mentally he was dull and tearful, all reflexes were so greatly exaggerated, together with tremor of tongue and facial muscles and inco-ordination of speech, that it was at first thought that he was an advanced infantile general paralytic. By referring to the table on parathyroid action it will be seen that most of this boy's symptoms are consistent with under-action of this gland. His mother stated that for many months previous to admission he had been having more than 100 fits a month while taking bromides. During the first month under our observation, while having no treatment, he had 102 fits. He was for one month given a mixture of calcium lactate and potassium bromide and his fits fell to 30 for the month. For six months he took parathyroid gland, gr. 1-10 daily, he put on weight, ceased to salivate, the reflexes became normal, and after two months of treatment he was sufficiently well to work at gardening. During the fifth month he became very dull, with unsteady gait and almost cessation of the epileptic attacks, having for this month only 6 fits. His blood-pressure was at this time very low, varying from 85 to 105 mm. Hg.; because of this low blood-pressure, and because it is stated that parathyroid action is antagonistic to suprarenal, he was given for six weeks suprarenal gland extract instead of parathyroid, and the bromide and calcium were suspended. He improved in physical health, his blood-pressure rose, and the monthly average of his fits rose to 43. For the next three months he was again given parathyroid gland and the mixture of calcium and bromide. For this period he remains well, physically and mentally, and resumes his work and averages 14 attacks a month.

Another case of similar type and build and with exaggerated reflexes we have treated in the same way.

This patient, Case 40, has been an epileptic since 10 months of age, and is now *æ*t. 26. A record of his attacks has been kept by his mother for several years. She states that for four months previous to admission he had averaged 18 fits a month while being treated; for two years previous to this he had averaged 10 attacks monthly. For the first month after admission, without treatment, he had 10 fits. For seven months he had been treated with parathyroid gland together with bromide and calcium chloride, with an average of 3 fits monthly, ranging from 1 to 4. Before being treated he was subject to attacks of irritability and violence, which were the reason of his being admitted. He has since had no trouble in this way, but is, in fact, a quiet and trusted worker.

Case 7 is another case that has made considerable improvement on parathyroid gland.

He had been an epileptic since 15 years of age. He was dull and lethargic, the sort of case that, apart from epilepsy, often improves on thyroid gland. This patient, without treatment, averaged 20 fits a month; treated for nine months with calcium and bromide alone or in combination, together with thyroid or thymus glands, he averaged

24 fits a month ; treated for five months with parathyroid gland and calcium and bromide he averaged 10 fits a month.

Thymus.

In a former article (12) we stated that thymus gland was the one we had found most useful, and the only one from which apparent harm had not in some case or other occurred. After a more prolonged use we have seen in one or two cases more epileptic attacks taking place while this gland was being used and an immediate fall on its discontinuance. We believe that it has a distinct use in epilepsy. To form a clear idea as to what might be taken for thymus insufficiency is not easy, but there are several reasons why thymus might be expected to be useful in this disease.

(1) Epilepsy more commonly commences at the time of life that the thymus becomes functionless.

(2) It causes a retention of calcium (13), and in cases of thymus insufficiency there is an excessive excretion of this salt (14).

(3) It prevents an excessive accumulation of acids in the body, especially phosphoric acid (16). Epileptic attacks can be increased by giving this acid to patients (17). It has been shown by Pugh (18), and confirmed by ourselves, that the blood of epileptics is less alkaline than normal, and at the time of taking a fit this becomes more accentuated.

(4) The thymus is stated to be absent in the mentally deficient children (15); the majority of epileptics whose attacks commence in early life are mentally deficient.

In thymus insufficiency there is increased action of the thyroid (19), suprarenals (20), and gonads (21). Thyroid and suprarenals will in some epileptics increase the number of attacks, but in many others suprarenal seems decidedly beneficial. Many epileptic patients show an increased sexual irritability at the time of taking fits, this irritability we think can be lessened by giving thymus gland.

In our series of nineteen *post-mortem* examinations all but six showed microscopically some signs of persistence and activity of the thymus gland. In Cases 48 and 49 the thymus was of extreme size ; in both the thymus was about as large as the palm of the hand. Both were cases of sudden death in young and apparently healthy subjects, death in each case, for want of a better reason and with hardly sufficient justification, being attributed to suffocation while in a fit. In Case 50, also one of sudden death, in which there was no question of suffocation, as the patient, who was thought to be in his usual health, had a fit while an attendant was beside him, and died immediately afterwards, while on his back. This man had a large and very vascular thymus, he was an alcoholic, æt. 37, and his first epileptic attack had occurred five years before. Might not the enlargement of his thymus be a com-

pensatory one, to combat the chemical changes that alter the calcium metabolism in epilepsy or which lessen the alkalinity of the blood? It is said by Blair Bell that this gland will enlarge after removal of the ovaries (22), and it is said to persist in eunuchs (23).

CASE 6.—For twelve months while taking bromides, had an average of 16 attacks monthly; for sixteen months has been taking thymus gr. x daily, in addition to calcium and bromide, for which time he averaged 8 fits a month.

CASE 37.—A lad, who, without treatment for eleven months, averaged 6 fits a month. His epileptic attacks are preceded by much sexual irritability. For the first month on thymus gland he had no fit, a thing that had not been recorded against him before; for the first three months on this treatment he averaged $1\frac{2}{3}$ attacks a month, and during this time the sexual irritability was much less. For nine months on thymus gland he has averaged 4 fits a month. Whether the apparent wearing-off of effect is due to the action of the thymus in inhibiting or stimulating some other gland, it is difficult to say.

In Case 3 it appears as if a change in the glandular treatment is helpful. This patient on bromide averaged about 100 attacks monthly; after three months' treatment with calcium, bromide, and suprarenal gland, the average falls to 9; in the third month he has only 2 attacks. In another period of treatment, after the patient returns from leave of absence, when the number of attacks return to their former average, during the third month on suprarenal extract, he has 2 or 3 attacks daily, which immediately fall to about 2 weekly when thymus replaces the suprarenal gland.

CASE 28.—For seven months without treatment, averages 18 attacks a month; on calcium lactate for three months averages 10; with calcium, bromide, and thymus for five months the average is 7 a month.

Suprarenals.

Of the suprarenal glands from fourteen epileptics examined microscopically eleven showed considerable vacuolation of the cortex. After removal of these glands, death is preceded by convulsions (36).

Epilepsy may be associated with Addison's disease (3), and the suprarenals play an important part in the calcium metabolism. From these facts, it might be expected that suprarenal extract would be of use in epilepsy.

We have been much interested in seeing a reference to the work of Cotton, Carson-White, and Stevenson (25), who, by the aid of Abderhalden reaction, concluded that at least one type of epilepsy may be produced by over-action of these glands. They lessened the activity of the adrenals by giving pancreatin, and with good results. It is stated by Waller (37) that in cases of pneumonia the suprarenals are profoundly affected. We have under our care a chronic case, who was an epileptic, and who, about sixteen years ago, had an attack of lobar

pneumonia and has not had a fit since; we have also read of one similar case, in which epilepsy ceased after an attack of acute pneumonia. We have seen 2 or 3 epileptic attacks occurring daily during the course of a double pneumonia. Is it not possible that the first two cases were of the kind in which there is over-action of this gland, which the attack of pneumonia might have reduced? We think we can show that in some cases suprarenal extract is of benefit to the epileptic patient.

Case 20 was for twelve months taking bromide, with an average of 41 fits monthly. With calcium chloride combined with bromide for nine months the average is reduced to 13 a month. For two months he receives suprarenal extract in addition, with a resulting monthly average of 10 fits. This patient has since died of pneumonia, and the result of the microscopic examination of his glands is given below, where it will be seen that his suprarenals had undergone fibrotic changes.

CASE 20.—For five months without treatment averages 33 fits a month. On bromide for three months and on bromide combined with calcium for five months, averages 28 attacks a month. On the latter treatment, together with suprarenal gr. x daily for eight months, averages 17 attacks a month.

Cases 30 and 23 have improved on suprarenal, the latter having without treatment for six months an average of 21 attacks monthly, with calcium and suprarenal extract and without bromide for three months, this average is reduced to 7. Case 30, having an average without treatment of 15 attacks a month, with calcium and bromide for eight months, an average of 9, which for the next five months is reduced to a monthly average of 4, when suprarenal gland is added. With the exception of Case 30, which is one of alcoholic origin, occurring late in life, they are all young patients, of poor physical development and with low blood-pressure. Suprarenal gland in Case 39, already referred to as having improved under parathyroid, seemed to increase the number of attacks, but while on the gland the patient made considerable physical improvement.

Thyroid.

It is said by Falta (38), that the thyroid is intimately associated with the control of the central nervous system, and that "this is instanced in the association of epilepsy with thyroid disease, especially exophthalmic goitre." He also records a case of epileptiform convulsions occurring for the first time while the patient was taking large doses of thyroid extract (39).

Murray Auer (40), quoting from Bolton, says, "Genuine epilepsy is a chronic auto-intoxication arising through metabolic processes in which, as a result of hypofunction of the thyroid and parathyroid glands, the poisons are not thoroughly neutralised or removed." Auer confutes the statement. Thyroid is also stated to be harmful in epilepsy, as by its action the excretion of calcium is increased. In one case of

myxœdema we have seen epileptiform convulsions occurring shortly before death. We have seen epileptic cases made worse by the use of thyroid gland.

CASE 34.—A girl who never excreted more than a trace of calcium in her urine, was given thyroid extract gr. v. daily for four months, the average number of her fits remained almost unaltered. Without treatment for six months, the monthly average was 4, while taking thyroid it was 3 a month; for three months she received calcium chloride as well as the thyroid extract, for which time the monthly average was the same as on thyroid alone.

CASE 9.—In this case thyroid was apparently of slight use. This patient, on bromide for twelve months, averaged 14 fits a month; for seven months while taking thyroid gland as well as bromide, the average was 10 attacks a month; for seven months on calcium chloride and thyroid, but without bromide, the average was 11 a month.

CASE 23.—Referred to as having improved with suprarenal extract, was for one month on thyroid gland, during which month she had the greatest number of fits ever recorded against her, *viz.*, 34, which fell immediately the gland was discontinued.

Gonads.

In our series of *post-mortem* examinations the female patients have shown more constant changes in these glands than the male patients. The ovaries for the most part were found fibrotic with atrophy of the interstitial cells; in one case the testicle showed atrophy of the corresponding cells.

Menstruation in most epileptics is irregular. Of forty of our cases in whom the function was established, and upon whom note had been kept as to their catamenia for twelve months, in only three did the periods recur twelve times during the year. Eighteen of the total number menstruated six times or less in the twelve months, and eight of these only once. In only two cases was the period at all prolonged or the loss excessive, and in these two only occasionally.

This irregularity and slight loss might point to deficient ovarian action (26). In thyroid (27) or anterior pituitary (28) deficiency there may be absence of, or irregular menstruation, also when there is a deficiency of calcium in the system (29). The epileptic attacks are very apt to occur at about the time of the period, probably due to the increased amount of calcium excreted at these times. Contrary to what might have been expected, we do not find the average number of fits much greater in the months in which there is menstruation than in those in which there is amenorrhœa, but in the former the fits are mostly grouped around the period. One of the female patients at times shows pronounced erotic tendencies, but this is not especially associated with the fits or menses. The epileptic attacks in three male patients

are directly associated with symptoms of sexual activity, two are sexually perverted, and in several sexual irritability is a common symptom, but we think that perverted or excessive sexual manifestations are not commoner in epileptics than in other insane patients.

We have used didymin extract in cases with high blood-pressure, acting upon the dictum of Ludlum and Corsin-White (30), that Brown-Sequard fluid is useful in a somewhat similar type of cases of primary dementia. We have also used didymin or ovarian extract in cases that habitually excrete but little calcium in the urine; with didymin we have increased the amount of calcium excreted, but cannot say that in these cases the epileptic attacks have been diminished, nor have we observed cases improve on ovarian extract.

CASE 19.—One with a high blood-pressure and an average of 35 fits a month while taking bromide, and 32 a month while taking calcium and bromide; for six months has didymin gr. xv. daily in addition, for which time he averages 17 attacks a month.

REPORT OF MICROSCOPICAL EXAMINATION OF ENDOCRINE GLANDS.

CASE 2.—L—, died October 9th, 1916, æt. 26. Pneumonia.

Testis.—Tubular epithelial cells show mitotic figures. Large numbers of interstitial cells which contain yellow granular pigment.

Thyroid.—Colloid vesicles large. Epithelium very much flattened. Colloid neutrophil.

Pituitary: Pars anterior.—Eosinophil cells greatly predominate.

Pars intermedia: No colloid vesicles. *Pars posterior*: Very few hyaline bodies. Some intermedia cells are seen invading this portion.

Pineal.—Alveolar arrangement well shown. A large area shows degenerative changes like area of softening in brain.

Thymus.—Not examined.

Suprarenal.—Capsule much thickened. Cells stain well and show no degenerative changes.

Pancreas.—Very few islets are seen, and these show degenerative changes, staining poorly and apparently disorganised.

CASE 20.—W. S. L. W—, died June 20th, 1916, æt. 28. Suddenly.

Testicle.—The tubular cells are actively proliferating and mitotic figures are seen. Groups of interstitial cells are present here and there, but appear to be deficient.

Thyroid.—The vesicles vary in size, and are filled with eosinophil colloid. The epithelium is cubical. There is an increase of interstitial cells.

Pituitary.—This organ was extremely small, and was evidently missed when the sections were being cut.

Thymus.—This consists of fatty tissue with islets of thymus tissue here and there. These are acutely congested.

Suprarenal.—The cytoplasm of the cortical cells has a reticular appearance. The medullary cells appear granular. There are several round cell masses in the medulla.

Liver.—Shows congestion, fatty degeneration, and cloudy swelling.

Pancreas.—Exhibits cloudy swelling. The islets appear normal.

CASE 58.—C. C—, died November 26th, æt. 50. Pneumonia.

Testicle.—The tubules are normal, and the usual interstitial cells are present, and contain yellow pigment.

Thyroid.—The vesicles are very large, and the lining epithelium is flattened. There are no interstitial changes.

Pituitary.—*Anterior lobe*: Is much larger than usual, the cells are mostly eosinophil. *Pars intermedia*: There are no colloid vesicles.

Pars posterior: Is small, there are no hyaline bodies or invading cells.

Suprarenal.—The cortical cells stain well and show very slight degenerative changes. The medulla is normal, and the cells contain much pigment.

Thymus.—Apparently of persistent infantile type, with large masses of gland tissue. Hassall's corpuscles are in evidence.

Liver.—Normal.

Spleen.—The capsule is thickened, and arterioles show thickening of their walls.

CASE 56.—J. T—, died June 1st, 1916, æt. 28. Status. Onset of fits at 17.

Testicle.—Not examined.

Thyroid.—Vesicles of uniform size, lining epithelium flattened. There is an increase of interstitial fibrous tissue.

Pituitary.—Not examined.

Thymus.—Not examined.

Suprarenal.—The *cortical* cells stain very poorly, some show finely granular cytoplasm, but in most the cytoplasm does not stain at all, except as a network of fine threads. The *medulla* does not show these changes, and the cells contain much pigment, either fine yellow granules on large dark brown particles.

Liver.—Exhibits cloudy swelling.

CASE 57.—G. J. D—, died April 4th, 1916, æt. 51. Convulsions.

Testis.—Not examined.

Thyroid.—The vesicular epithelium is cubical, in places the cells appear to be proliferating. There is also a great increase of the interstitial cellular elements.

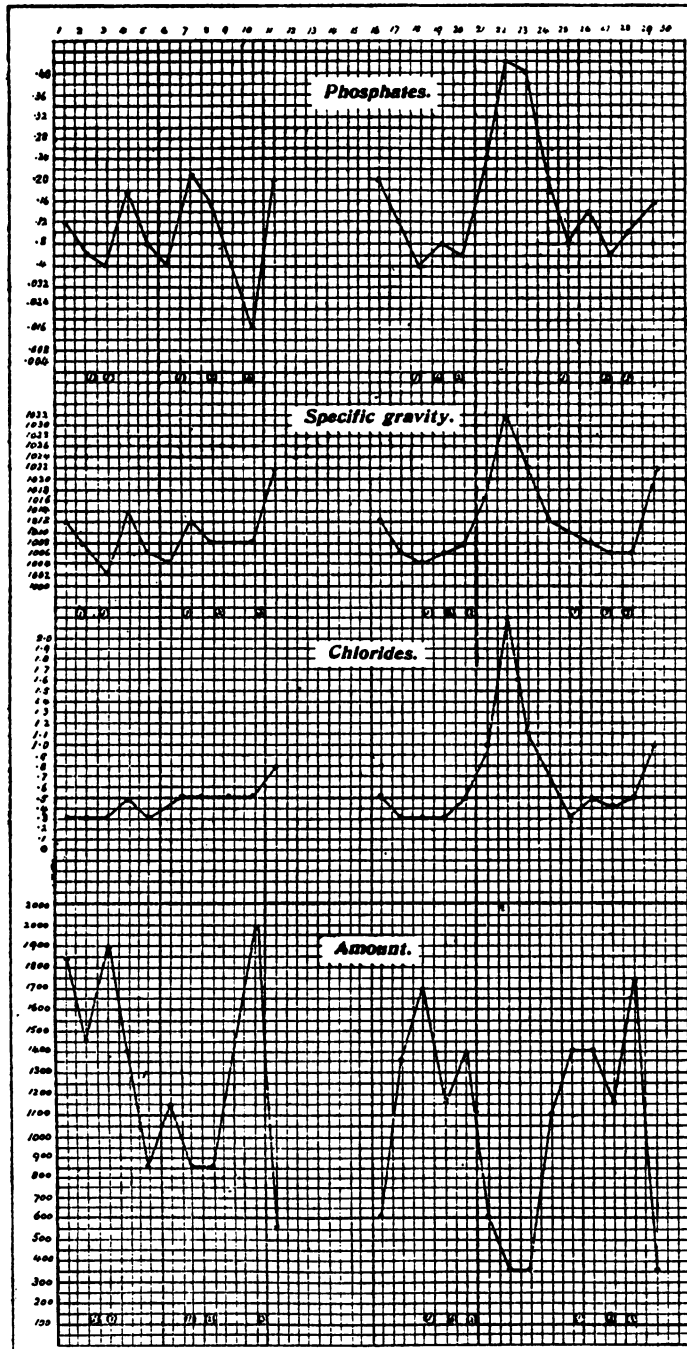
Pituitary.—*Pars anterior*: Eosinophil cells predominate. *Pars intermedia*: There is a large colloid vesicle, the lining cells are degenerating.

Pars neurosa: Contains a few hyaline bodies. There are no invading cells. The whole organ is acutely congested.

Thymus.—There are scattered foci of lymphoid tissue in which an occasional corpuscle may be seen. It is noticeable that the blood-vessels are large in proportion to the amount of gland tissue. The gland is probably of regenerative type.

Suprarenal.—The cortical shells show advanced degenerative changes. Everywhere the cytoplasm fails to stain, except as a network of fine fibrils. The medullary cells appear normal and contain pigment.

Liver.—Shows early fatty degeneration and chronic venous congestion.



CASE No. 44.

CASE No. 60.

Charts showing amount of urine passed, its specific gravity, the amount of phosphates and chlorides in grammes *per cent.* in 24-hourly specimens, and their relations to epileptic attacks.
 Fits thus O. Equivalents in form of tremors thus —.

CASE 55.—G. W—, died, æt. 73. Epileptiform convulsions.

Testicle.—Not sectioned.

Thyroid.—Vesicles large, epithelium flattened. Very few interstitial cells.

Pituitary.—*Pars anterior*: Cells mostly basophil. There are many small vesicles enclosed by cubical epithelium, some of which contain homogeneous neutrophil colloid. Many cells show vacuoles in their cytoplasm. *Pars intermedia*: There are several very large colloid vesicles containing neutrophil colloid. *Pars posterior*: Neuroglia network less dense than usual. Contains hyaloid bodies and pigment granules. No invading cells from *pars intermedia*.

Thymus.—Not examined.

Suprarenal.—This organ is very large. The *cortex* shows an extremely advanced stage of degeneration; the nuclei stain well, but the cytoplasm appears as a network of fine threads with large spaces. Some cells show less advanced changes, and in these the cytoplasm is markedly granular. The *medulla* is affected to a less extent and some parts stain well.

Liver.—Chronic venous congestion. Early fatty degeneration of cells of zones of hepatic vein.

CASE 54.—M. E. H—, died November 27th, 1916, æt. 39. Bronchopneumonia following status.

Ovary.—This organ consists of more or less cellular fibrous tissue in which are a few corpora fibrosa. The blood-vessels are surrounded by very thick fibrous walls. The cortical zone is less cellular than the central portion. No follicles are seen.

Thyroid.—The vesicles are of medium size, and are more or less uniform and filled with eosinophil colloid, except in some instances where the epithelium has proliferated and filled the vesicle. There is a slight degree of interstitial fibrosis and multiplication of interstitial cells. The vesicular epithelium is cubical.

Pituitary.—*Anterior lobe*: Eosinophil cells predominate, with here and there nests of basophils. There are numbers of vesicles containing eosinophil colloid. Many cells contain large blood pigment granules. *Pars intermedia*: There are several vesicles containing eosinophil colloid. The lining epithelium is very much flattened. *Pars posterior*: There are very few hyaline bodies. No pigment granules and no invading cells are to be seen.

Thymus.—Not examined.

Suprarenal.—The *cortex* shows a slight degree of degenerative change. In many cells clear spaces having appearance of vacuoles are seen. The *medullary* cells contain much blood pigment, and in some are found homogeneous eosinophil globules.

Liver.—Shows early fatty degeneration and infiltration.

CASE 53.—S. J. M—, died May 25th, 1916, æt. 57. Exhaustion after series. Fits began at 16.

Ovary.—This organ is small and intensely sclerosed. The subcapsular layer consists of interlacing bundles of spindle cells, whilst the centre of the organ is occupied by large, faintly-staining masses of fibrous tissue with a few septa represented by fibroblasts (hyaloid

bodies). The blood-vessels are surrounded by immensely thickened fibrous walls. There is no evidence of follicular tissue.

Thyroid.—The colloid vesicles are mostly small and separated by proliferated cellular tissue. The vesicular epithelium is cubical.

Pituitary.—*Pars anterior*: In subcapsular regions eosinophil cells predominate and vessels are distended; the central cells are chromophobe with a few basophils. *Pars intermedia*: There are a number of small colloid vesicles. A few eosinophil cells are seen passing towards the *pars nervosa*. *Pars posterior*: A number of eosinophil hyaline bodies are seen in the meshes, and yellow pigment granules are also present in considerable numbers.

Thymus.—Not sectioned. Probably not found *post-mortem*.

Suprarenal.—This is firmly attached to the kidney with only the fibrous renal capsule between the two organs, though in places this is absent and renal tubules and columns of suprarenal cells are seen intermixed. In some places in the suprarenal tissue small spaces lined by cubical epithelium are found; some are filled with a homogeneous neutrophil substance whilst others are empty. These, perhaps, represent aberrant renal tubules. The suprarenal cells stain well except in one part, where in the subcapsular region degenerative changes are in evidence.

Spleen.—Capsule is thickened and there is vascular sclerosis and waxy degeneration.

Liver.—Shows an advanced stage of fatty infiltration.

CASE 51.—H. D—, died October 7th, 1916. Status epilepticus; æt. 50. Has had fits since two years of age.

Ovary.—Shows extreme degree of fibrosis. There are several large corpora fibrosa, and no Graafian follicles can be seen.

Thyroid.—Not examined.

Pituitary.—*Pars anterior*: Chromophobes predominate. *Pars intermedia*: There are no colloid vesicles. *Pars posterior*: This portion is more cellular than usual, but no hyaline bodies or invading intermedia cells are visible.

Pineal.—There are numerous small particles of lime.

Thymus.—There are numerous islets of true thymus tissue containing Hassall's corpuscles, scattered amongst fatty areolar tissue. The type is regenerative.

Pancreas.—The alveolar cells are normal, but there are very few islets of Langerhaus.

Spleen.—The vessels are sclerosed. There are small hæmorrhages in evidence.

Suprarenal.—The cortical walls show a moderate degree of degeneration; the medullary cells contain much pigment.

CASE 52.—M. M—, died June 15th, 1916, æt. 50. Lymphadenoma.

Ovary, thyroid, and pituitary.—Not sectioned.

Thymus.—Vascular gland tissue is present, containing many Hassall's corpuscles. The type is probably regenerative.

Suprarenal.—*Post-mortem* changes present—shrinkage of cortical columns and cloudy swelling of cells.

Spleen.—Interstitial fibrosis; large amount of granular pigment; chronic venous congestion.

Liver.—Shows an extreme degree of fatty infiltration.

CASE 50.—C. H. B.—, died August 12th, 1916, æt. 40. Suddenly, in a fit. Fits commenced at 34.

Testis.—Not examined.

Thyroid.—The vesicles are small and irregular and do not contain much colloid; the lining epithelium is cubical and appears to be actively proliferating, so that in places there are masses of cells. The intermedial tissue is increased. The blood-vessels are congested.

Parathyroid.—This is attached to the above section and is 3 mm. in length by 2 mm. in breadth. Apparently it shows no abnormality.

Pituitary.—*Pars anterior*: Eosinophil cells in excess. *Pars intermedia*: No colloid. Apparently there is an extensive effusion (of lymph), which in parts has a fibrillar structure, whilst in others it is granular; in it a few red cells may be seen, but no vessels or fibroblasts. In places cells of *pars intermedia* appear to be forming a layer. *Pars posterior*: Large numbers of darkly-staining intermedia cells are streaming out into this portion. Masses of pigment granules are to be seen in some numbers—the appearances suggest that they are derived from the invading cells.

Thymus.—Represented by numerous small collections of lymphoid cells in fatty areolar tissue. Hassall's corpuscles are present. The gland tissue is very vascular, the capillaries being large and thin-walled. The type is regenerative.

Suprarenal.—The cortical cells exhibit degenerative changes—though the nuclei show up well the cytoplasm appears merely as a network or has a granular or vacuolar appearance. The cells of medulla stain well, but even amongst these the cytoplasm has a vascular appearance.

CASE 31.—W. S.—, died suddenly November 1st, 1916, æt. 25. Aorta small. Thymus very large. Onset of fits at 15.

Ovary.—This organ consists of fibro-cellular tissue, which in places is extremely vascular. Only one small follicle is seen in the section.

Thyroid and pituitary.—Not examined. *Pineal.*—Normal.

Thymus.—This is apparently of retrogressive infantile type. The thymus tissue contains numerous Hassall's corpuscles; there are also lime particles.

Suprarenal.—Appears normal.

Pancreas.—Cells are shrunken. Very few islets seen.

Spleen.—Shows numerous small hæmorrhages.

CASE 48.—C. E. P.—, died August 11th, 1916, suddenly, æt. 22. Fits commenced at 15.

Testis.—Apparently normal. Interstitial cells are present.

Thyroid and pituitary.—Not examined.

Thymus.—This is a large organ of persistent infantile type. There is much gland tissue with numerous Hassall's corpuscles. The blood-vessels are large and thick-walled.

Suprarenal.—Both cortex and medulla show degenerative changes.

Pineal.—Contains some particles of "sand," otherwise normal.

CASE 21.—C. A. R.—, died February 27th, 1916. Status. Æt. 41. Fits since 2 years of age.

Ovary.—This organ is small, and consists almost entirely of cellular fibrous tissue. Only one small Graafian follicle is seen. There are several corpora fibrosa, some in the early stage of formation being comparatively cellular and containing spiral capillaries. The arterioles have thick walls, while the capillaries are very large and thin-walled.

Thyroid.—The alveolar spaces are large and the lining epithelium moderately flattened. In places there are masses of proliferated interstitial cells.

Pituitary.—*Pars anterior*: Cells are shrunken and are mostly chromophobe, though there are considerable numbers of eosinophils.



CASE 21.—Epileptic. Showing vacuolation of cortical cells of suprarenal body. High power. Camera lucida sketch.

Pars intermedia: There is one vesicle lined with cubical epithelium and containing basophil colloid. Within another space lined with cubical cells is seen a mass of pink-staining material broken up by numerous round cells. About some of these cells are more or less clear spaces having a faint reticular appearance. *Pars posterior*: There are no invading cells. A few hyaline bodies are seen.

Thymus.—There are numerous foci of gland tissue with many Hassall's corpuscles.

Suprarenal.—Both cortical and medullary cells show poorly-staining cytoplasm; the change is more marked in the former.

Liver.—Shows advanced fatty degeneration.

Pancreas.—The acinar structure in parts is lost, so that the gland has the appearance of an adenoma. The islets of Langerhans stain faintly, and in the cell nuclei mitotic figures may be seen.

RÉSUMÉ OF CHANGES FOUND IN THE ENDOCRINE GLANDS.

Gonads.—Constant changes of the nature of obliterative fibrose are present in the female, but there are no corresponding changes in the male.

Ovary.—The ovaries were examined in five of the six female patients. Microscopically they appeared shrunken and atrophic. Histological examination revealed constant and advanced changes. In all cases the organ was extremely fibrosed, the stroma being made up of fibro-cellular elements whose appearance resembled that in a fibroma. In areas the cellular elements had almost completely disappeared and the tissue stained faintly—these are the so-called corpora fibrosa. In two instances small Graafian follicles were seen, but were absent in the others. The arterioles were surrounded by relatively very thick fibrous coats, while the capillaries were thin-walled and large. These changes must be taken to indicate a great deficiency in the activity of the ovaries.

Testis.—Of the eight males the gonads were examined in four, and in only one of these was a definite pathological change evident; this was in "W" 20, a case of dystrophia adiposa genitalis, whose testis showed a deficiency of interstitial cells.

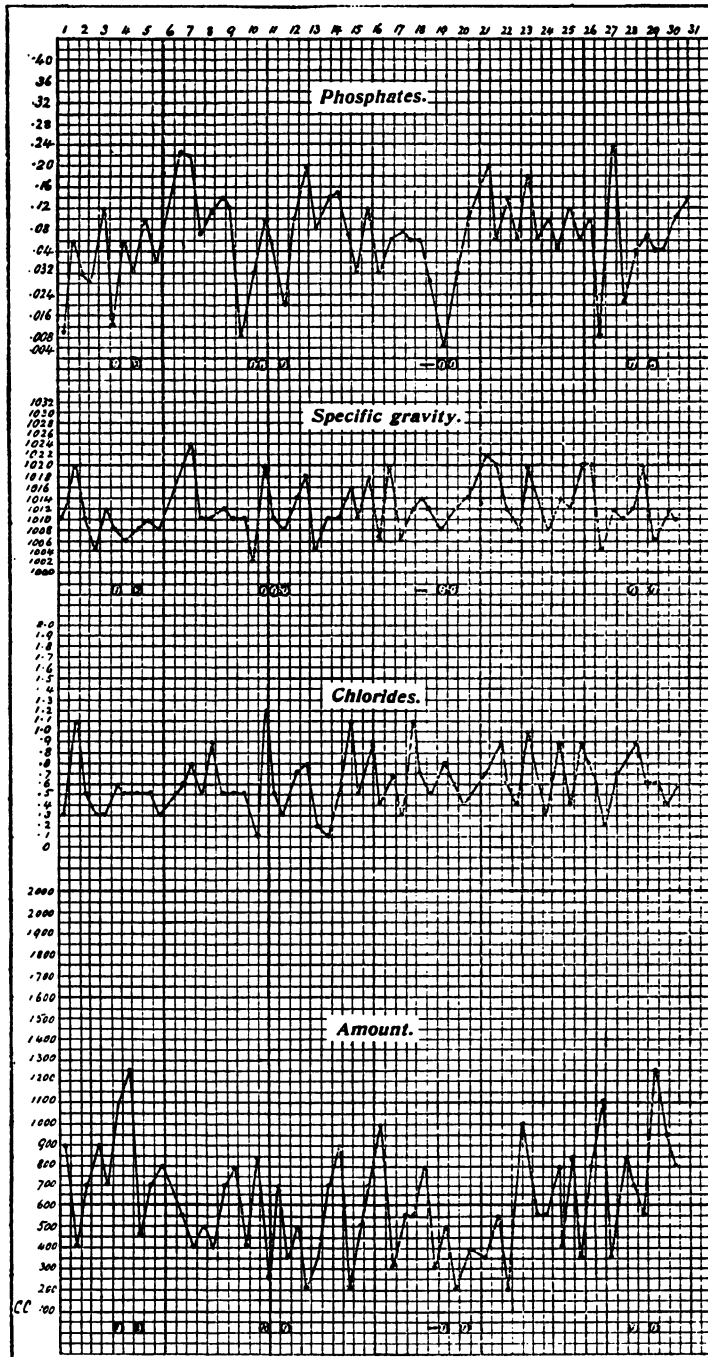
Thyroid Gland.—Two types were recognised on histological examination. In one the vesicles were large and lined by flattened epithelium, whilst interstitial cells are few in number. In the other the vesicles were relatively small and lined by cubical epithelium which appeared to be proliferating, and there were large numbers and masses of interstitial cells. From the resemblance to the appearances seen in the thyroid in exophthalmic goitre, the latter type may be considered to represent an active phase, whilst the other represents a quiescent state. Of the eight males, the thyroid was not examined in one case; of the other seven, four were classified as quiescent and three as active. Of the six females the thyroid was examined in three, in two it was of active type, in one it was of quiescent type.

Parathyroid.

The gland was not specially examined, but in one case 50 "B" (20) in which it was cut with the thyroid, no pathological changes were evident.

Pituitary.—No constant changes were found, although there were frequently seen indications that suggested that the gland was over active in some cases.

Thymus.—The thymus was present in five out of eight males and in four out of six females. In some cases it was as large as the palm of the hand, whilst in others it was only recognised on section of the



CASE No. 59.—Chart showing amount of urine passed, its specific gravity, the amount of phosphates and chlorides in grammes *per cent.* in 12-hourly specimens, and their relations to epileptic attacks. Fits thus O. Equivalents in form of tremors thus —.

mediastinal fatty tissue. Two types were recognised: (1) The persistent infantile type has the macroscopic and microscopic appearance of the infantile thymus; this was present in two males and three females. (2) The regenerative type—in this the thymus tissue was recognised microscopically, and appeared in islets of true thymus tissue embedded in fat—this was the case in three males and one female. In all cases the glands were extremely vascular.

Suprarenals.—Almost constant changes were found in the gland. The cortical cells failed to stain at all well; usually the nuclei stood out well, but the cytoplasm was coarsely granular or represented by a fine network enclosing clear spaces. It is difficult to determine whether the change is degenerative or merely exhaustive, but the fact that it is most advanced in cases that have died of status points to the latter conclusion. The medulla, as a rule, shows the change but slightly. In one series the granularity of the cortex was present in an advanced degree in six males and one female, moderately in one male and three females, and absent in one male and two females.

Pancreas.—In several cases in which the pancreas was examined it was found that the islets of Langerhaus were few in number. In a further series of five epileptics, three males and two females, whose endocrine glands have been recently examined, the following changes were found.

Gonads.

Testes.—In two cases there were fibrotic changes affecting chiefly the basement membranes of the tubules. *Ovaries:* In one case advanced fibrosis was present, in the other the ovaries were not examined. *Thyroid:* In one male and two females the type was active, in two quiescent. *Pituitary:* Changes indicating unusual activity were present in two males and two females. *Suprarenal:* In all cases there was vacuolation of the cortex. *Thymus:* Active thymus tissue was present in three males and one female; in one male the type was persistent infantile, in the others regenerative.

Chemistry.

We, in a former paper (31), pointed out the chemical changes in the blood and urine that we had observed to occur before and after epileptic attacks. Since then we have in a certain number of cases made examinations of the urine twelve-hourly instead of every twenty-four hours, and have in this way found some of the changes more accentuated. In a twenty-four-hourly specimen of urine the pre- and post-epileptic effects often become confused. We have also in one case examined the blood twice daily, and in this way found the changes before a fit more pro-

nounced. To repeat, shortly, the changes we formerly stated or have since found to occur are :

In the urine, before a fit or series : An increase in the calcium excreted ; a fall in the amount of phosphates excreted ; a fall in the amount of chlorides excreted. The calcium change varies in different patients, some habitually excrete little or none, and in these no change is observed. The change in the phosphates and chlorides, more especially the former, is, with an occasional exception, constant.

In the blood, before a fit or series : A fall in the degree of alkalinity ; a fall in the leucocyte count. The coagulation time, which we formerly thought was shortened before a fit, we have since seen in some cases lengthened, and in other cases the change is so variable as to be no guide. The calcium blood index was also variable, sometimes being high and sometimes low.

After a fit or series there is in the urine : An increase in the amount of phosphates excreted, which in some cases greatly exceed the inter-fit interval amount ; there is also a rise in the amount of chlorides excreted, but this is not so marked or so consistent, and occurs earlier than the phosphatic rise.

In the blood after an attack there is found : An increase in the number of leucocytes ; a shortening of the coagulation time ; a rise in the degree of alkalinity ; a rise in the calcium blood index.

We have also noted in many cases previous to an attack that there is an increase in the amount of urine passed, which in some cases habitually amounts to from 100 to 130 oz. per diem, falling during a series or after an attack to from 10 to 15 oz., this last being of much higher specific gravity than the former. We claim that by examinations of the urine twice daily and daily examinations of the blood, we can, in the majority of cases, foretell an epileptic attack, in some cases a day or two before, in others only a few hours before.

The indications we find of greatest use, and subject to fewer exceptions than the others, are the change in the percentage of the phosphates and chlorides excreted, and the change in the leucocyte count ; the other indications we have named are useful confirmatory points but are subject to more variation ; all these are subject to much alteration by other influences than the epileptic attacks.

We believe that in many cases before an attack there is an increase in the amount of calcium excreted, in all a diminished amount of phosphates excreted, with generally a fall in the amount of chlorides. Can these changes in any way directly or indirectly be connected with the epileptic attack ? We think they can. It is stated that calcium is for the most part excreted as calcium phosphate, that phosphorus is mostly excreted as the sodium or calcium salt, and that the chlorides are mostly excreted as sodium chloride. There being an increase in the

calcium excreted, together with a fall in the phosphates and chlorides, we think this might be taken to show that there is a retention of sodium. Sabbatani (32) has stated that the surface of the brain is rendered more excitable by the application of sodium, and less excitable by the application of calcium salts. Substances that precipitate calcium heighten the excitability of nerve (33). Falta states that common salt given to children suffering from tetany brings about full anodal hyperexcitability (34). Epileptics are known to improve on a restricted salt diet, but has the benefit that follows a saltless diet been attributed to the right cause?

In some cases before an attack there is a lengthening of the coagulation time, which may mean a diminished amount of fixed calcium. In female epileptics attacks are commonest at the time of the menstrual period, when the coagulation time is lengthened and there is an increased loss of calcium. We think that these changes all point to a lessening of the calcium in the tissues and a retention of sodium, and that the bad effects of sodium chloride on epileptics may be due rather to the sodium than the chloride. Both the amount of calcium and phosphorus excreted by the urine are greatly influenced by food and drugs, *e.g.* magnesium sulphate will increase the amount of calcium eliminated by the bowel and diminish that passed by the urine, lime will diminish the amount of phosphorus passed in the urine and increase that passed by the bowel (35). Until the *fæces* have been examined daily as to the quantity of these salts excreted, and the relation of the amount to that lost by the urine and to the epileptic attack, it is not possible to state the effect of these salts on the disease. We have endeavoured to abort attacks that we have foretold, by increasing the phosphates excreted, by creating a leucocytosis and increasing the calcium blood index and shortening the coagulation time, but so far with only partial success. Nuclein will cause a leucocytosis, and it is stated that it will cause an increase in the amount of phosphates excreted. Calcium injected subcutaneously will cause a shortening in the coagulation time and an increase in the calcium blood index; it is said to diminish the amount of phosphates excreted by the urine and to increase the amount eliminated by the bowel. We have often observed after its use a high leucocytosis. We used nuclein, thinking that its action might be similar to that of thymus extract, with the additional advantage that it can be subcutaneously injected.

CASE 35.—A female patient, to whom we gave injections of nuclein every third day, had previously averaged 20 fits a month; for the first month on this treatment she had no fit; at no time before had her record been less than 11 attacks a month. During the second month of this treatment her average returned to its former level. We discontinued the treatment for several months, after which interval we gave her nuclein *per os* every alternate three days. For the first month,

while taking this, she had 8 attacks, all at the time of her menstrual period, being her lowest record with the above exception. The constitutional effects of the fits were less than usual. For two more months this treatment was continued, but without benefit, except that the after-results of the attacks were rather less.

We have given injections of nuclein in a few isolated cases, when the patients have told us that they were about to have an attack and the attack has not taken place. It is impossible to draw any conclusions from these results, but they are suggestive, and the action of this drug in epilepsy is worthy of study. If our idea as to sodium retention is correct, it is possible that nuclein might do good by promoting the excretion of sodium phosphate, and the leucocytosis that it causes may help to ward off the attack.

Case 45 is the one in which we have tried nuclein most freely, and is the case in which we have continually endeavoured to abort attacks. This is a case of great interest, and is worth some remarks, we having made daily, or twice daily, observations on him for nine months. He came under our care in October, 1916, with but little as to his past history and only six months of his fits, which varied from 4 to 20, giving an average of $8\frac{1}{2}$ attacks a month. He is a happy, good-natured imbecile, æt. 35, and said to have been an epileptic since childhood. Preceding a fit, for from a few to twenty-four hours, he has intense general clonic-muscular spasms, during which he is quite conscious, will talk rationally, and attend to his wants. It is while in these attacks that he will have the typical *haut mal* fits, the clonic spasms afterwards easing down for about half an hour, when they will return and continue if not treated for from thirty-six to forty-eight hours, ceasing gradually. These attacks will, if not interfered with, recur with fair regularity about every ten days; if postponed by treatment the tendency is to recur at a shorter interval. We have charted the observations made upon this patient, and we think have prevented the *haut mal* attacks by treatment at the time we expected them to occur, but have not been so successful with the accompanying attacks of spasms; but we think we have at times postponed them, and have lessened their severity. It will be seen, by reference to the chart, that this case shows a decided fall in the phosphatic excretion before an attack and a marked rise afterwards, that the quantity of urine excreted rises greatly at the time of the attack and falls after. There is a pre-fit fall and a post-fit rise in the chlorides excreted. The calcium excretion in this case is always low, seldom more than a trace, and is not sufficient to bear any direct relationship to the attacks. His blood changes for the most part are such as we have stated to occur.

Epitome of Treatment.

Case No.	Treatment.	Gland.	Number of months.	Monthly average no. of fits.
2	K. Br.	<i>Nil</i>	12	41
	Ca. Cl. et Br.	<i>Nil</i>	9	13
	<i>Idem</i>	Suprarenal	2	10
3	<i>Nil</i>	<i>Nil</i>	51	110
	Ca. et Br.	Suprarenal	3	9
	<i>Idem</i>	Thymus	3	48
6	K. Br.	<i>Nil</i>	12	16
	Ca. et Br.	Thymus	16	8
5	K. Br.	<i>Nil</i>	12	27
	Ca. et Br.	<i>Nil</i>	4	15
	<i>Idem</i>	Thymus	9	14
7	<i>Nil</i>	<i>Nil</i>	3	20
	Various treatment	—	9	24
19	Ca. et Br.	Parathyroid	5	12
	K. Br.	<i>Nil</i>	4	35
	Ca. et Br.	<i>Nil</i>	3	30
	Ca.	Didymin	3	25
	Ca.	Pituitary	2	33
20	Ca. et Br.	Didymin	6	17
	<i>Nil</i>	<i>Nil</i>	5	33
	Ca. et Br.	<i>Nil</i>	5	28
	K. Br.	<i>Nil</i>	12	22
	<i>Idem</i>	Suprarenal	6	17
39	<i>Nil</i>	<i>Nil</i>	6	100
	Ca. et Br.	<i>Nil</i>	1	30
	Ca. et Br.	Parathyroid	8	17
	<i>Idem</i>	Suprarenal	2	38
	K. Br.	<i>Nil</i>	12	10
22	Ca. et Br.	Parathyroid	10	3
	<i>Nil</i>	<i>Nil</i>	5	18
	K. Br.	<i>Nil</i>	4	13
	K. Br.	Parathyroid	3	18
	Ca. et Br.	Parathyroid	5	9
23	<i>Nil</i>	<i>Nil</i>	6	21
	Ca.	Thyroid	1	34
	Ca. et Br.	Suprarenal	3	12
	<i>Idem</i>	Thymus	4	8
	Ca.	Suprarenal	3	7
24	Ca. et Br.	<i>Nil</i>	4	3
	<i>Nil</i>	<i>Nil</i>	6	9
	Ca. et Br.	<i>Nil</i>	6	3
	<i>Idem</i>	Thymus	4	2
	K. Br.	<i>Nil</i>	7	18
28	Ca.	<i>Nil</i>	3	10
	Ca. et Br.	Thyroid et Thymus	4	9
	<i>Idem</i>	Thymus	5	7
	<i>Nil</i>	<i>Nil</i>	7	10
	Ca. et Br.	<i>Nil</i>	4	10
29	<i>Idem</i>	Thymus	13	7
	<i>Nil</i>	<i>Nil</i>	4	15
	Ca. et Br.	<i>Nil</i>	8	9
30	<i>Idem</i>	Suprarenal	5	4

CONCLUSIONS.

Among statements and results which are apparently absolutely contradictory and opposed, is it possible to co-relate these more than confused actions?

We have seen that epileptiform convulsions, according to various authorities, may occur with apituitary, hypo- and hyper-thyroid, hypo- and hyper-suprarenal and aparathyroid conditions. All these glands play an important part in the calcium metabolism. In apituitary, hyperthyroid, hyposuprarenal, and aparathyroid affections, there is an increased loss of calcium from the tissues. If this salt has the influence that we think in the causation of epilepsy, this may be found to be the common ground upon which all these glands act. In over-action of the suprarenals there is a calcium retention, which makes it difficult to explain how an over- and an under-action of this gland can both cause convulsions. If an over-action of the suprarenals should be a factor in the causation of the phenomena it may be through these glands that the thyroid, pituitary, and parathyroid act, as thyroid secretion stimulates the suprarenals to action, and the cortex of the suprarenals hypertrophies in apituitarism, and there is an ill-understood relationship between the parathyroids and the suprarenals. The subject is full of difficulties, and probably not at present capable of explanation. That the ductless glands have some part in the production of epilepsy, and that their extracts may be beneficial in this disease, we think is proved. But, except in cases of apituitarism and marked cases of aparathyroidism, it is not possible to give definite indications as to which gland will be useful in any given case. One can only be led by general glandular symptomatology.

Our thanks are due to Dr. Oliver Latham for kindly preparing, and cutting of, and advising as to the sections; and to Mr. R. C. Dent for much help in forming the tables upon the action of the glands.

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Mutism in the Soldier and its Treatment. By COLIN McDOWALL, M.D., late Capt. (Temp.), R.A.M.C., Ticehurst House, Ticehurst.

MANY varieties of functional disturbance are found in men enlisted for the present war, and not the least interesting is mutism. In a hospital set apart for the treatment of nervous disorders many cases of complete loss of speech are met with, and these may be divided conveniently into three main categories as follows: Mutism arising in the field, in hospital, and previous to participation in active service.