patience and good temper, and that is why I consider that the nursing staff really determine the success or failure in an institution for mental defectives. I think it will be generally conceded that too much attention cannot be paid to the selection and careful progressive training of members of the staff, and in this direction the Association has always been very encouraging and helpful.

Our method of discharge for some time past has been that adopted by the Board of Control, namely, long leave of absence "on trial," and I think this is undoubtedly the best method. This may be further developed by the institution of hostels, but in this matter one must bear in mind the very bad state of the labour market over the whole country. One also has to remember that the cases which might reasonably be expected to be discharged are those of the highest grade, and unfortunately it is amongst these that we have the greatest number of potential wrong-doers, especially among the women, and this is a point which has to be firmly borne in mind when the question of discharge or of leave on long absence or of transfer to a hostel is recommended.

Mental deficiency inevitably costs the nation money, but the kindest and most economical way for suitable cases is, in my opinion, institutional care. Neglect to deal with this problem means a cost in misery, vice and industrial inefficiency which cannot be properly estimated, and all the time the problem becomes more and more serious, and is bound, in the long run, to affect our position among the other great nations of the world.

The Iodine Content of Thyroid Gland.[1] By F. A. PICKWORTH, B.Sc., M.B., Ph.C., Pathologist to the Joint Board of Research for Mental Diseases, Birmingham.

AT the Annual Meeting of this Association held at Belfast last July, Sir Frederick Mott gave you an address on the thyroid gland and promised a further contribution with regard to the iodine content. This paper is an attempt to correlate the iodine content with histological structure and with the mental and bodily condition of the patient. I must apologize for the work being far from complete, as most of the time since then has been taken up with the examination of the published methods for the estimation of iodine in the gland, and owing to certain objections to these methods it

[1] A paper read at the Annual Meeting held at Birmingham, July 9, 1925.

has been necessary to invent a process without these objections, and which, at the same time, is carried out with a minimum expenditure of time and material.

The literature on the subject is so enormous that it would be quite impossible to review the past work satisfactorily; certain important facts, however, may be briefly referred to.

We know that the slowness of thought and ideation and the defect of speech as shown by patients suffering with myxœdema are due to thyroid deficiency, and the symptoms are removed by administration of the gland, also the non-development of the brain in cretinous idiocy is to be attributed to absence of the thyroid gland, and such cases are benefited often in a miraculous manner by administration of the gland; no other treatment has a comparable or even appreciable effect upon these cases, and this suggests the importance of the thyroid in the study of mental diseases.

Although salts of iodine have been used since 1820 in the treatment of thyroid diseases, it was not until 1895 that Kocher suggested that iodine might be present in the thyroid gland.

A search for it was made at Berne, but none found; however, Baumann, in the same year, evolved a method by which he could satisfactorily demonstrate it.

It was soon found that the activity of thyroid gland was by no means to be supplanted by iodides. Hutchinson remarked, "One would conclude that the iodine in thyroid gland, if it plays an essential part at all, does so simply by nature of the special form of combination in which it exists."

An important advance was made by Reid Hunt and Seidell, who demonstrated experimentally that the activity of thyroid gland was definitely proportional to its iodine content—a parallelism which has since been repeatedly confirmed in the clinical treatment of myxœdema and cretins. Since, therefore, the physiological activity of the gland is proportional to its iodine content, the latter may be used as an index of the value of the gland in the animal economy. The necessity of a reliable method for its estimation is therefore evident.

Iodine is very reactive and volatile, so that its estimation is not easy. The first search for it found none at all; later so many methods were advocated that it was said, "The methods for estimating iodine may be divided into two—those which give some and those which give none." Recently better methods have been put forward, the most important of which are briefly criticized below. In comparing them with the method to be given later, attention is drawn to the desirability of avoiding all processes

involving unknown factors, and also those subject to a large personal equation (such as the colorimetric).

Baumann's method and its large number of modifications consists in the fusion of the gland with sodium hydroxide, the completion of destruction of the organic matter being effected by potassium nitrate. Acidification of the dissolved melt sets free nitrous acid from the reduced nitrate and liberates iodine, which is then extracted by means of an organic solvent. The solution is suitably clarified and evaporated, and the iodine estimated colorimetrically or by titration. The objection to all modifications of this method is that the effervescence which occurs on acidification causes a loss of iodine; passage of the evolved gases through some of the organic solvent has been suggested and reduces the error, but makes the process unwieldy.

Hunter's method destroys the organic compounds by heating with a mixture of potassium and sodium carbonates and nitrates. The dissolved melt is treated while still alkaline with sodium hypochlorite. The solution is acidified and boiled to expel excess of chlorine, potassium iodide added and the iodine titrated with thiosulphate. The objections are the possible formation of oxychlorine compounds (Kendall), which would invalidate the result, and also the fact that the fusion process, although satisfactory for such easily decomposed substances as sulphonated aromatic iodine compounds (chosen by Hunter as a test substance), is inadequate with organic iodine compounds such as are met with in thyroid. Kelly and Husband also find that the process gives low results with seaweed.

Kendall's process as modified by Kelly and Husband appeared recently in *Bioch. Journal*, 1924, No. 5, while the present work was in progress. It consists of alkali fusion with sodium hydroxide and completion of the oxidation with potassium nitrate, as in the Baumann method, acidification with phosphoric acid, prolonged boiling to get rid of the nitrous acid; sulphite is added and the SO_2 boiled off; then addition of bromine, excess of which is also got rid of by prolonged boiling, cooling, adding potassium iodide and titrating the iodine liberated. One objection, as in the Baumann method, is the possible loss of iodine in the neutralization of the mixture with acid, which liberates nitrous acid and much carbon dioxide. Another objection is the fact, easily demonstrable in a test-tube, that bromides liberate iodine from potassium iodate; bromides are necessarily formed in the process of oxidation.

In Fellenberg's process, *Biochemische Zeit.*, 1924, 152½, the fusion process differs from the foregoing in that no potassium nitrate is added, but iodine is estimated colorimetrically. This method is not

intended to be exactly quantitative, since the results are multiplied by $\frac{5}{4}$ to allow for loss. It is, however, a good method for the detection of minute amounts of iodine.

The general results by these methods show a very low iodine-content of the gland in infants and children. A seasonal variation has been demonstrated in sheep's thryoids in America by Seidell and Fenger, but Martin's results for English thyroids show much less variation.

It is also stated that animals near the sea have more iodine than those inland, and that herbivorous animals have more iodine than carnivorous.

The diet, especially vitamins or their absence, influences the iodine content in a remarkable manner.

The normal iodine content of the adult human thyroid is given by Aschoff as 2 to 9 mgrm. per gland, or 30–90 mgrm. per 100 grm. of dry gland. Zunz analysed the thyroids of a large number of Belgian soldiers and concluded that 15·0 mg. was the average normal amount per gland. Jolin analysed a number of thyroid glands in 1906, but could find no relation of iodine content to conditions of health or disease. Remardin and Marchand, 1908, examined a large number of thyroids from mental hospital patients, and stated it was impossible to establish any constant relation between thyroid change and the form of mental disorder of the patient. Pellegrini states that there is no definite relation between the amount of colloid and that of iodine in the gland. Mott and Kojima established the fact that the weight of the thyroid had no relation to the body-weight of the patient in mental hospital cases.

The basal metabolic rate is generally accepted to correspond very closely with the activity of the thyroid gland, and is a valuable clinical index of its efficiency.

We have made a considerable number of determinations of the basal metabolic rate of patients, details of which are to be found in the *Annual Report of the Birmingham Joint Board of Research for Mental Diseases*.

The new method depends upon the destruction of organic matter by fusion with alkali without addition of any oxidizing material; the melt is dissolved in water and a few drops of sulphite solution added. The solution now containing iodine as sodium iodide is acidified and the iodide oxidized to iodate by potassium permanganate, excess of which is got rid of by animal charcoal (which is shown by experiments not to reduce the iodate); the mixture is filtered and the iodate decomposed by adding iodide, and the resulting iodine is titrated with thiosulphate.

The method has been tested with experimental mixtures of iodide

and dried meat, and found to give results agreeing with the theoretical figure, and concordant results were obtained with thyroid gland at different times and under conditions so that the results could not be anticipated during the analysis.

(For practical details see the complete process, which has been sent to the *Biochemical Journal*.)

Results Obtained.

The following charts show the results obtained from various specimens of thyroid gland. Sixty of these have been supplied to Sir F. W. Mott by the Maudsley Hospital, the Camberwell Infirmary (through the kindness of the Medical Superintendent, Dr. E. W. G. Masterman), and the London County Mental Hospitals (by the kindness of their respective medical superintendents); 10 have been supplied by the Queen's General Hospital, Birmingham, by the kindness of Prof. Haswell Wilson, and 48 are from autopsies at Hollymoor.

The histological structure of 57 of the above glands has been investigated, under the supervision of Sir Frederick Mott, by Dr. Hilda Cunnington, who has been working for some time under Dr. Williamson, the Arris and Gale Lecturer on the Thyroid.

The extremes of 0·4 and 50·6 of iodine in the whole gland obtained in one group of cases would be quite meaningless if expressed as an average of 25·5 mg.; it is therefore obviously useless to express the results in averages; in addition the factor of variability would be missed. It is probable that conditions showing extreme variability in the iodine content of the gland are the conditions in which the thyroid hormone is of great use to the system, and, of course, these groups include cases both of thyroid stimulation and of thyroid exhaustion.

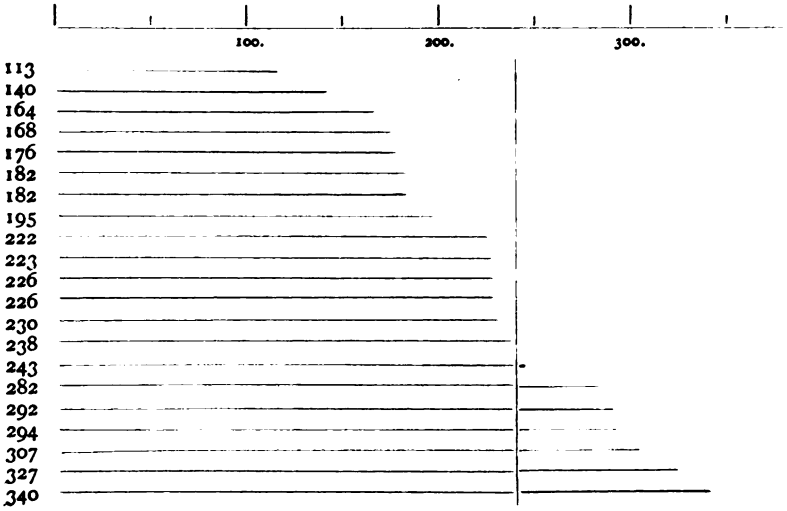
The results are therefore expressed in charts in which the amount of iodine in each gland and the variability of iodine in the whole group can be seen by inspection. The amount of iodine is represented by horizontal lines, the normal being given for comparison.

The normal for the whole gland has been taken from Zunz figures of 15 mgrm., and the percentage of iodine in the dried gland is calculated from this figure and an assumed average normal gland weighing 25 grm. and containing 75 *per cent.* of water, which is 240 mgrm. per 100 grm. of dried gland.

The following charts show the relation of the iodine content to histological structure.

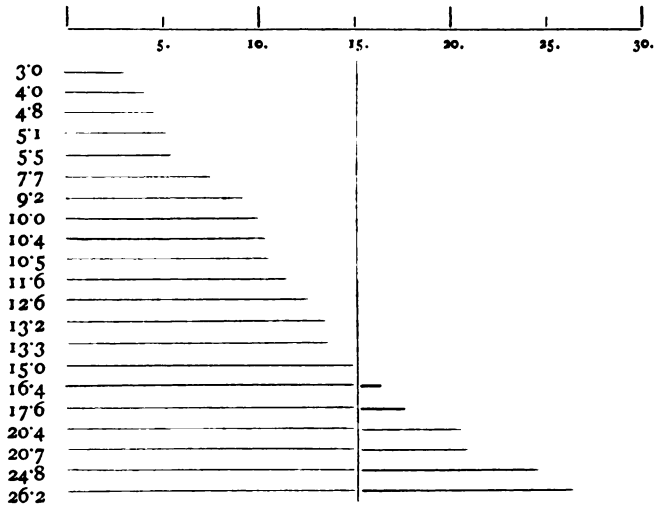
HISTOLOGICALLY NORMAL (Colloid storage nucleus resting).

A. *Mgrm. Iodine in* 100 *grm. Dried Gland.*



Normal = 240 mgrm. per 100 grm. dried gland.

B. *Mgrm. Iodine in Whole Gland.*

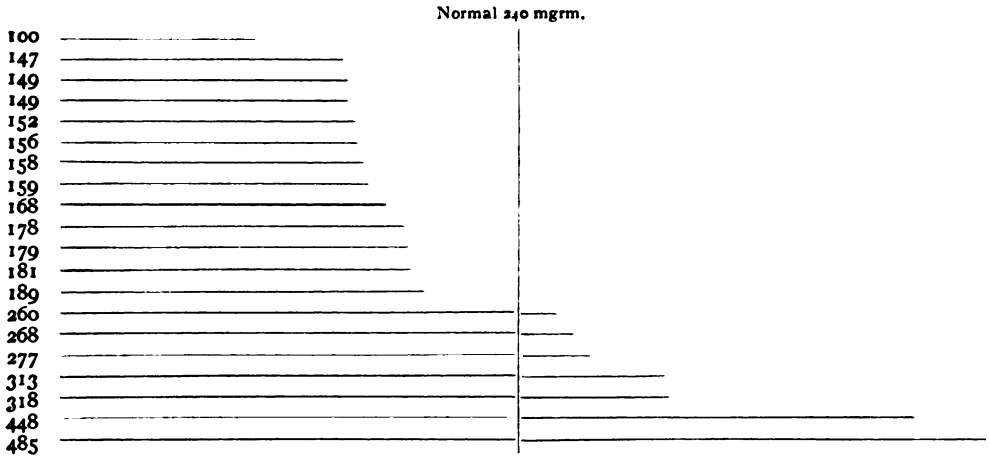


Inspection of the above chart A shows the iodine percentage to be almost normal and variations are not great. This is in close agreement with the histologically normal appearance.

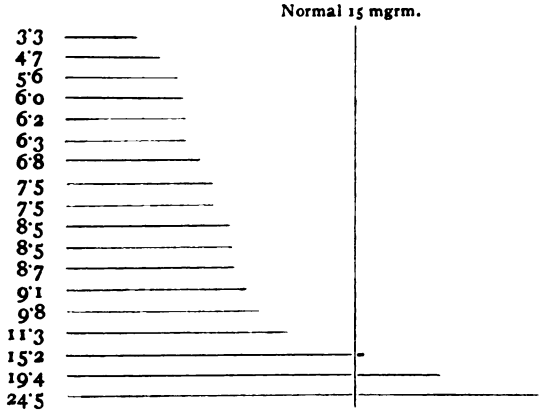
The total iodine varies owing to the varying size of the glands, being in most cases much less than the normal of 25 grm.

HISTOLOGICALLY NORMAL, EXCEPT FIBROSIS PRESENT.

A. *Mgrm. Iodine in 100 grm. Dried Gland.*



B. *Mgrm. Iodine in Whole Gland.*



The percentage chart above shows most of the specimens to have a low iodine content in accordance with expectation in a gland containing fibrous tissue. The few specimens showing higher iodine percentage are to be explained by the fact that the fibrous tissue shuts off the secreting cells from the normal supply of blood; the epithelium continues to store iodine in the vesicle till it atrophies from lack of proper blood-supply and leaves a vesicle containing a high iodine-containing colloid, but which is not accessible to the blood-stream for utilization.

The total iodine in the gland is low, as would be expected in a fibrotic gland.

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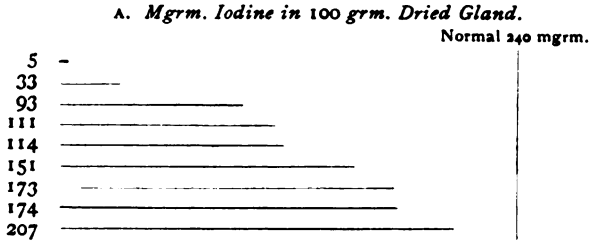
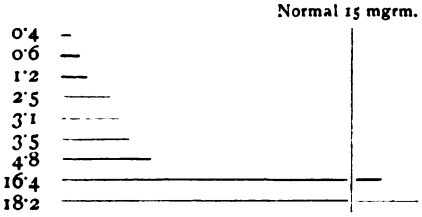
HISTOLOGICAL THYROIDS: FIBROSIS MARKED.

A. *Mgrm. Iodine in 100 grm. Dried Gland.*

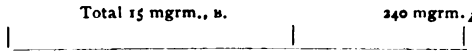


B. *Mgrm. Iodine in Whole Gland.*



The above two charts establish the fact that fibrosis of the gland is definitely associated with both low total iodine and low percentage iodine; a great variability is also to be noticed.

PATHOLOGICAL THYROIDS.



A. 33
B. 0·6 } *Lymphadenoid goitre.*

Iodine, both total and percentage, abnormally low.

A. 173
B. 3·5 } *Abnormal colloid.*

Colloid of abnormal microscopical appearance.

A. 105
B. 5·2 } *Interstitial thyroiditis.*

Marked low total iodine and moderately low iodine percentage.

A. 144
B. 5·2 } *Graves's disease.*

Marked low total iodine and moderately low iodine percentage.

A. 93
B. 16·4 } *Adenoma.*

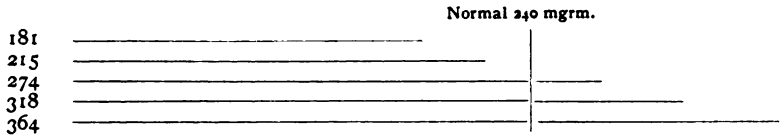
Low iodine percentage and high total indicates large storage of poor colloid. The size of the gland and the colloid are increasing.

A. 111
B. 18·2 } *Toxic thyroid.*

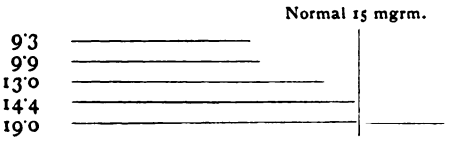
Low iodine percentage but higher total iodine agrees well with activity of epithelium, absorption of colloid and probable recent enlargement of the gland. The store of iodine and colloid is decreasing by being utilized.

HISTOLOGICAL: ARTERIOSCLEROSIS.

A. *Mgrm. Iodine in* 100 *grm. Dried Gland.*



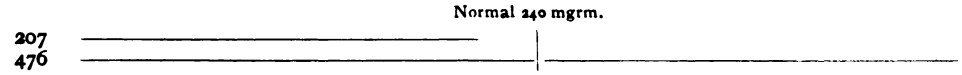
B. *Mgrm. Iodine in Whole Gland.*



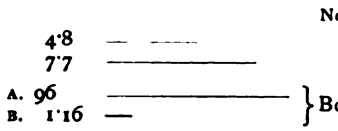
Not very abnormal iodine content in this condition.

THYROID INDIFFERENT PHASE.

A. *Mgrm. Iodine in* 100 *grm. Dried Gland.*



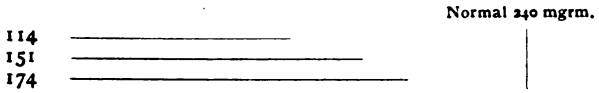
B. *Mgrm. Iodine in Whole Gland.*



Nuclei resting, small thyroids, one of high iodine percentage; low total iodine.

THYROID SECRETORY PHASE.

A. *Mgrm. Iodine in* 100 *grm. Dried Gland.*



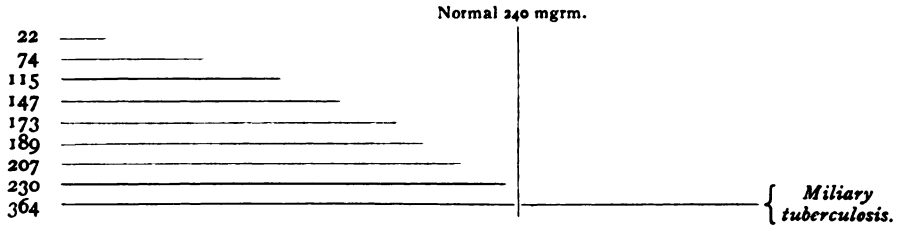
B. *Mgrm. Iodine in Whole Gland.*

All small glands, so that activity is essential to keep up amount of secretion which is probably being actively utilized in the body in this condition.

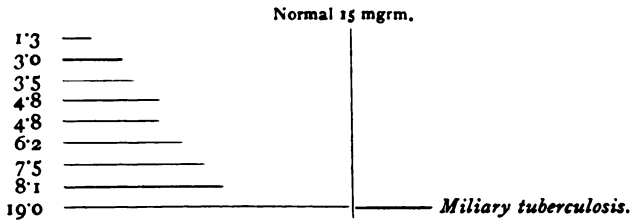
Another set of charts shows the relation to sepsis, tuberculosis and the clinical types of insanity. The tuberculosis chart shows a very low total iodine and a moderately low percentage of iodine in the dry tissue, the percentage showing extreme variation and therefore thyroid activity in this condition. The one case of miliary tuberculosis is interesting if we regard it as being parallel with pyæmia and septicæmia, that is to say, if we view miliary tuberculosis as the end-result of a tubercular septicæmia which the system has, in part at least, successfully made a strenuous effort to overcome; it shows both high percentage in the dried gland and an adequate amount of total iodine.

TUBERCULOSIS (9 cases).

A. *Mgrm. Iodine in* 100 *grm. Dried Gland.*



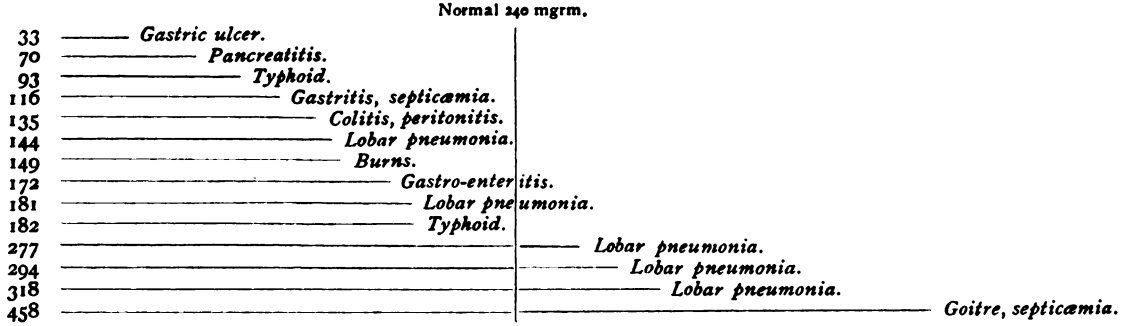
B. *Mgrm. Iodine in Whole Gland.*



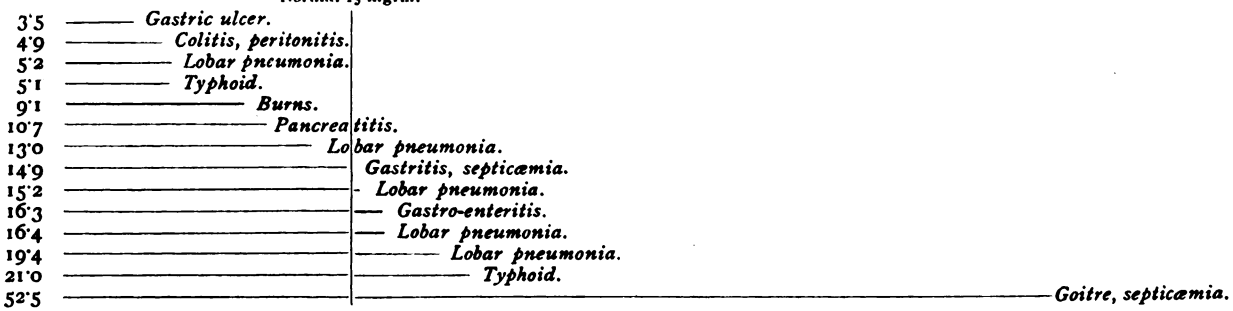
The variation is important and shows the activity of the thyroid in tuberculosis.

Sepsis (14 cases).

A. *Mgrm. Iodine in 100 grm. Dried Gland.*



B. *Mgrm. Iodine in Whole Gland.*



The extreme variation which exists here shows the very marked relation between thyroid activity and septic processes.

General Paralysis (39 cases).

A. *Mgrm. Iodine in* 100 *grm. Dried Gland.*

Normal 240 mgrm.

8	126	167	179	227	307
32	134	168	181	233	327
105	140	174	195	243	339
108	151	175	217	274	448
113	152	176	222	282	476
114	164	178	226	284	485

B. *Mgrm. Iodine in Whole Gland.*

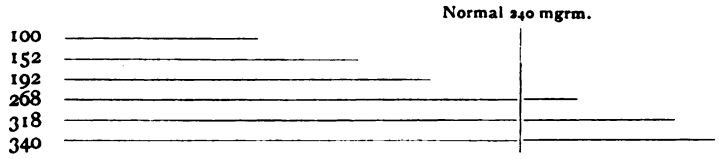
Normal 15 mgrm.

0·4	5·2	8·5	13·3	22·5
1·2	5·5	9·2	13·3	24·0
1·2	6·8	10·0	14·4	24·5
2·5	7·0	10·3	15·0	26·2
3·0	7·5	10·4	16·4	27·0
3·1	7·7	10·5	18·4	38·4
4·0	7·7	11·6	20·3	50·6
4·0	8·3	13·0	20·4	

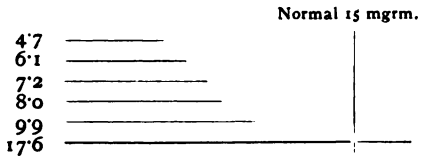
The great variation in the iodine in this group of patients shows that the thyroid gland is markedly affected by processes causing or associated with general paralysis. Charts can readily be constructed from these data.

Mania.

A. *Mgrm. Iodine in* 100 *grm. Dried Gland.*



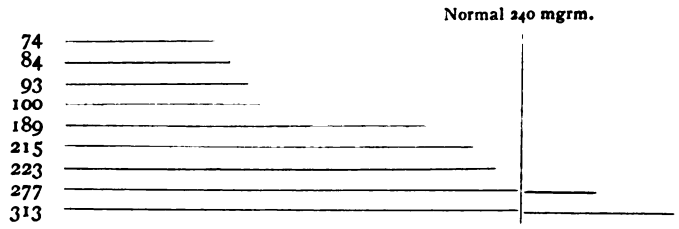
B. *Mgrm. Iodine in Whole Gland.*



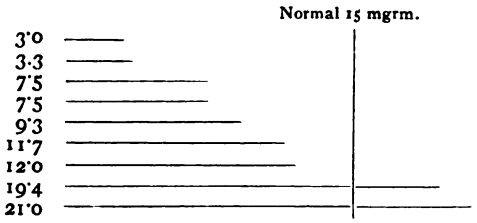
Variability of both percentage iodine and total iodine indicates considerable changes of the thyroid in this condition.

Melancholia.

A. *Mgrm. Iodine in* 100 *grm. Dried Gland.*



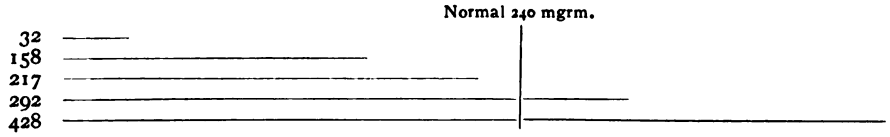
B. *Mgrm. Iodine in Whole Gland.*



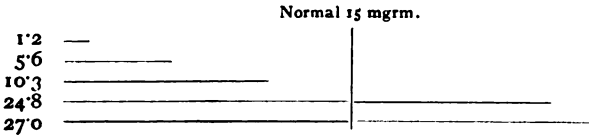
As in mania the variation indicates thyroid changes in this condition.

Epilepsy (5 cases).

A. *Mgrm. Iodine in* 100 *grm. Dried Gland.*



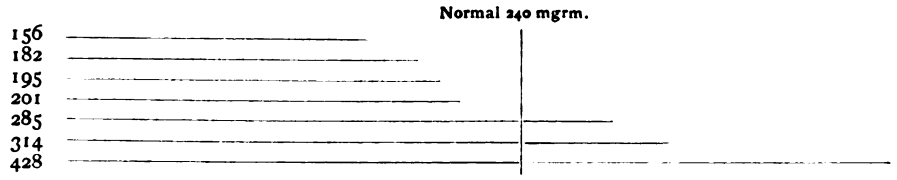
B. *Mgrm. Iodine in Whole Gland.*



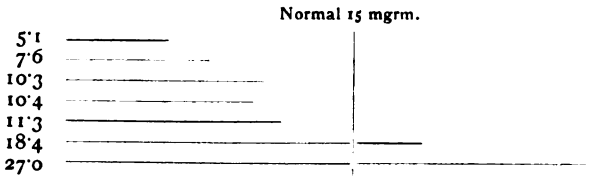
Great variation indicates that changes are present in the thyroid in this condition.

IDIOCY AND IMBECILITY (7 cases).

A. *Mgrm. Iodine in* 100 *grm. Dried Gland.*

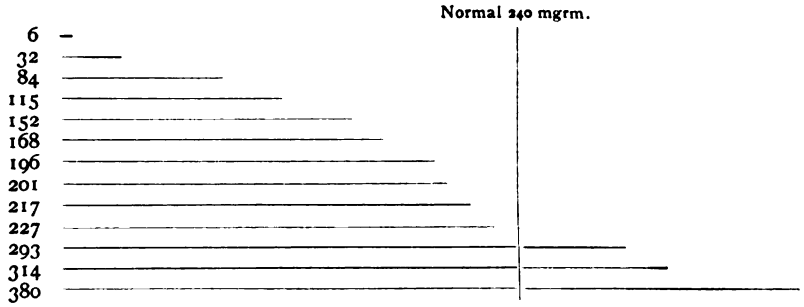


B. *Mgrm. Iodine in Whole Gland.*

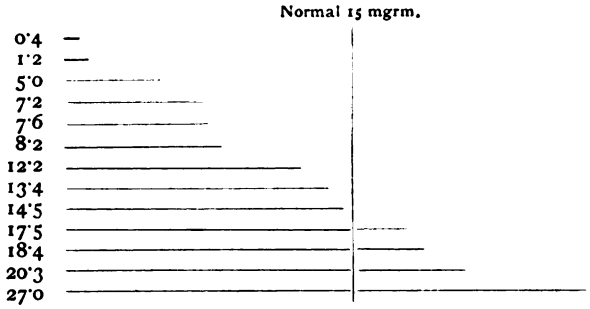


DEMENTIA (13 cases).

A. *Mgrm. Iodine in* 100 *grm. Dried Gland.*



B. *Mgrm. Iodine in Whole Gland.*



This group includes several cases of general paralysis and shows great variation in the iodine.

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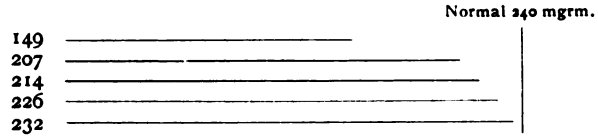
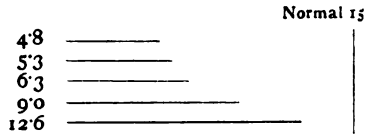
Paranoia (5 cases)

A. *Mgrm. Iodine in* 100 *grm. Dried Gland.*



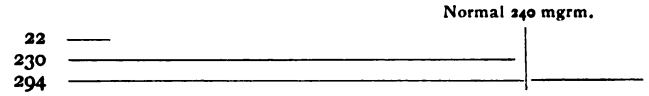
B. *Mgrm. Iodine in Whole Gland.*



Low total iodine, but normal percentage of iodine in the dry gland.

Confusional Insanity (3 cases).

A. *Mgrm. Iodine in* 100 *grm. Dried Gland.*

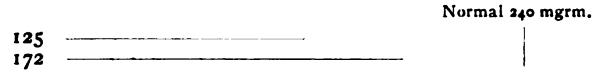


B. *Mgrm. Iodine in Whole Gland.*

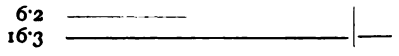
Thyroid disturbance indicated by the variation.

Post-Encephalitis Lethargica (2 cases).

A. *Mgrm. Iodine in* 100 *grm. Dried Gland.*



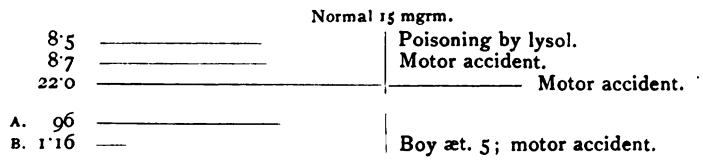
B. *Mgrm. Iodine in Whole Gland.*



? Normal (4 cases).

A. *Mgrm. Iodine in* 100 *grm. Dried Gland.*

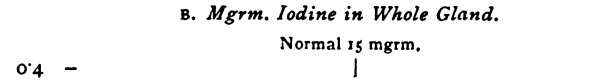
B. *Mgrm. Iodine in Whole Gland.*



Myxœdema (1 case).

A. *Mgrm. Iodine in* 100 *grm. Dried Gland.*

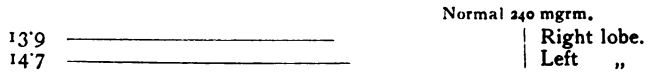
B. *Mgrm. Iodine in Whole Gland.*



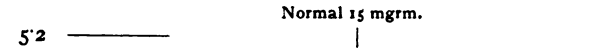
A case of toxic thyroiditis, which was X-rayed, resulting in destruction of the whole of the thyroid glandular tissue.

Graves' Disease (1 case).

A. *Mgrm. Iodine in* 100 *grm. Dried Gland.*



B. *Mgrm. Iodine in Whole Gland.*

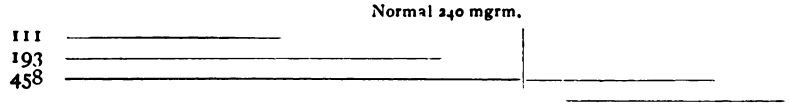


The low total iodine in the gland is evident; the percentage is also low.

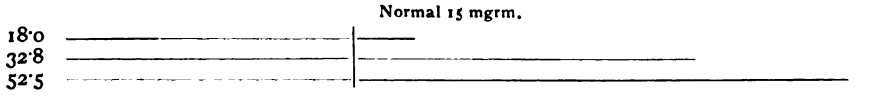
The patient had previously had the greater part of the left lobe removed by operation.

GOITRE (3 cases).

A. *Mgrm. Iodine in* 100 *grm. Dried Gland.*



B. *Mgrm. Iodine in Whole Gland.*



Indicates colloid storage with little absorption.

The above results, indicating the amount of iodine in the thyroid of mental hospital patient, show (1) a distinctly low average iodine content and (2) a marked variability in the amount of iodine in the whole gland, and also (3) a marked variability of iodine content of the dried tissue. The groupings above show only one aspect of the patient's condition; other factors, such as age, are omitted as separate groupings on account of space. It seems probable that by extension of the work we shall arrive at a definite cause underlying these results, and also be able to correlate thyroid change with some aspects of mental disease. The present work tends to show a relation on the one hand of septic processes to thyroid change (see chart showing cases of pneumonia), and, on the other hand, a relation between changes in the thyroid and mental disorder.

Two cases may be quoted.

F. E—, an apparently normal individual, developed a toxic thyroiditis, which was X-rayed, resulting in total destruction of thyroid tissue; she developed mental symptoms, and when admitted into the hospital had definite myxœdema, and showed emotional deterioration with auditory hallucinations and impulsive attacks; she had a very low basal metabolic rate—59·2 *per cent.* of the normal—which on treatment with thyroid gland by the mouth was raised to 78·5 *per cent.*

The patient improved considerably by treatment with the thyroid and coincidently developed a temperature and showed other reactions to chronic septic foci in the nasal sinuses and elsewhere, which Dr. Graves demonstrated by X-ray evidence to have been present for some time.

Cessation of thyroid treatment caused the basal metabolic rate to return to the original low figure of 59·2 *per cent.* of the normal. Chemical examination of the thyroid at autopsy showed almost complete absence of iodine in the gland, which consists histologically almost entirely of fibrous tissue.

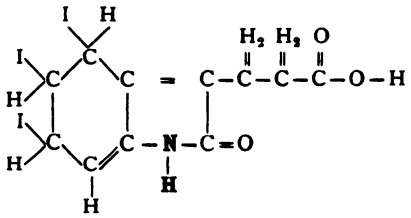
N. G—, a case of dementia præcox, had the abnormally low basal metabolic rate of 19, *i.e.*, 49·5 *per cent.* of the normal, and, it may therefore be inferred, a very inadequate supply of thyroid hormone. The interesting correlation is the fact that the patient showed on more than one occasion a bacteriæmia of *B. cloacæ*—an organism of the *coli* group also present in the fæces. Without assuming too much as to the causal factors in this case, it is interesting to compare with the published experiments of feeding pigeons on polished rice, *i.e.*, vitamin-free, which showed progressive hyperplasia of the thyroid with absorption

of colloid followed by epithelial desquamation and atrophy. They "died from invasion of the blood by micro-organisms of the *coli* group which originally inhabited their intestines as harmless saprophytes."

Sajous believes that thyroid secretion is identical with the little known but demonstrable substance Wright's opsonin.

Dr. Rollier bases his prognosis of the treatment of tubercular bones and joints upon the clinical demonstration of the thyroid: "When I feel a good thyroid I give a good prognosis."

One fact of great importance is the disappearance of the myxœdematous mucoid infiltration of the tissues which follows the administration of thyroid, and lends support to the idea that the thyroid catalyses the destruction of waste tissue products and amine compounds. That thyroxin can combine with amino-compounds by virtue of its imino grouping—



has been shown, and if this reaction is prevented by acetylation of the group, the compound at once loses its characteristic physiological properties for mammalians although still active in tadpole metamorphosis.

The changes which are known to occur in the gland at puberty marriage, pregnancy and the menopause are especially interesting because of the slight but distinct change of disposition which marks this disturbance of endocrine balance.

It is clear from the foregoing that the thyroid is of great importance in combating infections, although it may need co-operative action of other endocrine products—probably those of the adrenal cortex.

The work is being continued together with the determination of the fat cholesterol lipoid content of the suprarenal gland.

My best thanks are due to Sir Frederick Mott for suggesting this work and for his valuable assistance and advice.