An Investigation into those Factors Relating to the Etiology of Toxic Goitre.

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INDEX.

Introduction.

The object of this thesis has been to collect, corelate and discuss those factors which relate to the etiology of toxic goitre: to examine the theories held regarding its etiology and to submit evidence in support of the hypothesis that toxic goitre is a condition of general intoxication, dependent upon the existence in the patient of a previous neuroendocrinopathy which may be inherent or acquired, a condition analgous to the Graves' Constitution described by certain authors, and which requires an igniting stimulus - in the vast majority of cases one of psychic trauma, to set into flame its classical signs and symptoms.

Evidence is also brought forward to support the existence of a precise relationship between the supra renal bodies and the thyreoid gland, the latter being stimulated by the secretion of the former, in part through the medium of the sympathetic nervous system, and in part by a direct influence upon the thyro-neural junction of the sympathetic nerve endings.

As a result of the work certain other facts came to light regarding the iodine content of the blood, and considerable evidence is adduced that in its assay lies an index which may be of value in diagnosis - particularly in early or doubtful cases, and especially when estimated

before and after the injection of .5 c.c. adrenalin hydrochloride 1/1,000 solution.

Further, it has been shown that the iodine content of the blood bears certain relationships to the basal metabolic rate and that its estimation may be used with advantage to identify the potentially myxoedematous person, to assess the degree of recovery of thyreoid function where there has been operative interference, and as a useful clinical accessory in watching the progress of the disease.

The investigations were carried out in the Wards of the Victoria Infirmary, Glasgow, the Biochemical and Pathology Departments of that Institution, and in the Department of Surgery, Glasgow University. The clinical material consists of a series of seventy eight cases of toxic goitre treated during the years 1935/1938 in the Victoria Infirmary, and examined during the past year and a half by the writer.

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In the year 1786 medical literature was enriched by the description, written with remarkable fullness,of a syndrome, which up to that date had been unrecognised. The author was Calleb Hillier Parry, and his subject that condition which is now recognised as toxic goitre. It is a paradox that the disease has rarely been called after the original author, that honour having been given instead to a Bath physician, Dr. Graves, who recognised, and in 1835 described it for the second time in the literature.

Graves detailed notes on three cases, but with less exactitude than did Parry, to whom also belongs the distinction of having been the first to describe a case of toxic adenoma.

In the years which have followed, and especially during this present century which has been so prolific in contributions to the world of Medical Science, there has accumulated a host of information regarding the two diseases, so bewildering in its complexity, so vast in its scope, and so frequently contradictory in its translation, that Truth has to a large extent become obscured by a maze of words. Since it is the determination of every earnest research scholar to elucidate Truth, the fact that the literature is so full of contradiction, and yet so abundant in description of work well done, is a striking testimony to the intricacies of these diseases first observed over one century and a half ago.

A prominent feature of most discussions on toxic goitre is confusion in nomenclature. The disease has been endowed with many names, all unsatisfactory in one respect or another and none universally accepted, but it appears to me that the simple term 'toxic goitre' is as suitable as any. Even that, however, may be criticised upon the grounds that the presence of goitre is variable, and that even when present it is not of necessity the cause of toxic symptoms; nevertheless it is no less accurate than any other, and is accordingly used throughout this thesis to indicate that condition of characteristic general intoxication in which a prominent part is played by the thyreoid gland.

Section 1.

Definition... Geographical Distribution... Racial Incidence... Sex Incidence... Age Groups...

Definition.

At a meeting of the Liverpool Medical Association on November 8th, 1937, Professor Cohen [1] said he doubted if it were possible to define thyrotoxicosis with greater accuracy than 'as a state of intoxication dependent upon the thyreoid.' Eason [2] states that "Exophthalmic goitre is a syndrome of nervous and endocrine disorders", while according to Bram [3] it is an inherited neuroendocrinopathy which requires but the stimulus of psychic trauma, emotional strain, or possibly at times infection for its production.

There is no common definition of toxic goitre which is at once brief, comprehensive and accurate in substance.

The clinical syndrome is an established and familiar entity, the staring eyes, exciteable temperament, moist skin and thin emaciated frame bring at once to mind the glib and obvious diagnosis: but what of the early or atypical case which may be masked in signs and symptoms not pointing to nervous system, eyes or gland ?

1. B.M.J. 8th November, 1937.
2. Eason. Exophthalmic Goitre. 1.
3. Bram. Exophthalmic Goitre. 39-41.

In my series I have several persons who were afforded permanent relief from symptoms simulating gastric or duodenal ulcer by treatment directed towards the thyreoid. Hay [1] mentions the thyrotoxic heart syndrome where cardio-vascular symptoms colour the picture, and McEwan [2] also comments upon such thyreoid 'masks' where toxic goitre assumes an atypical form and renders diagnosis difficult. An accurate definition of the disease can be arrived at only after there has been gained a full understanding of its physiology, etiology and pathogenesis, its signs, symptoms and pathology, and the varieties which may be presented clinically.

In the absence of that full understanding a provisional definition may be made embracing these facts which have up to date been elucidated, and when that has been given the question of etiology may be approached keeping these facts in mind.

The observations from which this definition has been evolved will be detailed in the course of the text, but to the writer it appears that toxic goitre is a condition which is dependent for its development upon the previous existence in the patient of a neuroendocrinopathy which may be inherited or acquired, and which requires but the stimulus provided by the influence of infection, psychic trauma, or the force of environment, or a combination of these, to produce a clinical syndrome which is characterised by elevation in the basal metabolic rate, tachycardia,

1. Hay. Lancet. 2. 1378. 1936.
2. McEwan. B.M.J. 14th May, 1938. 1041.

increased perspiration, loss of weight, tremor of the fingers, emotionalism, increased sensitivity to the action of adrenalin, an elevation in the iodine content of the blood, and which is found more in females than in males by a proportion of about seven to one.

Bram [1] defines the disease as being a catabolic neuroendocrine dysfunction characterised by increased basal metabolic rate, loss in weight, tremor, emotionalism, persistent afebrile heart hurry, weakness, dermographia, and a relative immunity to cinchonism, and at times by hyperplasia of the thyreoid gland and exophthalmos.

There is a notable similarity between the two definitions and that because they are based upon similar interpretations of the phenomena at work in the production of the disease, and upon a recognition of the constitutional neuroendocrine deficiency.

1. Bram. Exophthalmic Goitre.

Geographical Distribution.

Toxic goitre is found all over the world, but is more common in the so-called civilised countries, Europe, America, Australia, New Zealand, the African Colonies, India, Japan, China and the Near East.

Berry [1] states that toxic goitre is not an endemic condition and that its distribution does not coincide with that of simple goitre, in fact he says that it is rare in places where simple goitre is common, and that it is certainly found in areas where simple goitre is unknown.

This view is supported by McCarrison [2] who remarks that while little is known of the geographic or climatic distribution of toxic goitre it is certainly rare in regions where simple goitre is endemic, and he notes that during ten years experience in the goitrous areas of the Himalayas he saw few cases of toxicity.

Campbell [3] in 1925 compiled a map of the distribution of the disease in Great Britain based upon the death statistics furnished by the Registrar-General: and McEwan [4], in May, 1938, published a similar report with a map compiled for England and Wales alone, and from the same statistics, but for the year 1936. McEwan's map does not include Scotland or Ireland, but for England and Wales there is a remarkable similarity to Campbell's, the highest death rate occurring in the mountainous areas of

1. Berry. Diseases of the Thyreoid Gland. London. 1901. 177
2. McCarrison. The Thyreoid Gland in Health and Disease. London.1917
3 and 4. Campbell. Quart.Jrnl.Med. Jan. 1925. (195.

Wales, Westmoreland and Huntingdon Counties, while it is noticeable that the large towns have comparatively small death rates. McEwan compares the death rate for 1936 with the annual average death rate for the years 1913 to 1919 and his figures may be quoted with advantage.

County	Number of Deaths.	
	Annual Average Years 1913/19.	Year 1936
Westmoreland	1.57	7
Huntingdonshire	3.43	6
Shropshire	3.28	18
Cornwall	7.85	22
Cambridgeshire	1.43	9
Sussex	11.28	47
Derbyshire	8.71	38
Lancashire	71.14	241
Lincolnshire	8.43	28
Buckinghamshire	2.57	12
Yorkshire	49.71	192
London and Middlesex	48.00	155

It is obvious that there has been a great increase in the number of notified deaths during 1936 as compared with the average for each of the years 1913 to 1919. In England according to both Campbell and McEwan the death rate from toxic goitre is higher round the coast than inland, while in Scotland...Campbell...it is rather higher inland than round the coast, and in the seven largest Scottish towns the disease has a lower mortality than the rest of the country. Campbell concludes that the influence of the mountains appears to be the most important single factor in

England and Wales, but in Scotland on the other hand his map shows a comparatively low incidence in the mountainous areas.

Campbell states that in Devon and in Cornwall the high incidence of toxic goitre may be due to the inhabitants of these counties being endowed with the excitable temperament of the Celt.

The notable similarity between the two maps compiled at intervals of ten years by different men and based upon the same statistics compel one to regard the information to be derived from their study as absolutely authoritative, but certain points arise in this connection which are worthy of discussion. Does the incidence of the death rate furnish a reliable guide as to the incidence of the disease in a condition such as toxic goitre which frequently terminates fatally through the onset of other diseases, pneumonia, cardiac decompensation, hyperpiesia, or infectious illness which might lead to some confusion in death certification ? It may well be that in many of the areas with a low certified death rate the actual death rate is higher.

Does the death rate distribution coincide with the geographic distribution of simple goitre ?

This point was carefully studied by Campbell, who found it was impossible to obtain reliable information regarding the incidence of simple goitre but he concluded that the evidence available pointed to some degree of correspondence between the incidence of simple goitre and the deaths from toxic.

As we have seen above, McCarrison and Berry concluded that there was little or no correspondence between the incidence of simple goitre and toxic, and that the association between the two was, in their extensive experience, rare.

A map showing the incidence of simple goitre for England and Wales was compiled by Joll, and demonstrates that that condition is most common in the South West of England and in Cornwall. Most of Wales and Herefordshire find second place, then Lancashire, Cheshire, Derbyshire, most of Notts., Oxford, Bucks., and most of Northants., while the disease was least common in Glamorgan, Monmouth, Essex, Hertford, Middlesex and in the Eastern Counties. This is in accord with the findings of Stocks [1] based upon the examination of 375,000 children aged twelve in the English schools.

From Joll's findings it appears that there is a good deal in common between the incidence of simple goitre and the higher areas of death from toxic. The two areas correspond in Devon and Cornwall, in the mountainous regions of Wales and in the Southern Midlands of England.

The questions further arise; are cases of simple goitre being notified in error as toxic, or are cases of simple goitre assuming toxic properties, or is the association merely coincidence ? To imply such a consistent error in notification is to imply a lack of skill and care generally which should be foreign to the

1. Percy Stocks. Quart. Jrnl. Med. Jan. 1928.

attentive general practitioner and resident physician. One may assume that this is not the explanation.

As regards the possibility of cases of simple goitre assuming toxic properties, this is a question difficult of decision. Within recent years iodine therapy has been more commonly adopted generally than it was in the earlier days of this century. Practitioners are becoming more expert in detecting the case of mild simple goitre, and it may be said that probably there is a certain lack of discrimination in the use of iodine, there being a tendency in my experience for doses to be given which are far beyond the organic requirements.

McLendon and Hathaway [1] observe from careful studies on the iodine metabolism of the body that a healthy adult male ingests approximately twenty gammas of iodine per day on a normal diet, one gamma being one thousanth part of a milligram. Orr and Leitsh quoted by Joll, found that the minimum amount of iodine required for equilibrium in an adult male is about fifteen gammas per day, and in a child, about fifty, but that slightly more is required when there is more activity, since exercise stimulates thyreoid secretion thus calling for more iodine.

It would thus appear that upon a normal diet the average adult person ingests just sufficient iodine for his requirements and that the iodine excretion should be practically nil.

1. McLendon and Hathaway. Proc. Soc. Exper. Biol. & Med. 1923/24. 21.

It is also obvious that the maintenance requirements are practically the same as the total quantity ingested thus leaving a very small margin upon which to come and go, and so in areas where there is iodine lack in the soil and water a condition of iodine deficiency may readily be produced. It will be recalled that the effect of iodine deficiency is to promote thyreoid hyperplasia and simple goitre, and that conversely, in simple goitre iodine administration causes the thyreoid to undergo involution, and the epithelium and the amount of colloid in the follicles to revert to a normal state.

Throughout these two cycles of events there are no noticeable differences in the thyreoid function as noted by estimation of basal metabolic rate or upon clinical examination; the sequence is symptomless.

The point at issue is however; what is the dose of iodine which is necessary to restore the gland to normal and what is the effect of exceeding this dose ?

Thomson [1] who investigated the minimal iodine requirements found that in endemic goitre the prophylactic dose of iodine in terms of the compound tincture is .1 milligram per diem. Since one minim of the compound tincture contains six milligrams of iodine, .1 milligram is an extraordinarily small quantity indeed, and even in the established case of simple goitre there is little doubt but that a dose of twelve milligrams of iodine, that is to say, two minims of the compound tincture is an ample daily dose.

1. Thomson. Arch. Int. Med. 1930. 45.

How many patients with simple goitre are given iodine in such small quantities ? A more common figure is five minims, thrice daily, this being a surplus of twelve or thirteen minims, or nearly eighty milligrams of iodine with a minimal requirement of some twenty.

What is the fate of this surplus ? In the normal case it is excreted, the patient continues to take the medicine and no harm is done.

It has been suggested that in a proportion of cases the unduly high iodine intake may stimulate the thyreoid to a condition of toxicity. Of that there can be but little doubt. Many cases are on record in which the onset of toxic symptoms has been related to the ingestion of iodine or of thyreoid extract. The effect of iodine in these cases is at first to restore the colloid and epithelium to normal and to reduce the hyperplasia, but, that having been effected, a stimulating influence follows; colloid is removed from the vesicles, the epithelium becomes active and the gland vascular, some hyperplasia may follow and there is increased secretion with toxic symptoms. How many of the many thousands of cases described have been produced after this fashion ? The percentage must be practically negligible, and when such does take place it can only be when there is a constitutional liability with the iodine acting as the igniting stimulus.

So it appears that the significance of the association between the death rate from toxic goitre and the incidence of simple is difficult to assay.

When all factors are considered, however, probably there is no relationship between them at all. The figures have been compiled for what is a very small country and it is not surprising that certain areas in the two maps should correspond.

One feature of absolute importance that arises from study of the maps of Campbell and McEwan is, however, the high incidence in the parts of the country which are naturally sequestered, and "far from the maddening crowds' ignoble strife". Even in Scotland the large towns have a lower death rate than the country areas.

McEwan [1] says "The stress and strain of modern life has by some been regarded as an important factor in causation. Campbell's map does not bear this out, outlying mountainous countries not being the areas of greatest stress. Now, if during the twenty years that intervene between the maps...the mortality rising from an average of 442 to 1696...the stress of life were an important factor, the distribution must have altered in favour of the big cities. It has not changed, therefore the stress and strain of life is, if a factor at all, a minor one, whereas the geographical factor is the major one."

The weight of evidence in support of the suggestion that the stress and strain of modern life do play an important part in the etiology is substantially convincing, coming from such authoritative sources as

1. McEwan. B.M.J. May 14th, 1938.

Crile [1], Eason [2], Bram [3], Agnes Conrad [4], McCarrison [5], Marine and others who have made of the subject an extensive study.

Why then are their opinions not being supported by the findings of McEwan and Campbell ?

A number of possible suggestions may be advanced to explain this seeming paradox, but all are in the realm of pure theory however convincing their arguments may appear to be.

The possible fallacies in certification have been mentioned which might mask the true state of affairs, rendering the death rate statistics null and void. Should that be so then the same errors have been perpetrated throughout twenty years and by a new generation of practitioners, a state of affairs which is improbable.

There is one other possibility which may explain why the death rate distribution may not be a true index of the actual incidence of the disease.

Medical services and clinics are most numerous in the city areas and city dwellers derive most benefit from them. Country people may not be inclined to travel to the nearest large medical centre for treatment until compelled by the urgency of their condition, by which time they may be unsuitable subjects for treatment and may raise the death rate for the country areas considerably.

What do the words 'stress and strain of modern life' imply ?

1. Crile. Diseases Peculiar to Civilised Man, 1934.
2. Eason. Exophthalmic Goitre. 41.
3. Bram. Exophthalmic Goitre. 39/41.
4. Agnes Conrad. Amer.Jrnl.Psychiatry. Novr. 1934. 91.521.
5. McCarrison. Thyreoid Gland in Health and Disease. London, 1917.

They imply not only the hustle of city life but also the necessity to make money and live: they suggest search for employment and fear of unemployment, worry as to health and strength, the problem of guiding a family, all these and many other problems which combine to make life in even the wildest and most remote Hebridean Island more complex than it was even one century ago.

These factors, with the exception of the business of city life, are just as real in the country areas as in the towns, and in the truth of that statement may lie the explanation of Campbell and McEwan's findings varying, at first glance, from the views of those who adhere to the 'stress and strain' theory.

From the available evidence it would appear that the Geographical distribution of the disease is not a factor of importance in determining its onset.

Racial Incidence.

Toxic goitre is generally speaking, a disease of the so-called civilised countries, but cases have been described in all the races, White, Yellow, Black, Brown and Red. It is certain however, that it is uncommon in the peoples who are developmentaly primitive; I have enquired from persons resident in New Guinea, Borneo, West Africa and the Fiji Islands as to whether or not the disease was recognised among the natives, and the question was invariably answered in the negative. In Means' series there were Negroes and Chinese, but all had been resident for some time in America, and, in certain cases had been involved in criminal law proceedings, thus bringing in psychic trauma as a coincident factor.

There can be no doubt but that Civilisation carries with it an atmosphere of unrest, it intensifies ones mode of living, and often promotes a feeling of uncertainty and insecurity which probably reflects adversely upon the nervous system and also upon the endocrine organs.

Diseases which emphasise the nervous system are, with few exceptions, peculiar to our civilisation and amongst them is included toxic goitre.

A study of the racial incidence again emphasises the psychological aspect of the problem, that feature which permeates every stage of the disease, and little other than a realisation of that fact can be gained by the study of this etiological factor.

Sex Incidence.

It is accepted that the disease is pre-eminently found in the female subject. The figures given by various authors correspond closely, there being in the present series one male to seven females. Joll, quoting the figures for the Mayo Clinic, gives 85% females and 15% males. The significance of this fact is discussed in full in connection with the Gonad Theory of Etiology, (Page L12) where the more important points shall be found to be as follows.

1. The basal metabolic rate is in the adult male five to ten times more stable than in the adult female.
2. There is a greater complexity and finer adjustment of emotional structure in the female than in the male, especially in relation to the pituitary and reproductive organs, these being in a continual state of ebb and flow which renders them more unstable than their male homologues, and thus more liable to be thrown out of balance by external stimuli.
3. In the female, pregnancy, menstrual upsets, and the menopause may act, in the person constitutionally liable, as the precipitating cause of toxic goitre, but the number of such cases is small.

Of the seventy eight cases at present under consideration, sixty nine were females, and of these, the onset of the disease was in five associated with pregnancy, and in five with the climacteric, while in each of these, other factors such as psychic or physical trauma also played a part, and in all ten the persons gave a clear history of having a constitutional liability to the condition.

Most clinicians admit that while the disease is more common in women yet it is more serious in men, and in them is associated with a higher death rate.

The reason for this is not far to seek. One of the essentials for obtaining a good result in the treatment is that convalescence be prolonged and untroubled, being accompanied by as little worry, fear, and emotional upset as is practicable.

Few men are placed in the happy position of being able during that period of convalescence to lie back, take things easily, and refrain from worrying. So soon as they are at all able they demand permission to return to work, and as a rule, incidentally to precisely those same influences which played a prominent part in determining the initial onset of their disease...the worry of finance, supporting a home, and the like...while even if they are persuaded to prolong their convalescence they inevitably worry about their responsibility as wage earners, and fail to derive the benefit which a person unhampered by such emotions would certainly derive.

Age Incidence.

The incidence is maximal during the third and fourth decades of life, but the disease is found at all ages, has even been described in the newly born [1], and although extremes suffer least, it would appear that none is immune.

In the present series the youngest patient was a girl aged thirteen with marked signs and symptoms of toxicity, the condition having been present for two years and increasing progressively in severity, while in Bram's series of 5,000 cases 162 were under fifteen, the youngest being thirty months old, and the oldest 78 years.

It is of interest to note that the incidence is maximal during the third and fourth decades of life, because it is during these years that the average person's responsibilities are reaching their peak, and the stresses of life are claiming their highest toll.

According to the degree of one's predisposition so does it take a longer or a shorter time for toxic goitre to develop and since comparatively few persons are born with a neuroendocrine system so unstable that it is upset by the first traumatic attack made upon it, thus we see that a number of years are required during which time it is being bombarded by traumatic influences varying in degree and in duration, but steadily weakening and overcoming its resistence until during these unduly strenuous periods of the third and fourth decades the crisis comes, the battle is finally won and the disease takes the upper hand..

1. Bram. Exophthalmic Goitre.

Section 11.

Constitutional Factor... Laboratory Test for Graves' Constitution/Factors which may precipitate the production of toxic goitre... Heredity and Familial Influences.

Constitutional Factor.

It is emphasised in this thesis that the majority of persons who develop toxic goitre have a previous constitutional liability to the disease, a liability described by Bram and named the Graves' Constitution.

The evidence for the existence of this liability is conclusive. Cameron [1] states that evidence of the constitutional factor is supported by the actual, though rare occurrence of the disease in very young children, and the occasional histological appearances in foetal thyreoids suggesting its presence, while Fraser and Dunhill [2], though saying the cause is unknown, yet admit that a constitutional factor is probable.

Eason [3] explains that the reason individuals respond differently to psychic trauma is because those who develop toxic goitre have an inborn or acquired diathesis rendering them more liable than the average person, while Means [4] believes that the activating episode, be it psychic trauma, infection, parturition, the menopause or other factor, probably does no more than pull the trigger of a gun in a person endowed by

1. Cameron. Recent Advances in Endocrinology.1934. 73.74.
2. Fraser and Dunhill. B.M.J. 9th Jan. 1937. 84.
3. Eason. Exophthalmic Goitre. 38.
4. Means. Thyreoid Gland and its Diseases.

heredity or sensitised by previous experience to make the type of response which constitutes toxic goitre, the activating episode probably merely making manifest a latent malady just as pregnancy may make manifest tuberculosis.

The clinical description of a person with a Graves' Constitution has been detailed by Bram and his description is quoted in connection with his Theory of Etiology (Page 130), but it is suitable to describe it also at this point.

The stigmata of the Graves' Constitution are

1. Heightened cerebration.
2. Autonomic and emotional instability.
3. Excitable heart.
4. Vasomotor Ataxia.
5. Unduly sparkling eyes.
6. Unduly palpable thyreoid.
7. Lowered threshold of emotional reaction.

Further, it shall be critised (Page130) on the ground that the gland need not be palpable, while it shall also be observed that a constitutional elevation in the basal metabolic rate with, not infrequently, an increase in the iodine content of the blood is also present.

The vision of a thin highly strung emotional child who is restless and ill at ease in company, who fidgets on sitting long in one position, and yet who may show considerable precocity, wit, and intelligence when the shyness has been overcome is familiar. Frequently such a child is born of highly strung parents and excitability is increased by the mode of upbringing, correction and praise both being exaggerated, the child living in a world of extremes, which intensifies the constitutional nervousness by environment, and paves the way for an upheaval in the

neuroendocrine system at some period later in life.

Not infrequently the parents will say that as a child the patient was very studious, 'took things seriously and was very sensitive, but not clever at games'. The exact meaning of the word 'sensitive' is often doubtful, but the parents may further explain and say that the child took a scolding seriously, or was 'too gentle to be spanked because it seemed to upset him'. In other words the patient had, as a child, a lowered threshold of emotional reaction and reacted in an exaggerated fashion to the ordinary stimuli of childhood life.

Such a one may be said to have a Graves' Constitution, but as has been already remarked in this paper, that constitutional liability may be modified or intensified by environmental circumstances.

Children are essentially susceptible to 'atmosphere'. They can sense when there is worry or trouble, and although to the normal young person such impressions may not do more than have a temporarily subduing effect, yet in the sensitive, such stimuli may intensify the inherent emotional instability to a degree which is dangerous to future well-being.

Should however, such a child be placed under the care of people with a placid disposition, who know how best to use the instruments of praise and correction with discretion, where the temperamental level of environment is upon an even plane, then the child may be relied upon to respond to this more equable existence. Nervousness may improve with the years, and shyness give place to a normal outlook upon the world. Emotional instability shall probably be curbed, vasomotor ataxia reduced in degree, restlessness give way to evenness of poise, and

the hurrying heart revert to a normal frequency. Improvement all along the line will in many cases be found, and beyond a certain sparkle in the eye, some slight heightening of the basal metabolic rate and an accompanying rather subnormal physique, a ready wit and tongue and some vivacity of manner, little else may be present in later adolescence to tell the tale of the emotional childhood.

Such a constitutional liability was definitely present in 60% of cases examined by myself, and the stigmata admitted by the patients upon close questioning with regard to their earlier childhood. In a number of cases the parents were questioned and not infrequently they agreed that many of the symptoms detailed above had been present during the patient's earlier life.

It was evident, however, that in no instance did either parents or patients consider that state of affairs as other than quite normal, and it is this failure to observe the true position which may lead parents into error in their relationships with their children. Often such children are temperamental and resentful of correction, the parents become irritated and a vicious circle is set up which never leads to improvement but serves invariably only to intensify the difficulties.

According to the degree of liability present so a greater or a less degree of trauma...physical or psychic or otherwise...is required to initiate the disease, and a longer or a shorter time required for its development.

As we have seen, during the third and fourth decades of life when the stresses of life are maximal, then also is found the peak incidence of toxic goitre; these are cases where resistance had to be overcome by a long succession of disturbances, while on the other hand

there are clear cut instances noted of one stimulus and one alone being sufficient.

The disturbances mentioned may assume one of many forms, but not infrequently they are emotional in nature...psychic traumata...and of these, again there are many varieties. The disturbance may take the form of normal body processes...puberty, pregnancy, or the menopause; infections are commonly noted, and not uncommonly physical shock is the precipitating factor.

The varieties of these influences will be analysed and their relative incidence discussed, but at present it is sufficient to have noted broadly the form they may take, and to observe that in this series they accounted for the onset of all cases with two possible exceptions.

Eason, quoting Eppinger and Hess [1], describes a hyperexcitability of the nervous system characterised by signs of increased tone in the para, and sympathetic divisions . It is noted chiefly in young people who have hitherto generally been regarded as neurasthenic, who are able to get about quite normally but yet, who cannot suffer any considerable mental or physical strain. Under such strain, or sometimes without any apparent cause, trivial symptoms referred to the heart or gastrointestinal tract may appear and initiate a long period of invalidism.

Eason goes on further to say that these people change colour easily, hands are cyanosed, cold and clammy, perspiration is free, sometimes confined to the face, axillae, or extremities, patchy hyperaemia of the skin of chest and neck is apparent, enlarged tonsils and adenoids are seen in the young subject and in the adult there are

1. Eason. Exophthalmic Goitre. 23/24.

sore throats while the heart shows marked irregulatities, extrasystoles and irritability.

This description is of interest in that it emphasises the enlarged tonsils and adenoids in the child. Blackford and Fry (Page 110) considered that Lymphoid hyperplasia should be regarded as a result and not as a cause of thyreoid hyperplasia; here however is an opinion emphasising Lymphoid hyperplasia but this time in association with the potential development of more gross thyreoid disease.

In the adult the sore throat is commonly found because of the known diminished resistance of such persons to infection. The vasomotor ataxia is noted, the excitable heart and lower threshold of emotional reaction, and the descriptions by Bram and by Eppinger and Hess are substantially similar in their essentials.

Laboratory Test for the Graves' Constitution.

An investigation was carried out by the writer regarding the sensitivity of the goitrous and normal human subjects to adrenalin.

It was found that in certain persons assumed to be normal, upon subcutaneous injection of .5 c.c. of adrenalin hydrochloride 1/1,000 solution, a response was obtained characterised by an increase in the pulse rate of 40% or over of its initial frequency, and an elevation in the iodine content of the blood, that increasing by 100% or more above the normal value. Estimations of the iodine content of the blood were made hourly for three hours following upon injection of the adrenalin, the peak of the curve being reached at the end of two hours, the third reading again approximating to normal.

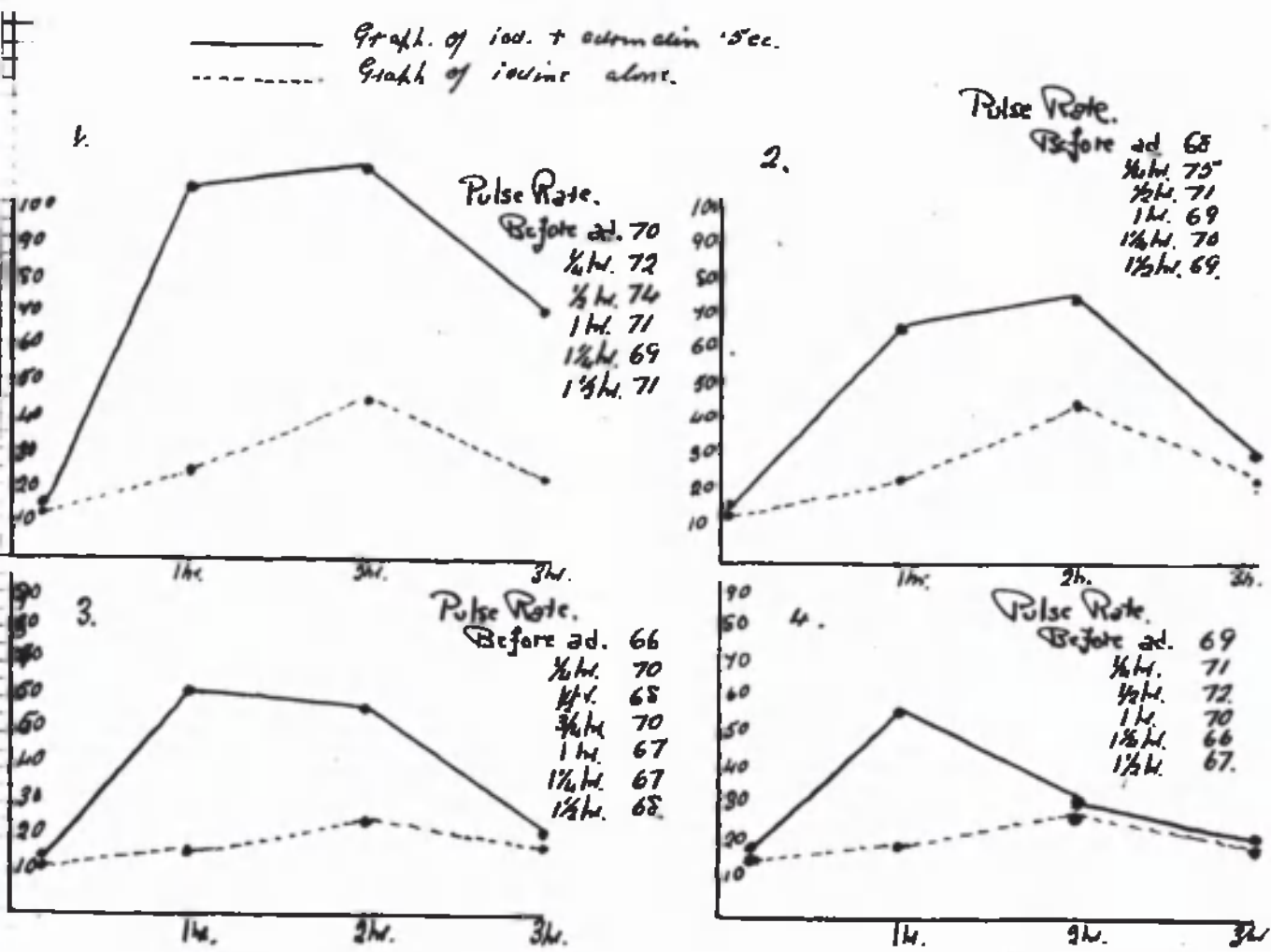
In those so-called normal persons, I found upon further questioning that they were of the typical Graves' Constitution type.

The full description of the technique for estimating the iodine content of the blood and the mode of carrying out this adrenalin-iodine sensitivity test is described in a later section (Page 68), but for the present it suffices merely to detail the results found in this connection.

Should a normal subject be given a dose of 60 mgms. of iodine in the form of Lugol's solution orally, it will be found that there follows an elevation in the iodine content of the blood from the value found immediately before taking the drug, to a higher figure, varying in different subjects. If the iodine is estimated hourly it will be found that the peak is reached

during the second hour, the reading falling by the end of the third.

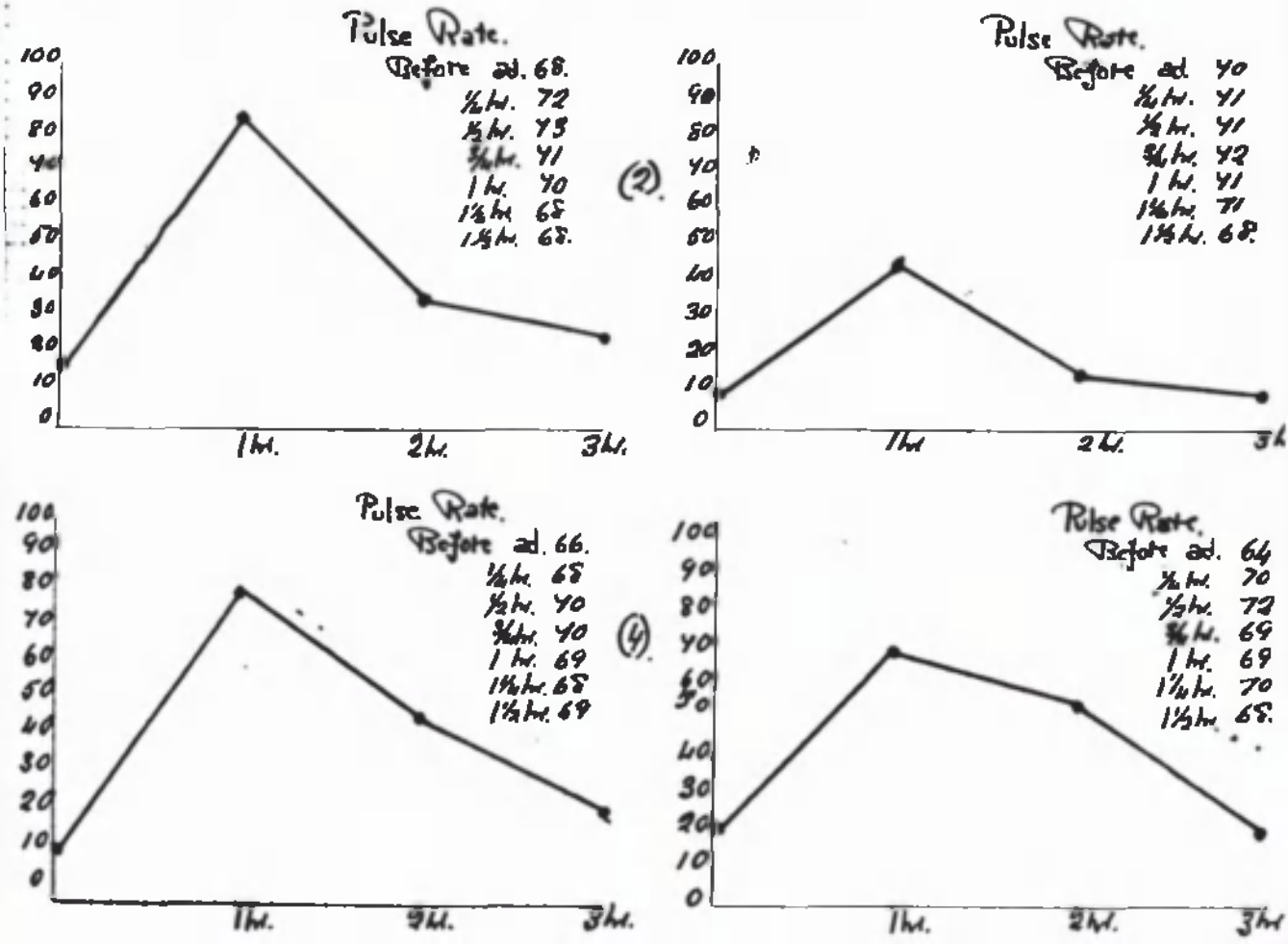
The blood iodine is estimated immediately before the patient is given the Lugol's solution, and thereafter hourly for three hours, the readings are graphed and a curve obtained. The test is carried out in the afternoon, the patient having had no lunch but an ordinary breakfast. One week later the same test is performed upon each patient but with the addition of .5 c.c. adrenalin hydrochloride 1/1,000 solution subcutaneously at the same time as the iodine is given orally. The blood iodine is again estimated and a graph obtained. In each instance an elevation in the original curve is found. See graphs below.



From these examples it is obvious that the effect of the adrenalin was to increase the height of the iodine tolerance curve.

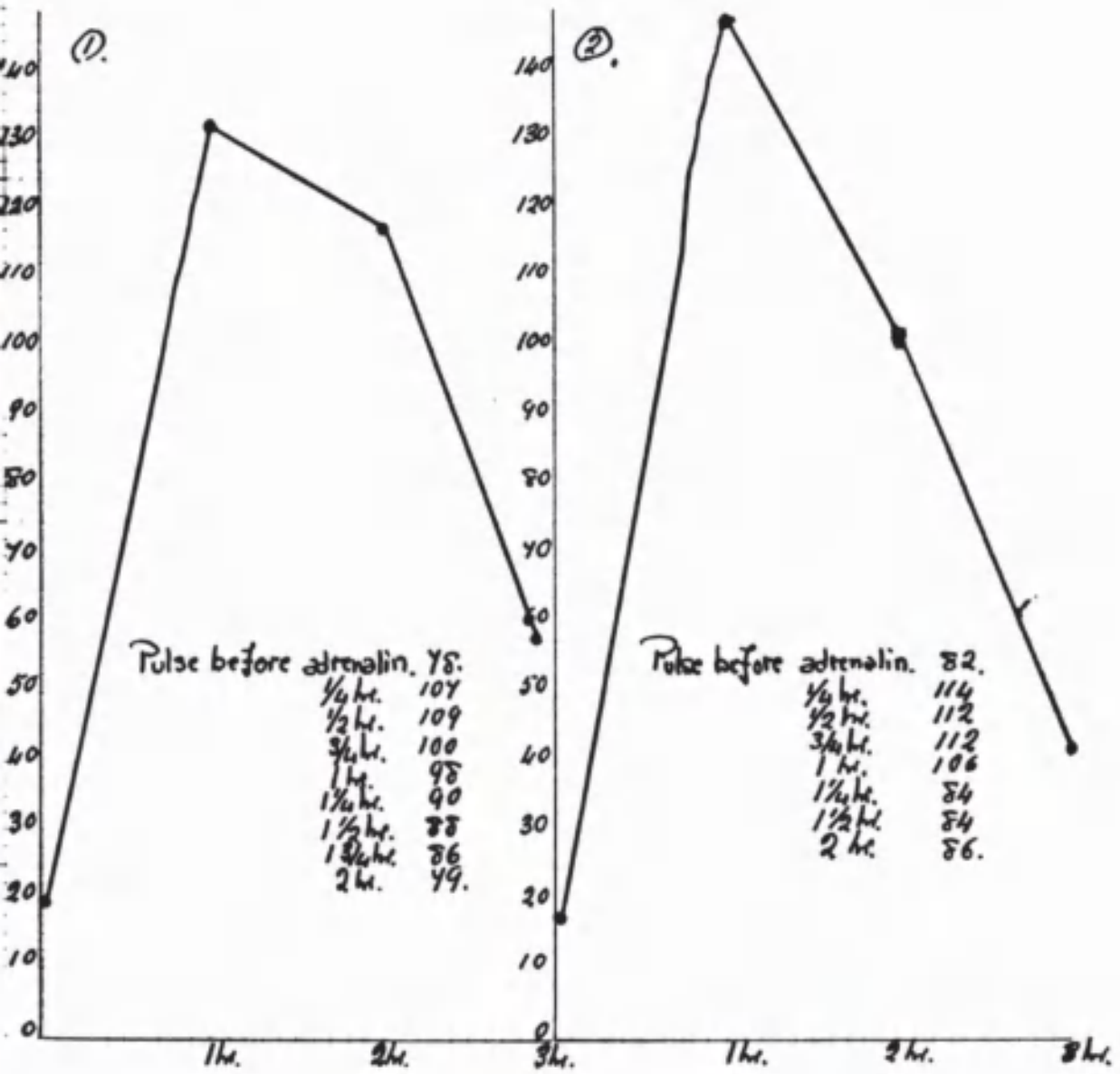
This test was performed in four patients after the manner described. It was then decided to modify the test, performing it under the same conditions but giving only the adrenalin, a specimen of blood to be withdrawn and its iodine content estimated immediately after withdrawal, the .5 c.c. adrenalin to be injected subcutaneously and the iodine hourly estimated for three hours; for one hour and a half after administration of adrenalin the pulse rate was taken at quarter hour

Graph of blood iodine in γ following injection subcutaneously of .5 cc cathenalin hydrochloride 1/1000 soln..



It is observed that the effect of the adrenalin was to elevate the iodine content of the blood in these four patients, but, with this elevation there was no undue increase in the frequency of the pulse, and in each case the highest iodine value recorded was below 100 gammas per 100 c.c. of blood.

In a further two cases the same test was performed and with the following results.



Examination of these two curves shows that the maximal value was considerably above 100 gammas in both cases, that at the end of the second hour the figures were still above 100 gammas and that by the end of the third there was still 100 per cent increase from the initial value. At the same time the pulse rate increased in frequency by more than twenty five beats per minute.

The patients upon whom all of these ten curves were performed were admitted to surgical wards for treatment directed toward conditions such as chronic inguinal hernia, or hallux valgus. Surgical patients such as these were chosen for the purpose because there was no condition present to interfere with their endocrine system. The tests were performed either before operation or later than the fourteenth post operative day.

In the case of patients nine and ten in whom I regard the Adrenalin-Iodine Test as being positive, it was found that they were definitely of the Graves' Constitution type, and furthermore in the case of patient ten there had been friction between he and his ward neighbour during the time that the test was being performed, thus bringing the question of emotion and its attendant effects upon the suprarenal glands, into effect.

It is not wise to deduce too much from the limited data detailed above, but I regard it as significant, and consider that this adrenalin-iodine test might be used with advantage as a means for detecting persons considered to be possessed of this liability to toxic goitre. Unfortunately I have found no other patient suffering from the Graves' Constitution since I evolved the test, upon whom it might be again performed and regret the scantiness of the material upon which the opinion is based.

A full investigation into the iodine content of the blood was performed in connection with the adrenal-thyreoid relationship discussed in a later section (Page 82), when the value of this iodine estimation will again be considered and the views of others as to its value submitted.

The importance of this constitutional factor in the etiology of toxic goitre has been more and more recognised during recent years and emphasised by many writers. The condition has been described clinically by two different authorities with descriptions closely in accord one with the other, clinical and biochemical evidence supports its existence, and from being a possible theory, a hypothesis, a figment of some fertile imagination, it has been brought to life and endowed with living character. There is no reasonable ground for doubting either its existence or its significance.

Those Factors which may act as precipitating stimuli in the production of toxic goitre.

Those may assume one of several forms, may act independently or in varying combinations, and with varying degrees of intensity. The most important are psychic or physical trauma, infection, influences such as puberty, pregnancy or the climacteric, and occasionally some intra thyreoid condition...simple goitre, adenoma, or malignant tumor. These shall be discussed in order.

1. Psychic trauma.

A clear history of psychic trauma was elicited in 61 cases of the present series, that is in 78.2 per cent of the total. Joll notes that "It is possible to trace a history of one or other of anxiety, worry or other emotional strain in at least 50% of cases of toxic goitre, and that amongst women ,domestic difficulties associated with frequently recurring pregnancies, marital infidelity, sexual incompatability, disorders of the genital system, anxieties over the health or upbringing of children, or conversely worry over stirility or repeated miscarriages may be traced in some cases. In men also the question may elicit worries in connection with the responsibility of maintaining a home, sexual upsets of one kind or another may be admitted, and business or financial difficulties may be found." Joll maintains however that it is not possible to assess the value of these considering how many people nowadays sustain psychic traumata of one kind or another but yet do not develop toxic symptoms, and in reply to that it is emphasised that the normal person does not develop the toxic symptoms, that these develop

only in the subject constitutionally liable, and that in no other disease is the association with such emotional upsets so insisted upon by all observers. The percentage incidence psychic trauma given by other authors are, Means 25%, Bram 90% and Eason 96%, based upon large numbers of cases. Such evidence is overwhelmingly significant and cannot lightly be ignored.

These emotional upsets may assume one of several forms, and examples are quoted, but the form adopted is of no more account than is the type of match used to kindle a fire. The form may vary, but the effect when the fire is set and ready to be ignited is the same.

The main groups are...

1. Multiple psychic traumata.

Mrs. C. During all of 1937 had a good deal of worry nursing her husband who suffered from severe bronchial asthma and who was critically ill in October. In the beginning of December, 1937, her only brother died suddenly, and a few weeks later symptoms of toxic goitre began to appear.

Mrs. T. For four months prior to the onset of symptoms the patient suffered a good deal of worry through misbehaviour on the part of certain members of her family, the exact nature of which was not revealed. Shortly before the onset of symptoms her husband's work became uncertain, there were many outstanding debts to be met and much financial worry.

Mr. McL. In January 1935 patient had a gastroenterostomy performed. He worried about the operation and during convalescence business was not prospering. One year prior to operation he quarrelled with his best friend who had proved deceitful over a money transaction. Nine months after operation he required treatment on account of toxic goitre.

Mrs. J. Enjoyed good health until she was 24 when she had enteric fever, since when she has been nervous and of an excitable disposition, symptoms which were

aggravated by a 'fright' she got while pregnant ten years later. Some years later still she fell from the top of a ladder and since then has been a 'Bundle of nerves' which during the past few months have been becoming steadily more excitable, while in addition other signs of toxic goitre developed.

Mrs. G. Patient says she has always been very nervous but that this has increased in degree since August 1937 when her youngest child ran into the house saying that he had been assaulted by a man. About this time she was also worried concerning her condition, she being pregnant and thinking that the pregnancy was not normal. In September she noticed exophthalmos, and her doctor told her that she had toxic goitre.

Miss I. During the past ten years patient has had a great deal of strain physical and mental, through nursing first her father who died seven years ago and next her mother who died five years ago. Following the death of her mother she began to perspire freely and became nervous.

Mrs. C. Patient has been worried for many years about her son who is an asthmatic, and over a period of several ending three years ago, she nursed different relatives through severe illnesses. Just over two years ago there was a good deal of financial worry in the home shortly after which she became unwell, developing the full picture of toxic goitre within one year.

Mrs. B. In 1922 there was much domestic worry on account of certain relatives trying to make mischief between the patient and her husband. At this time she was nervous and noticed the presence of a swelling in the front of the neck. For several years following this trouble she worried about a daughter who suffered from a chronic chest complaint and also about the irregular work of her husband. Symptoms of thyreoid disease recurred, but improved with medical treatment only to recur once again in increased severity a year ago following upon the death of her husband.

Mrs. McD. Eighteen months ago her eldest daughter developed Pott's disease of the spine. Some months later her youngest daughter had an unfortunate love affair and ran away from home. A few months later the patient was told by the doctor that she had toxic goitre.

2. Death of a near relative.

Miss B. Patient was deeply attached to her mother and nursed her through a long illness which ended in death. A few weeks later she became unwell and by the end of three months showed the classical signs of toxic goitre.

Miss S. Patient nursed her mother during the last five years of life and throughout the last illness. After the death of her mother she began to complain of symptoms diagnosed as a gastric ulcer, but later with the development of other signs, amended to toxic goitre.

Mrs. S. Three months ago her husband died suddenly, since when the patient has become introspective, nervous, and has suffered from insomnia. There is profuse perspiration, loss of appetite, tremor of the fingers, and elevation in the basal metabolic rate.

Miss W. Five years ago her father died suddenly. This came as a great shock to the patient, a shock increased by the sudden illness of her mother a few months later. The patient nursed her mother for some months before the mother's death and since then she has become increasingly more nervous and has recently developed toxic goitre.

3. Financial worry.

Mrs. T. For the past year the patient has been worrying about the future because of heavy expenditure in the home in comparison to income. This worry was aggravated by her husband becoming unemployed. During the past three months she has developed toxic goitre.

Mrs. McI. Patient is happily married but her husband is a spendthrift and their expenditure exceeds their income more often than it should. Patient is a more than usually economical person and is annoyed to see the money being spent, it has been worrying her so much now that it amounts almost to an obsession and in the course of the past two months signs and symptoms of toxic goitre have developed.

4. Psychogenic Maladjustments.

Mr. D'A. Eighteen months ago the patient became very friendly with a young lady to whom he became engaged six months later. During the period of courtship he was unduly nervous, excited and worried. This nervousness has increased since his engagement until during the past six months he has developed toxic goitre.

Miss D. When patient was fifteen years old she fell upon a spiked railing, tearing her vulva, which required to be repaired. Since then she has had profuse leucorrhoea which is a source of annoyance and worry. Recently she has begun to believe that she is sexually abnormal and unable to have a family. In addition sexual desire is more intense than in the normal girl.

5. Worry over real or [illegible] hile pregnant two years ago had [illegible] of asthenia and lack of energy. Patient w[illegible] noted that these disappeared b[illegible] occasional periods of asthenia and lack of energy. After the birth she noted that these disappeared but continued to worry lest they might return. She examined possible causes in a doctor's home book, and concluded that she was suffering from some incurable disease. A short time later she developed a mild toxic goitre.

Mrs. C. A lipoma over the left scapula was successfully removed two years ago. She is convinced that the tumour was malignant and lives in fear of metastatic growths appearing.

6. Worry over uncongenial occupations.

Miss F. Patient is a traveller for electrolux vacuum cleaners and works upon a commission basis. She is shy and does not care to meet the many people which her business demands. The work involves travelling about a good deal and she does not care for this. She does not enjoy her work but for financial reasons is obliged to continue with it.

Mr. O'D. For 23 years the patient has worked as a surfaceman on the railway. Some years ago one of his friends was killed by a passing train since when the patient has been afraid that Fate might possibly have such an end in store for himself. He has allowed the dangers of his occupation to prey upon his mind to such an extent that the very mention of his work is now sufficient to reduce him to tears.

7. Domestic incompatabilities.

Miss S. Three months before the onset of symptoms the patient was the central figure in a domestic quarrel concerning her brother who wished to marry someone of whom she did not approve. She was very unpopular on account of certain views she expressed regarding the marriage and was obliged to apologise. Her parents say that she has always been very impetuous.

Mr. G. The patient does not get on well with his wife, and the home life was a series of unpleasantnesses, which culminated in his wife threatening to commit suicide if he continued to stay in the same house. Shortly after this he became ill and toxic goitre was diagnosed.

It is thus seen that the varieties of psychic trauma are numerous but this classification indicates the more important groups into which they may be divided.

Physical Trauma.

This is less common than psychic trauma but may be at times very dramatic.

Several cases have been cited in the literature of a severe shock being immediately followed by the development of toxic goitre, and one such in the writer's experience is quoted (Page 125) which developed following the Castlecary rail disaster.

The effect of the Great War upon the incidence and death rate of toxic goitre has been a subject of much discussion. Here, if either physical trauma or psychic, or the 'stresses and strains of life' are of importance at all, one would expect to find some noteworthy influence upon the incidence of toxic goitre.

The figures from which Campbell's map were compiled (Pages 7- 15) included the years 1914 to 1919 and Campbell states that if the figure for 1913 can be taken as a standard for peacetime then there was no great increase in the death rate from toxic goitre during the War, but...he says that there was an increase in the incidence of the disease in men during the War years.

Joll states that most people, excepting Eason, are agreed that there was no increased incidence during the War [1], though the precise reasons for that opinion are not expressed, while the same may be said of Eason when he remarks that the War was responsible for a great increase of deaths from toxic goitre [2]. When one considers that during the War only those men who were absolutely physically fit were sent at first to the front, that even in the later years none of the C.3 class were recruited, and when one further reflects that such physical and

1. Joll. Thyreoid Gland.
2. Eason. Exophthalmic Goitre. 42.

emotional influences act only upon suitable subjects, and that a constitutional liability is rarely found in association with perfect physical health, then it becomes apparent that the men in the forces were not so likely to develop the disease as those who suffered the long continued mental strain of waiting at home and hoping for the best.

The people who were most likely to develop toxic goitre as a result of the War were the women and the generations born of them during that period, since, if hereditory influences are important at all then they must inevitably have exerted an effect upon the minds and bodies of those children born during and after the War years.

It is recognised that a considerable number of years may elapse between the onset of toxic goitre and a fatal termination even in the untreated case, and that also a varying length of time is required for its development after the igniting stimulus has acted upon the system. That being so, one would expect to find an increase in the death rate rising steadily during the post War years to a peak at some indetermined date, and in conjunction with that, a steady rise in the incidence of the condition generally with especial regard to young people. A study of the figures at one's disposal bears out the fact that such a development did actually take place.

McEwan's map [1] for the year 1936 shows a universal increase in the death rate as compared with that in Campbell's time. His figures are herewith appended.

1. McEwan. B.M.J. May 14th, 1938.

Figures indicate death rate.

Year	1913	1914	1915	1916	1917	1918	1919	1920	1921	1922	1923	1924
Males	42	38	32	47	40	46	56	46	54	63	56	46
Females	368	434	400	399	395	357	473	464	533	590	569	574
Year	1925	1926	1927	1928	1929	1930	1931	1932	1933	1934	1935	1936
Males	64	84	91	119	128	112	138	165	168	181	183	208
Females	680	743	852	933	936	1114	1162	1239	1244	1315	1378	1488

This table proves definitely that there has been in every district a proportionate increase in the death rate, an increase affecting the whole country uniformly.

McEwan notes that there has been no alteration in the proportion of deaths as regards sex, but he notes also that the death rate is unduly high between the ages of ten and thirty years...precisely the ages which would be most affected by the strain of the War. It has been remarked that children are susceptible to 'atmosphere', and even those who were between two and ten years old at the onset of the War would have their liability to the disease increased as a result of the strain to which they were subjected during the War years.

It is generally recognised that the incidence of toxic goitre is on the increase, and it is reasonable to suppose, in the light of evidence already cited that the War years are in part responsible. So far as the experience of the men at the front were concerned, although there may not have been an increase in the incidence of toxic goitre existing as such, it is possible that many of the unusual nervous and other phenomena encountered at that time were thyrotoxic or hyperadrenaloid in origin.

Bram [1] says that the term 'shell-shock' is erroneous and, quoting Hoxie [2], notes that many soldiers were frequently returned to base hospitals showing a low

1. Bram. Exophthalmic Goitre. 38.
2. Hoxie. Medical Herald Saint Joseph. 1920. 39. 19.

blood pressure, dilated heart and signs of exhaustion. The blood pressure would gradually rise until the systolic reached about 160, and then there would be an associated urinary urgency, tremor, heightened reflexes and enlargement of the thyreoid gland.

Zunz [1] investigated the iodine content of the glands of soldiers killed during the Great War and found the average figure to be between .044 and .426 per cent of the dried organ. His results are unequivocal, the range of values being too wide to admit of any useful conclusions being arrived at, but since the normal iodine content of the thyreoid is .56 per cent of the gland in the adult male it would seem that in the organs examined by Zunz a proportion showed diminished iodine content while in others the values approached that of normal. Diminished iodine in the gland is indicative of hyperactivity whether associated with symptoms of hyperplasia or not, and the degree of hyperplasia is greater as the iodine diminishes, while in Man any large degree of hyperplasia is uncommon in the absence of symptoms of hyperthyreoidism [2]. Thus, in a proportion of Zunz' cases the thyreoids may have been hyperactive and in a condition of early toxicity.

There is no reasonable doubt but that toxic goitre may be induced by physical trauma.

1. Zunz. Compt. Rendu. de la Soc. de Biol. 1919. 82.
2. Cowell and Mellandy. Quart. Jrnl. Med. October, 1924.

Infection.

The part played by infection is that of any other stimulus, and the nature of the infection may vary from a common cold to enteric fever, but there is a tendency for focalsepsis in the teeth, tonsils or apendix to be present, while I have noted an association with rheumatism...both of the osteo and rheumatoid arthrithic varieties...and of course the association of tonsil and rheumatism is well known.

In this series infection was present in 24% of the cases and in association with some other factor. In two cases the disease improved markedly, a result amounting to cure being obtained, following upon treatment directed towards the removal of septic teeth.

In these two persons the symptoms and signs of toxic goitre cleared up but the patients were left as they had been before, suffering from a grossly nervous disposition, in exactly the same condition which had been their norm before the development of the disease. It is only in such cases of gross neuroendocrinopathy that one stimulus alone will suffice to evoke the toxoc response.

Factors which are normal body processes.

Pregnancy. In none of the five cases in which there was an associated pregnancy did that alone cause the condition. In each instance there was another factor present, either emotional upset or infection.

Campbell [1], when he says that "It is well known that Graves' Disease is most likely to occur in women who are not married or who have not borne children", implies that an association with pregnancy should be the exception rather than the rule, and for this reason. A woman who fails to fulfil her raison d'être in this world be it from circumstance or design, sooner or later may experience a feeling of failure to realise the greatest privilege with which Nature endowed her, and a regret that her purpose in life has been unfulfilled. This feeling and emotional crisis will affect her in varying ways and to a varying extent in different persons, but, should she be constitutionally liable, that inevitable emotional crisis may possibly lead to trouble either psychological or physical, and, if the latter, the response which constitutes toxic goitre is probable.

Again the converse is true. Pregnancy should be attended by a feeling of well-being, by an increased efficiency of the maternal body processes, and, in the normal person while complications such as albuminuria and the like are found, yet there should be no gross neuro-endocrine upset. Pregnancy, however, entails an adjusting of the female endocrine system to suit the temporarily altered requirement of the body, and so, where that system is inherently faulty in one respect or

1. Campbell. Quart. Jrnl. Med. 1924. xviii. 191.

another, this adjustment fails to take place and the result is the possible development of toxic goitre.

The same is true of puberty and the menopause. It is only under the circumstances mentioned in the preceding paragraph that these periods of unwonted endocrine activity are liable to be followed by toxic goitre.

Stimuli arising from within the gland itself.

In this connection it will be wise briefly to recall the normal processes which take place within the thyreoid before discussing the effect upon these processes, of abnormalities such as simple goitre, toxic adenoma, or malignant tumours of the organ.

The purpose of the thyreoid gland is tersely summed up by Professor Means when he says "The thyreoid is a factory and a warehouse for its own hormone."

Its function is to elaborate and store the active principle, distributing it to the body in quantities to meet the requirements of the moment.

It has long been recognised that the gland and its hormone are closely related to iodine, and it is probable that the cycle of activity is as follows.

Iodine, circulating in the blood as iodide, is absorbed by the cells lining the gland acini, and is at once converted into diiodotyrosin radicles in combination with a protein, thyroglobulin. A proportion of these radicles may at once be converted into thyroxin and excreted directly into the blood for distribution; the rest having passed through the cell membranes are stored in protein combination as iodothyroglobulin in the acini and recognised as colloid in the microscope section of the organ. As the body demands, the thyroglobulin is passed back into the acinar cells, the thyreoid principle is split off and excreted into the blood stream, through which it passes to all the cells in the organism.

It is deduced that thyroxin is formed within the thyreoid from tyrosin through the stage of diiodotyrosin, and that the thyroglobulin acts as a vehicle for storage,

transferring the active principle from the factory to the warehouse, and from warehouse to factory.

Little or no iodine normally exists in the gland in inorganic form but rather in organic combination with thyroglobulin, should however iodine have been administered to the subject recently, then an inorganic fraction may also be present. The acini of the gland are the storehouses and the cells of the walls secreting units. The organ is highly vascular and every cell is bathed in a plexus of small blood vessels to facilitate the removal of iodine from the blood stream. Normally the total quantity of iodine ingested is practically the same as the body requirements and excretion is minimal, thus the thyreoid cells have a constant amount of work to perform daily in health to remove this small quantity of blood iodine into the gland and to elaborate from it the hormone. Should there be a defficiency in intake, the cells of the gland have more work to perform in order to remove the same amount of iodine from the blood and hyperplasia is the result; should the amount ingested be below the minimal requirements of the organ, the hyperplasia increases and a condition of simple goitre is produced.

Conversely, should the intake of iodine be excessive the cells have correspondingly less work to perform. This can be proved experimentally when it is seen that if a large part of the thyreoid is removed the administration of iodine will render hyperplasia unnecessary, while if the same experiment is performed in another animal and no iodine given, a considerable degree of hyperplasia ensues.

In the gland made hyperplastic by iodine want the administration of iodine will cause it to undergo involution, the epithelium will return to normal, and

the colloid again be normal in quantity.

Thus the first effect of iodine lack is hyperplasia.[1]

In toxic goitre there may or may not be much hyperplasia, but there is invariably a reduction in the total gland iodine, considerable hyperaemia, epithelial activity and diminished colloid in the vesicles. Thus it would appear that there is some factor at work causing a continual drain upon the gland's resources so that the supply of hormone cannot keep pace with the demands of the body.

The theory has been propounded that in toxic goitre the mechanism governing delivery of the hormone to the body has broken down, and the term thyreoid diarrhoea has been given by Harrington to describe this escape. To compensate for this excessive liberation of hormone, the cells hyperfunction, undergo hyperplasia and work at a higher pitch in a vain endeavour to restore the balance of production and secretion. Thus the hyperplasia of toxic goitre follows from a different cause than that of simple.

In both simple and toxic varieties, however, iodine appears to be able to restore the gland to normal, although in simple goitre, provided the iodine intake is maintained, the effects are permanent, while in toxic, the response is intermittent and maximal as a rule only once.

The process at work in toxic goitre when iodine is given appears to be a flooding of the circulation with iodine causing some partial degree of check to the leak, owing to the increased ease with which the hormone is produced and stored. The supply of the hormone to the rest of the body is diminished and the thyreoid cells given the opportunity of resting. Iodine increases the

1. Marine. Jrnl. Amer. Med. Assoc. 1935. 104. 2334.

storage of acinar colloid in toxic goitre, and increases colloid secretion in simple goitre, and in both instances assists the reversion of the epithelium to normal.

In toxic goitre there is the picture of a very vascular gland with a good deal of thyroxin being constantly poured into the tissues, and thus it may be assumed that many of the signs and symptoms are due to this excess of thyroxin in the tissue.

What is the effect of thyroxin upon the cells of the organism ? Thyroxin acts directly or indirectly upon every cell and tissue of the body, exerting a calorigenic effect which stimulates the basal metabolic rate.

Aub, Bright, and Uridil, [1] state that the adrenals are not necessary for this action, and that they believe thyroxin stimulates resting cells to a higher level of combustion, while Wright [2] says that the outstanding effect of thyroxin is to stimulate the metabolic activities of the body. Berry [3] claims to have shown that no one has ever satisfactorily demonstrated that toxic goitre can occur when the thyreoid is absolutely normal. Should then the gland be grossly abnormal, as when there is present a malignant tumour or a simple adenomatous growth, or even a simple goitre, according to Berry's conclusions one may look for the probable development of toxic symptoms. Dunhill [4] and Berry [5] have described the onset of toxicity in cases of parenchymatous goitre, and similar cases also are quoted by Mori [6] in association with secondary deposits in the

1. Aub, Bright and Uridil. Amer. Jrnl. Physol. 1922.61.300.
2. Wright. Applied Physiology 1936. 255.
3. Berry. Lancet. March 1st, 1913.
4. Dunhill. Proc. Royal Soc. Med. March 1912. Surg.Sect. 62
5. Berry. Lancet. March 1st, 1913. 583.
6. Reference not verified and name of source from which quoted has been mislaid.

thyreoid gland from sarcoma of the pelvis, melano sarcoma of the eye and carcinoma of the breast; while Roussy and Clunet [1] have reported two cases of primary carcinoma of the thyreoid presenting definite symptoms of toxic goitre, and at the moment of writing the writer has a friend who appears to be suffering from a primary carcinoma of the thyreoid and who has marked evidences of toxicity.

In this present series five patients gave a history of having had simple goitre some years previous to the development of toxic.

The effect of a tumour is to stimulate the organ to hyperactivity, and there is no doubt but that in the thyreoid, abnormalities such as malignant neoplasms, or adenomata, predispose to the development of toxicity, but the proportion of cases caused by this means is small.

Lastly, there may be classified amongst influences stimulating the gland from within, the effect of iodine and thyreoid extract administered in excess. Iodine stimulates the sluggish gland of simple goitre to a normal and higher level of activity by increasing colloid excretion, by reducing storage to normal, and by increasing the blood supply of the organ with a view to the removal of the prepared hormone. Also, it will be recalled that iodine soothes the excited toxic organ, reduces the blood supply, facilitates the storage of colloid and diminishes excretion, and it has been shown that iodine may stimulate the gland to excess in the person constitutionally liable thus favouring the production of the toxic response. Thyreoid extract contains a high proportion of iodine in organic combination, and Boothby [2] concluded from his work upon the calorigenic activity of thyreoid extract that that was related to the total organic iodine content. Thus when thyreoid extract is taken orally, there comes

1. Reference not verified and name of source from which quoted has been mislaid.
2. Boothby. Treat. Assoc. Amer. Phys. 1925. 40. 195.

into play not only the metabolism stimulating effect of the hormone itself but also the thyreoid stimulating effect of the iodine it contains. These effects however, will only produce adverse results when the gland and neuroendocrine systems are faulty and where there is a liability for stimuli to evoke a response out of proportion to their driving force.

In none of the cases at present under consideration, excepting the one already mentioned, (Page104) where a patient with myxoedema developed a mild degree of toxicity did the disease originate after this fashion, and of Bram's series of 5,000 such influences were present in only 3% of the total.

An analysis of the varying factors at work in this series was made and found to be as follows.

A constitutional liability was proved beyond reasonable doubt in 60%, that is in 47 patients, in the remaining 40%, that is in 31 patients, factors at work were...

Psychic trauma alone	13	cases
Psychic trauma plus...		
Pregnancy	1	do
Menopause	2	do
Infection	5	do
Pregnancy plus Infection	2	do
Simple goitre	2	do
Other stimuli acting alone		
Menopause	1	do
Infection	3	do
Operation	1	do
Syphilis	1	do

Of the 47 persons endowed with the Graves' Constitution there was an associated history of psychic trauma in 36 while in the remaining 11, there was an association with other stimuli...

Menopause	2 cases
Pregnancy	2 do
Previous simple goitre	3 do
Infection	2 do
Physical trauma	1 do
Ingestion of iodine and thyreoid extract in case of myxoedema	1 do

There was no case in which the determining factor could not be traced with reasonable certainty.

The group which is of most interest is that in which there was no history of either psychic trauma or previous constitutional liability; it is small, a total of six persons; one was associated with the menopause, a circumstance known to be associated with a readjustment in the endocrine system; three were associated with infection, a factor which is known to stimulate the autonomic nervous system (Page 108); one was associated with an operation which although simple in itself, yet in all probability caused the patient some degree of worry; lastly, there was one case associated with a history of recent syphilis, a circumstance which in all probability was the outcome of some psychogenic problem not admitted.

It would appear that in every instance a definite influence has been traced capable of influencing either or both of the autonomic and neuroendocrine systems.

Heredity, and Familial Influences.

The question of hereditary and familial influences has already been discussed in part in association with the generations born during and after the Great War years, but further remarks are necessary with regard to assessing their importance.

The current opinions regarding the influence of heredity are conflicting. Means [1] states that heredity probably plays an important part in determining the incidence of the disease, while Joll believes that there is little evidence to substantiate any belief in the importance of hereditary influences. Cockayne [2] writes "In no family in which a pedigree is available does the number of members with exophthalmic goitre correspond with what would be expected were the disease transmitted as a Mendelian dominant. On the other hand the fact that it can be met with in a parent and in one or more children indicates that it cannot be a recessive character. The question becomes rather obstruse."

Cockayne, however, believes that it is not hereditary because...It is rarely present at birth, and it frequently occurs in the children of apparently healthy parents. He does believe that what is inherited is rather a constitutional weakness of the thyreoid gland, a thyrotoxic diathesis, a condition resembling the Graves' Constitution of Bram, in whose book there are accounts described by various writers emphasising that there is a definite hereditary tendency, and Bram states that an inherited neuroendocrinopathy is commonly exhibited by these patients [3]

1. Means. The thyreoid Gland and its Diseases.
2. Cockayne. Arch. Dis. Childhood. 1928. 3.
3. Bram. Exophthalmic Goitre. 19 and 20.

while he further observes that the tendency is transmitted by the male.

Russel Brain [1] working upon the influence of heredity upon the incidence of simple goitre, concludes that a hereditary predisposition is in some cases an important etiological factor; Danielopolu [2] recently concluded a series of observations upon the effects reflected upon future generations, of simple goitre in the parent, and he notes that goitre even more than syphilis or pellagra is a factor making for racial degeneration. There is little doubt but that in simple goitre at least, the influence of heredity is considerable, and it is probably also of importance in the toxic case.

In this series four patients gave a clear cut family history of toxic goitre and also gave definite proof by their description of childhood life that they had been endowed from earliest years with a constitutional neuroendocrinopathy.

№ 1. Female patient, no brothers or sisters, unmarried, aged 38. Mother died from toxic goitre.

№ 2. Female patient, married, aged 64. Mother suffered from toxic goitre, later developed accute rheumatism and died.
She has one brother and two sisters, the sisters are unduly nervous.
There is no history of toxic goitre in either her own children or in her nephews and nieces.

№ 3. Male patient, married, aged 48. Mother died of toxic goitre. One brother committed

1. Russel Brain. Quart. Jrnl. Med. April, 1927.
2. Danielopolu. B.M.J. October 9th, 1937. 711.

suicide. The family as a whole are all unduly nervous and excitable. Patient has no children.

№ 4. Unmarried female, aged 26. One sister suffers from a mild degree of toxic goitre. The parents were unduly nervous, and in the opinion of the patient always worried needlessly about trifles. The father died of carcinoma. Mother still alive.

There is no doubt but that familial and hereditary influences may be traced in a proportion of cases but not to an extent which permits of useful opinions being expressed as to their precise significance.

It is probable, however, that although the disease per se may not be inherited, the liability to it may be, and since it is known that in a small proportion of cases the disease can develop in the absence of this liability, especially when the precipitating factors are gross emotional upsets, or influences such as the menopause when the endocrine system is temporarily in a state of flux it becomes obvious that to describe the liability as a Mendelian dominant, or to say precisely what is the role of heredity, becomes almost impossible owing to the uncertainty of the figures upon which such conclusions might be based. No more can be said in this connection than that heredity does have an influence in determining the incidence of toxic goitre but that the exact nature of this influence is so far undetermined.

The etiology of this disease has now been discussed in some detail from the point of view of the varying influences which may play a part in determining

its onset, and it is concluded that toxic goitre is a response on the part of the body reacting in a characteristic manner to the influence, or combined influences, of emotional or physical strain, infection, pregnancy, or the menopause, and at times by the stimulation of intrathyreoid conditions, these factors acting by upsetting the neuroendocrine balance in persons constitutionally liable and thus promoting the onset of pathological processes within certain organs, notably the thyreoid gland.

It is essential, however, further to investigate the precise manner in which these influences do upset the body mechanism, to learn how the thyreoid comes to be preeminently involved, and to discuss in detail not only the part played by the autonomic system but also that of the other important endocrine bodies.

Section 111.

Symptoms and signs of Toxic Goitre... The Basal Metabolic Rate... Technique for Estimation of the Blood Iodine... The Blood Iodine in Toxic Goitre and in relation to the Basal Metabolic Rate.

Eppinger and Hess, quoted by Eason and by Bram, have theorised that the symptoms and signs of toxic goitre are due to abnormal activity on the part of the autonomic nervous system, and have even differentiated clinically two types of condition according to whether the para, or sympathetic divisions dominate the clinical picture; in the first instance the syndrome is named Vagotonia, and in the second, Sympathicotonia.

A table of compatison of the two syndromes is detailed herewith.

Sympathicotonia.	Vagotonia.
Tachycardia and subjective heart symptoms.	Heart symptoms scanty, none subjective, slight increase in frequency.
Exophthalmos, dilated pupil	Slight exophthalmos, contracted pupil.
Mobius sign. Adrenalin mydriasis.	Von Grafe's sign. Wide palpebral fissure.
No hyperidrosis.	Eyes moist.
No diarrhoea or bladder irritability.	Diarrhoea and bladder irritability.
No hyperchlorhydria.	Hyperchlorhydria.
No eosinophilia.	Eosinophilia.
No respiratory arrhythmia.	Respiratory arrhythmia.
Rise in temperature.	No rise in temperature.
Falling out of hair.	No falling out of hair.
Reduction in carbohydrate tolerance.	No reduction in carbohydrate tolerance.

Eppinger and Hess also emphasise that there may be a mixture of symptoms... sympathetic stimulation may be relative due to vagal inhibition, and conversely vagal stimulation may be relative due to sympathetic inhibition.

An analysis of the signs and symptoms present in my series failed to justify such a subdivision into two types. On the other hand, I consider that most of the signs and symptoms could be attributed to the effect upon the body of one, and one only, an elevation in the basal metabolic rate, as described in the following paragraphs.

The relative percentage incidence of the most important symptoms and signs were...

Elevation in basal metabolic rate	100%
Presence of goitre	90%
Increased degree of sweating	76%
Tachycardia	76%
Tremor of fingers or tongue or both	75%
General asthenia	63%
Exophthalmos and other eye phenomena	61%
Considerable loss of weight	58%
Abnormality in the blood pressure	
Below 110 systolic 18%	
Between 150-200 systolic 38%	
Above 200 systolic 2%	
Total	58%
Valvular or other heart complications	41%
Pigmentation of the skin	28%
Menstrual upset	18%
Urinary abnormalities	5%

When the pathogenesis of these phenomena is considered it will be found that the elevation in the basal metabolic rate is directly responsible for the tachycardia, tremor, loss of weight, weakness, perspiration and glycosuria.

Tachycardia.

When the basal metabolic processes are elevated the organism becomes warmer and works at a higher level of combustion, a level which demands a more active circulation and a more efficient gaseous interchange in the tissues, to effect which there is dilatation of the peripherial vessels, a lowering in the diastolic pressure and reflex tachycardia, the minute volume output of the heart being increased.

Tremor.

Sharpey-Schafer quoted by Eason [1] states that this is not a sympathetic effect. Other authorities have inclined to the belief that this is a manifestation of some parathyreoid lesion, and it is known that both the parathyreoid and the thyreoid gland secretions have an association with the calcium metabolism of the organism. It is further admitted that abnormalities in the calcium metabolism are a factor in the production of conditions of tetany.

In toxic goitre no consistent pathology has been described in connection with the parathyreoid gland, and in my opinion the tremor is, in this disease probably not a parathyreoid effect, but may be due rather to the fact that the organism as a whole is working at a generally increased pitch of efficiency and activity, that there is a corresponding reduction in the threshold of peripherial stimulation and that under these circumstances the increased tonus of the nervous system may be productive of the characteristic fine tremor which is so noteworthy a sign.

1. Eason. Exophthalmic Goitre. 78.

Loss of Weight.

This feature of the disease runs parri passu with the increased level of tissue combustion, and the taking of food appears to act by heaping fuel upon the fire, intensifying the calorigenic response, and leading to progressive loss of weight.

Weakness.

This symptom owes its being to a reflex depending upon the increased level of tissue combustion. Under such circumstances there is an increased accumulation and absorption of waste products in the organism generally with resulting symptoms of fatigue.

Perspiration.

The nerve control of the sweat glands is not concerned in the production of the perspiration of toxic goitre, that is rather a sign of an effort being made on the part of the body to adjust its heat regulating mechanism, the balance of which has been upset by the increase in heat production. At the same time it may be in part a defensive reaction with a view to promoting the excretion of accumulated waste products of tissue combustion.

Glycosuria.

This is associated with a glycogenolysis affecting both liver and muscle glycogen. Glycogenolysis is produced in the experimental animal both by adrenalin and by thyroxin. In toxic goitre it is probable that the glycogenolysis is a device on the part of the organism for the assimilation of a readily available supply of fuel, to cater for the increased tissue oxidation. In a proportion of cases there is a lowered renal threshold for glucose and glycosuria is present.

The other symptoms shall now be considered, that is to say, those which are probably not directly due to the increased basal metabolic rate.

Valvular or other Disease of the Heart.

Consideration of this feature must be approached bearing in mind the possibility of other conditions having been present in earlier life which may have left a legacy of cardiac disease behind...there is an association with septic tonsils and rheumatism in many of these patients, in others pneumonia or diphtheria has been responsible, but in all, the existing heart lesion is intensified by the tachycardia present in toxic goitre, which by itself may eventually promote weakening of the tone of the cardiac muscle, some slight valvular incompetence and dilitation, which, in the gross case may lead to decompensation and death.

Pigmentation.

The skin pigmentation is a manifestation of hypocorticoadrenalism, either relative or absolute.(Page 94)

Exophthalmos.

Opinions regarding the cause of exophthalmos are varied and conflicting. Mendel, quoted by Joll [1] believes it is due to an excessive accumulation of fat within the orbit...a view which has not survived more recent investigation.

Müller regards it as being due to an excessive innervation of the muscle of Müller, a thin sheet of unstriped fibres is attached below to the upper margin of the tarsal plate, and above to the deep surface of the levator palpebrae superioris, and which spans the inferior

1. Joll. Diseases of the Thyreoid Gland.

orbital fissure.[1] The muscle is supplied by small orbital nerves from the spheno-palatine ganglion, which fibres are derived in turn from the deep petrosal nerve reaching the ganglion from the plexus of sympathetic filaments round the carotid artery. The innervation is thus by way of the sympathetic, and when the muscle is in a state of contraction one may assume, from its origin and insertion that there is constriction of the veins passing through the inferior orbital fissure, causing a degree of orbital venous congestion and oedema. Müller's theory is not acceptable to all, but it has a strong foundation upon proven anatomical facts.

Parsons [2] regards the exophthalmos as being due to venous dilitation associated with some oedema of the orbital contents, but he notes that there is no evidence of this oedema in the peri-orbital tissues.

Plummer [3] observes that if hyperplasia of the thyreoid is of sufficient degree or extends over a sufficiently long period, symptoms of exophthalmos are almost certain to develop. In making this statement he implies that it is due to the presence of thyroxin in excess in the organism, and it is of interest in this connection to note the opinion of Langdon Brown [4] who believes that when exophthalmos follows the administration of thyroxin there is some other additional substance at work.

I have personally observed the occurrence of gross exophthalmos developing in rabbits within thirty six hours of their having received a subcutaneous injection

1. Walmsley. Manual of Practical Anatomy. Part 3. 1936. 31 and 205.
2. Parsons. Pathology of the Eye. London. 1908. Vol. 4. 1204-1205.
3. Plummer. Jrnl. Amer. Med. Assoc. 1912. iix 327.
4. Langdon Brown. Medical Annual 1937. 464.

of one and a half c.c. adrenalin hydrochloride 1/1,000 solution. Altogether eight rabbits were so treated but only in two did this sign develop and in both cases the eyes were again normal within forty eight hours of its first appearance. There can be little doubt but that in these two cases the exophthalmos was due to some sympathetic effect, and most probably to a spasm of the muscle of Müller. The available evidence is in favour of this sign being due to sympathetic stimulation.

Abnormality in the blood pressure.

The blood pressure even in the so-called normal subject is liable to considerable variation, and is undoubtedly elevated during conditions of excitement and strong emotional stress; this is probably an adrenomedullary manifestation since it is admitted by all that adrenalin has a marked vasopressor effect upon the arterioles.

The variations of the blood pressure in health are not statistically detailed in the literature, but from the observations available it is certain that this sign is, even in health very variable, and I consider that in toxic goitre it is of little significance in so far as the etiology or pathogenethis of the condition is concerned.

Menstrual upset.

The incidence of abnormalities in the menstrual cycle is so high generally, and the proportion of such complications in toxic goitre so small, and so inconstant in nature and in degree that they may be dismissed as having no bearing upon the subject as at present under discussion.

From a consideration of these symptoms and signs it has become evident that the one of outstanding importance is the elevation in the basal metabolic rate, and an understanding of the processes at work in this connection is essential to the adequate understanding of the processes evoking the responses which characterise the clinical picture of toxic goitre.

Basal Metabolic Rate.

It will be recalled that the basal metabolic rate depends upon the respiratory exchanges, and that by estimating these the energy produced within the organism can be indirectly determined.

Clinically the basal metabolic rate is calculated from the oxygen consumption which is measured as a rule by the Benedict-Roth apparatus, and the expression 'basal metabolic rate' means the energy output of an individual resting under standardised conditions of bodily and physical rest, and is expressed as a percentage above or below the theoretical normal standard for the individual taking into account height, age and weight.

It is elevated by the action of thyroxin upon the tissues; by adrenalin or by an intense fit of emotion, both of which are capable of raising it by about 20%; by the anterior lobe of the pituitary acting through its thyrotropic hormone, and in certain other conditions, notably splenomedullary and lymphatic leukaemia, pernicious anemia and heart disease with decompensation. The taking of a hearty meal can elevate the basal metabolic rate by about 20% and likewise, physical work.

It may be said, however, that if the basal metabolic rate is elevated by over 20%, in the absence of leukaemia, severe anemia or cardiac decompensation, then a thyrotoxic condition is definitely present.

In the present series the basal metabolic rate prior to treatment in seventy three cases was...

0-10.	10-20.	20-30.	30-40.	40-50.	50-60.	60-70.	70-80.	80-90.	90-100.	Over 100
8	12	17	8	12	6	2	4	1	3	Nil.

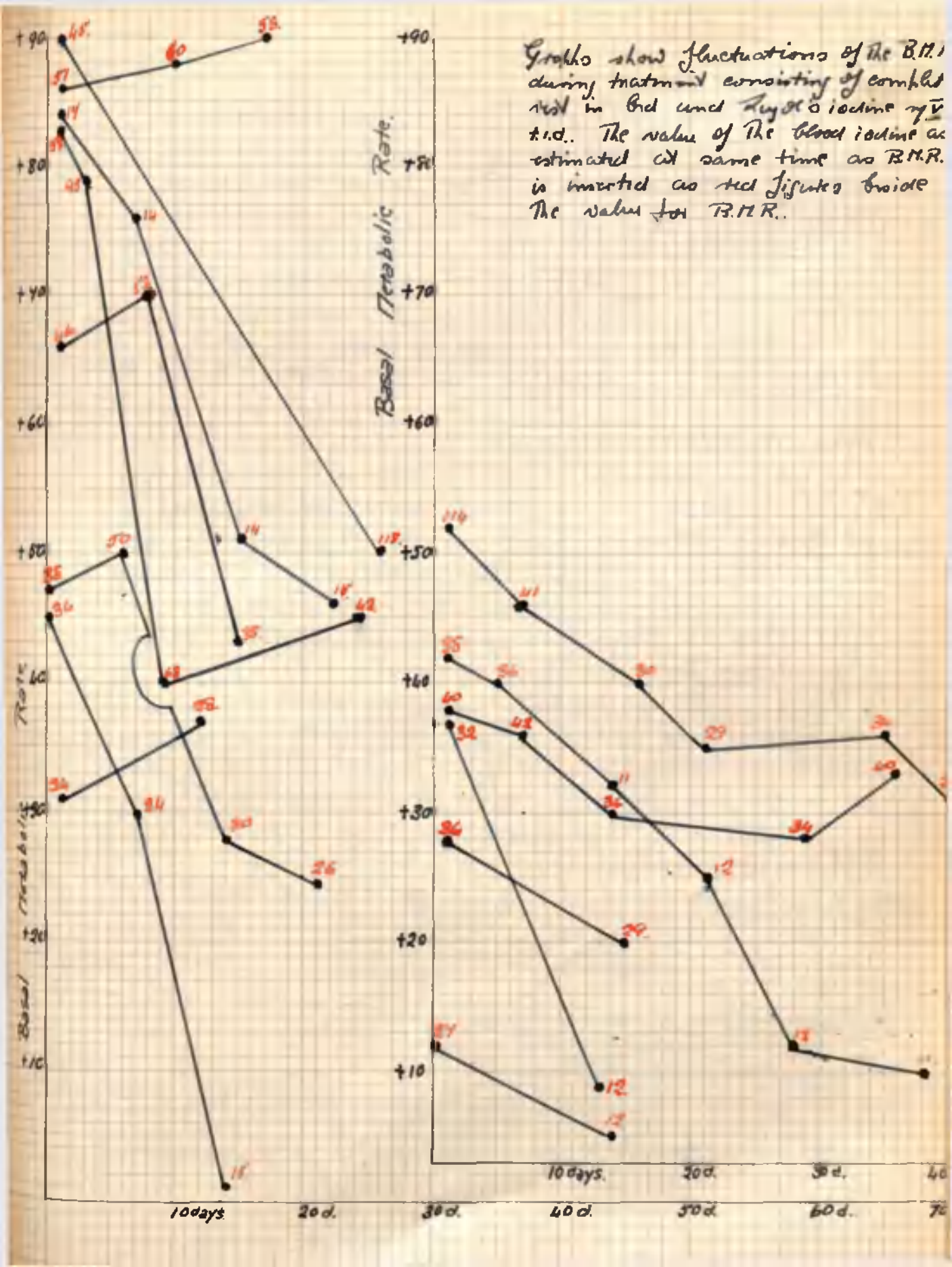
In spite of the fact that in twenty cases the basal metabolic rate was below plus 20% each patient was proved

definitely to be suffering from toxic goitre as evidenced by the clinical condition, history, iodine content of the blood and response to treatment.

Davies and Eason [1] found that there is a very close relationship between the blood pressure and the basal metabolic rate, provided that both are taken under the same conditions. Normally the blood pressure is 120/80 in young adults, that is to say the pulse pressure 40, is 50% of the diastolic pressure. This percentage of 50 is always increased in toxic goitre and the increase is proportional to the degree of basal metabolic increase. So also is the increase in the pulse rate above normal in accord with the elevated basal metabolic rate; according to Bram [2] the basal metabolic rate rises by ten points for every increase of twelve in the pulse rate of males, and ten points with every increase of fourteen in the pulse rate of females, seventy two being taken as the male norm and seventy six as the female.

I am of the opinion that there is a close parallelism between the basal metabolic rate and the iodine content of the blood in toxic goitre, increase in the blood iodine being paralleled by the rise in basal metabolism and vice versa.

In fourteen patients the basal metabolic rate and the blood iodine were estimated throughout the patients' illness, and the results graphed, a study of the graphs supports this opinion.


Graphs show fluctuations of the B.M.R. during treatment consisting of complete rest in bed and Lugol's iodine m.v. t.i.d.. The value of the blood iodine as estimated at same time as B.M.R. is inserted as test figures beside the value for B.M.R..
Basal Metabolic Rate.
+90
+80
+70
+60
+50
+40
+30
+20
+10
10 days.
20 d.
30 d.
40 d.
50 d.
60 d.

When all factors are considered it is evident that thyroxin is par excellence the stimulus of metabolism; but it has been demonstrated that the prime cause of toxic goitre lies outwith the thyreoid, and so one must determine what stimulus is brought to bear upon the thyreoid gland to produce this increased output of thyroxin and by what path this stimulus reaches the gland.

The suprarenal organs figure so prominently in connection with the various problems associated with toxic goitre that, believing that within their tiny structure lay the probable solution of the matter, an investigation was conducted into the thyro-adrenal relationship with a view to finding whether or not the thyreoid was stimulated by the secretion of the adrenal medulla, and if so by what means this influence was brought to bear.(Pages 79 - 98)

The activity of the thyreoid and its hormone is related to the iodine content of the gland, the activity of thyroxin bears a relationship to its total organic iodine, and in the toxic organ the iodine content is diminished. Thus it was considered that an investigation into the iodine content of the blood might lead to results which could be used as an index of thyreoid activity suited to the nature of the investigation to be performed.

Technique for estimating Iodine content of Blood.

The average iodine content of the blood in normal Man varies, with certain slight variations [1], from nine to thirteen gammas per 100 c.c of blood of which 34% is in inorganic and 66% in organic combination. Of the total content there are two fractions, one alcohol soluble and one alcohol insoluble, and in the normal person the insoluble fraction is constant at about four gammas per 100 c.c. When iodine is given the alcohol soluble fraction rises, and since in the toxic subject the insoluble fraction is much increased, it is thus supposed that the insoluble represents the thyroxin (organic) iodine and the soluble, the inorganic. [2.3.]

For practical purposes only the total iodine is estimated. The method adopted was that of McCullagh [4], and the technique as follows.

Fusion with potassium hydroxide.

Ten c.c. of blood is placed in a 300 c.c. nickel crucible with 12 c.c. saturated solution of potassium hydroxide and heated gently. When the foaming has somewhat abated the organic material is washed from the sides of the crucible with a small quantity of water. Boiling is continued for a few minutes and the crucible walls again washed. The mixture is boiled until foaming ceases at the end of about fifteen minutes.

The crucible is then placed in a muffle furnace at 250° Centigrade for thirty minutes to drive

1. Cameron. Recent Advances in Endocrinology. 1934. 84.
2. Dodds, Lawson & Robertson. Lancet. 1932. 2. 1608.
3. Means. Thyreoid Gland and its Diseases.
4. McCullagh. J. Biol. Chem. 107, Oct. 1934, 35.

off volatile and inflammable gases. The temperature is increased to 360° and kept there for ten minutes. The crucible is then removed from the oven.

Extraction with ethyl alcohol.

Sufficient water is added to dissolve all easily soluble material and excess of water boiled off until on cooling, a fluid paste is formed. The mixture is then extracted with frequent additions of 95% ethyl alcohol, the alcohol being decanted off into a 300 c.c. nickel crucible containing 1 c.c. of a saturated solution of potassium hydroxide. After extraction the remaining sludge contains no iodine. The alcohol is evaporated to dryness in a steam bath.

Ashing.

The crucible is now placed in the muffle furnace at 385° for ten minutes and a stream of oxygen, two litres per minute approximately, allowed to pass through the oven during ashing.

Purification by distillation.

The oxidised residue in the crucible is dissolved in water and filtered into a 500 c.c. Claisson flask, in which is a mixture of 10 c.c. of a 50% solution of sulphuric acid, 2 c.c. of a 10% solution of ferric sulphate, and throughout distillation frequent additions of 30% sulphuric acid are made. The end of the tube leading from the condenser dips under the surface of a mixture consisting of 25 c.c. water, .5 c.c. of a 3% solution sulphuric acid and .5 c.c. solution of sodium bisulphite, contained within a 250 c.c. Fresenius absorption flask.

The solution in the Claisson flask is distilled for half an hour, at the end of which time the distillate is transferred to a large beaker.

Determination of iodine.

The distillate is boiled for three minutes to expel carbon dioxide and sulphur dioxide, and a solution of 10% potassium hydroxide added until the solution is alkaline. The whole is then boiled and evaporated to a volume of 10 c.c. and transferred to a 50 c.c. Erlenmeyer flask. One drop of methyl orange is used as indicator and the solution neutralised with 3% sulphuric acid. A further two drops of acid is added and one drop of bromine. The solution is evaporated to about 2 c.c. and rapidly cooled on ice. A drop of 1% starch solution and a minute crystal of potassium iodide are added and the whole titrated with a .001 normal solution of sodium thiosulphate.

One c.c. of .001 thiosulphate solution equals 21.2 gammas of iodine.

All solutions were estimated for their iodine content and corrections made for possible error. Before proceeding with the work test estimations were made with known quantities of iodine in solution and an accuracy of possible error 5 to 7% achieved.

In eight normal male patients the iodine content of the blood was estimated with the following results. All readings are given :- g. = gammas per 100 c.c. blood.

1.	2.	3.	4.	5.	6.	7.	8.
12.4 g.	11.124 g.	12.72 g.	18.656 g.	13.568 g.	12 g.	10.6 g.	13.2

The average figure was 13.034 gammas per 100 c.c. blood. In the case of the first three the estimation was repeated one week later and the first and second results compared.

	First	Second	Difference
1.	12.4 gammas	12.36 gammas	0.04 gammas
2.	11.024 "	12.24 "	1.116 "
3.	12.72 "	11.6 "	1.12 "

The differences between the readings is trifling and for practical purposes the decimal points are ignored, the reading being given to the nearest whole number.

In thirty six cases of toxic goitre the iodine content of the blood was estimated before treatment had been established and the results are herewith tabulated.

	Iodine in gammas per 100 c.c. blood		Iodine in gammas per 100 c.c. blood
Case 1	19	Case 19	32
2	22	20	15
3	56	21	40
4	22	22	36
5	38	23	24
6	17	24	45
7	20	25	38
8	38	26	13
9	26	27	45
10	17	28	12
11	38	29	14
12	36	30	21
13	46	31	15
14	88	32	17
15	114	33	32
16	28	34	15
17	120	35	24
18	42	36	58

The average blood iodine for the thirty six cases of toxic goitre was 35 gammas per 100 c.c. of blood with extremes of 12 and 120 while in the normal series the average was 13 gammas.

The iodine was further estimated in a proportion of cases in relation to treatment.

1st Group X-ray therapy treatment. (Four cases.)

Case 1.	Before treatment	Date	10.2.38	40 gammas.
	After 1st "	"	17.2.38	42 "
	" 2nd "	"	24.2.38	36 "
	" 3rd "	"	8.3.38	40 "
	" 6th "	"	22.3.38	36 "
	" 7th "	"	29.3.38	27 "
Case 2.	Before treatment	Date	15.1.38	114 "
	After 1st "	"	22.1.38	31 "
	" 2nd "	"	1.2.38	19 "
	" 3rd "	"	8.2.38	19 "
	" 5th "	"	22.2.38	24 "
	" 7th "	"	3.3.38	16 "
	" 9th "	"	14.3.38	18 "
Case 3.	Before treatment	"	14.12.37	42 "
	After 2nd "	"	23.12.37	38 "
	" 4th "	"	28.12.37	35 "
	" 5th "	"	6.1.38	10 "
	" 6th "	"	13.1.38	11 "
	" 7th "	"	20.1.38	12 "
	" 9th "	"	1.2.38	10 "
Case 4.	Before treatment	"	10.3.38	36 "
	After 2nd "	"	24.3.38	29 "
	" 4th "	"	8.3.38	17 "
	" 7th "	"	27.4.38	20 "
	" 8th "	"	3.5.38	19 "

2nd Group. Medical treatment.

These patients in each case had the iodine estimation performed before the onset of treatment, and thereafter at approximately weekly intervals where possible. In each case the treatment consisted of complete rest in bed with Lugol's iodine orally in doses averaging a total of ten to fifteen minims per day.

Case 1.	Before treatment	Date	16.12.37	45	gammas
	At the end of course	"	11. 1.38	118	"
Case 2.	Before treatment	"	22.11.37	20	"
	Treatment begun	"	23.11.37		
		"	29.11.37	18	"
	Treatment ended	"	4.12.37	15	"
Case 3.	Before treatment	"	19.11.37	17	"
	Treatment begun	"	20.11.37		
		"	26.11.37	14	"
		"	3.12.37	14	"
	Treatment concluded	"	10.12.37	15	"
Case 4.	Before treatment	"	2.10.37	24	"
	Treatment begun	"	3.10.37		
	Treatment concluded	"	20.10.37	26	"
Case 5.	Before treatment	"	4.10.37	58	"
	Treatment begun	"	5.10.37		
		"	11.10.37	95	"
		"	17.10.37	68	"
	Treatment concluded	"	1.11.37	42	"
Case 6.	Before treatment	"	4.1.38	38	"
	Treatment begun	"	5.1.38		
		"	14.1.38	40	"
	Treatment concluded	"	28.1.38	34	"

Case 7.	Before treatment	Date	25.1.38	46 gammas.
	Treatment begun	"	7.2.38	52 "
	Treatment concluded	"	14.2.38	38 "
Case 8.	Before treatment	"	7.2.38	36 "
	Treatment begun	"	14.2.38	24 "
	Treatment concluded	"	18.2.38	15 "
Case 9.	Before treatment	"	13.1.38	32 "
	Treatment concluded	"	27.1.38	18 "
Case 10.	Before treatment	"	29.10.37	32 "
	Treatment concluded	"	12.11.37	12 "

An examination of these figures shows that in four instances there was a slight early rise in the blood iodine after oral administration of iodine, but that in every case with two exceptions, the figure at the conclusion of treatment was lower than the initial figure. In the two cases in which the end figure remained high the patient had failed to respond satisfactorily and had been discharged home for a "rest".

3rd Group. Patients treated in hospital prior to January 1st, 1937.

The object in this case is to note the iodine content of the blood in cases of definite toxic goitre which had been treated at least one year earlier and had been discharged with a satisfactory result at that time.

A. Medical Cases.

The results are tabulated; the basal metabolic rate as given in the table is that of the patients' condition when admitted for treatment to the hospital.

Case	1.	2.	3.	4.	5.	6.	7.
B.M.R.	27%	18%	39%	30%	40%	26%	33%
Date B.M.R.	7.7.36	5.1.37	12.6.36	13.5.36	12.11.36	3.7.36	4.1.36
Blood Iod.	17 g.	15 g.	32 g.	21 g.	23 g.	27 g.	23 g.
Date Bl.Iod.	3.2.38	21.3.38	22.3.38	5.2.38	22.4.38	22.3.38	3.3.38
B.M.R. at time of taking the blood iodine, but as calculated by Reid's formula.	6%	4%	10%	8%	12%	12%	9%

B. Surgical Cases.

In this group the patients had all had the operation of sub-total thyreoidectomy performed at an earlier date.

In the table the date of taking, and the basal metabolic rate figure as found prior to operation are given in the first two columns. The iodine content of the blood with the date of its estimation, and the basal metabolic rate at that time as calculated by Reid's formula are given in the other columns.

Reid's formula for estimating the basal metabolic rate is one which is of value only as a rough guide, the result being accurate to within only ten to fifteen percent.

The inclusion of results obtained from the use of the Formula, within the substance of a scientific paper can be excused only upon the grounds that it was quite unsuitable for the patients concerned to stay sufficiently long in the hospital for the calculation to be made using the usual apparatus. A considerable proportion of the patients had travelled some distance to report on their condition and one was anxious to inconvenience them as little as possible.

Case №	B.M.R. before operation	Date of B.M.R.	Bl.Iod. in gammas per 100 c.c. blood.	B.M.R. by formula.	Date
1.	12%	2.6.36	14 g.	5%	14.3.38
2.	10%	2.3.36	20 g.	8%	14.3.38
3.	24%	1.3.36	8 g.	-6%	15.1.38
4.	23%	21.4.36	19 g.	10%	16.1.38
5.	26%	1.3.36	14 g.	4%	14.3.38
6.	20%	23.9.36	10 g.	2%	15.1.38
7.	37%	18.7.36	45 g.	27%	15.1.38
8.	13%	13.6.36	10 g.	5%	22.3.38
9.	22%	16.9.36	14 g.	6%	24.3.38
10.	74%	17.3.36	32 g.	21%	24.3.38
11.	9%	15.12.36	14 g.	4%	24.3.38
12.	6%	3.11.36	16 g.	8%	22.3.38
13.	66%	22.8.36	17 g.	14%	22.10.37
14.	48%	11.8.35	14 g.	9%	21.10.37
15.	25%	26.10.35	24 g.	22%	14.10.37
16.	76%	19.12.35	25 g.	22%	21.10.37
17.	43%	29.7.35	15 g.	1%	24.3.38
18.	92%	3.10.35	31 g.	25%	5.3.38
19.	29%	9.9.35	22 g.	5%	7.3.38
20.	49%	2.9.35	17 g.	2%	3.3.38

For this series of former patients treated during the years 1935/36, and examined between the months of October 1937, and March 1938, the average blood iodine for the group which had been treated in the medical ward was 22.5 gammas per 100 c.c. blood, and for those who had been subjected to the operation of sub-total thyreoidectomy the average iodine content of the blood was 20.5 gammas per 100 c.c.

Of this third group the figures were further examined in regard to the patients' clinical condition at the time of re-examination, and it was found that in each case those persons whose iodine content was below 20 gammas had enjoyed good health following dismission from hospital, and that the basal metabolic rate as calculated by formula was under plus 10%, while in those cases where the iodine content was above 20 gammas, the patients still complained of the persistence of certain signs and symptoms, notable amongst these being undue nervousness, weakness, certain degrees of exophthalmos and not infrequently undue perspiration, while the basal metabolic rate was, with one exception, correspondingly elevated. In the five persons in whom the blood iodine was over 30 gammas per 100 c.c., the patients were unable to perform a full day's work.

From this examination of the iodine content of the blood the following conclusions may be made...

The normal iodine content as estimated in eight healthy male subjects averaged 13 gammas per 100 c.c. of blood with extremes of ten and eighteen.

The average iodine content as estimated in 36 cases of toxic goitre prior to treatment being instituted was 35 gammas per 100 c.c. of blood, with extremes of 12 and 120.

The effect of iodine therapy is, in a proportion of cases to cause an initial increase in the blood iodine, this increase subsequently falling throughout treatment to a level eventually below that of the initial value, and approximating to normal limits, the fall corresponding with the lowering of the basal metabolic rate.

In four cases who had been treated by means of X-ray therapy to the thyreoid gland, the iodine content of the blood fell progressively throughout treatment, the fall parallelling the basal metabolic rate, and being inversely proportional to the rise in the patients' general well-being.

The late results of treatment were investigated by relating the iodine content of the blood to the basal metabolic rate and the patients' clinical condition in a series of 27 cases. It was found that a good late result was associated with an iodine content of the blood approaching normal figures, but that there was little difference in the average blood iodine between the medical and surgical groups.

The iodine content of the blood falls with successful treatment in accord with the fall in the basal metabolic rate.

Section IV.

Investigation into the Relationship between the Thyreoid and the Supra renal Glands.

In the previous section it was shown that the injection of .5 c.c. adrenalin hydrochloride 1/1,000 solution administered by the subcutaneous route is capable of elevating the iodine content of the blood in normal subjects, and especially in those persons endowed with the Graves' Constitution.

In 1918 Goetsch devised a test for thyrotoxicosis based upon the assumed susceptibility of the thyrotoxic patient to adrenalin. .5 c.c. adrenalin hydrochloride 1/1,000 solution is injected subcutaneously, and an increase in the frequency of the pulse rate of from ten to thirty beats per minute follows should the person be adrenalin sensitive. In addition to that Goetsch describes in the positive case, an aggravation of all the symptoms of goitre and a rise in the pulse pressure.

The test was based upon observations culled from 500 cases and Goetsch concludes that the test shows an increased sensitivity of the sympathetic nervous system to the action of adrenal secretion when the thyreoid is overactive. The whole effect passes off in one and a half hours, but he admits that there is also a reaction in some normal people and in neurasthenia.

Viewed in the light of further developments in the study of toxic goitre it would seem that in these so called normal and neurasthenic persons neither normality or neurasthenia is present, but rather the constitutionally unstable neuroendocrine system which responds unduly to factors provoking, or tending to provoke an increase in this inherent instability.

I applied the Goetsch Test to a number of patients suffering from toxic goitre, but the response, characterised by palpitation, sweating, and in one case, by a feeling of impending death, was so severe that I concluded that the administration of adrenalin to such persons is quite unwarrantable. There is no doubt whatever in my mind but that the person suffering from toxic goitre is grossly susceptible to the influence of adrenalin.

The experience of Bram also led him to regard the test as being of value and convinced him that the thyrotoxic patient has a strong susceptibility to the influence of adrenalin.

Probably the reaction is of greatest value in the identification of the atypical case, or of the early one where the diagnosis is in doubt.

The general actions of adrenalin upon the system are briefly [1] ...

Dilatation of the pupil, retraction of the upper eyelid.

Acceleration of the heart with increased force of the beat.

Relaxation of the bronchial muscles.

Inhibition of the musculature of the intestinal wall with closure of sphincter.

Liver, glycogenolysis.

Spleen. Contraction of capsule.

Gall bladder. Contraction of muscles of wall.

Bladder. Relaxation of detrusser and contraction of sphincter and trigone.

Uterus. Stimulation of muscle in the Human.

Skin. Excitation of the arrectores pili and other smooth muscle.

Constriction of cutaneous arterioles and capillaries.

Splanchnic Area. Constriction of arterioles.

Skeletal Muscle. Effect of fatigue may be diminished.

1. Wright. Applied Physiology. 1936. 172.

In the thyrotoxic patient we have adrenalin not only intensifying all these effects but also causing...

Increase in the basal metabolic rate up to 20%. (Page 65)

Elevation in the pulse rate by from ten to thirty beats per minute and a feeling of palpitation.

Elevation in the iodine content of the blood.

An experiment was designed with a view to proving or disproving that the thyreoid is stimulated to secretion by the action of adrenalin.

In a series of eight male adult rabbits the thyreoid was exposed and a small section removed by biopsy for subsequent examination. At the same time a specimen of blood was withdrawn for estimation of its iodine content. The animals were then given a subcutaneous injection of one and a half c.c. adrenalin hydrochloride 1/1,000 solution. One half hour later a second portion of the thyreoid was removed, a third at the end of one to one and a half hours, and a fourth, when possible at the end of two hours. At the end of the first hour a second specimen of blood was withdrawn for iodine estimation.

The portions of thyreoid removed, after having been allowed for five minutes to cool were fixed in Sousa's Reagent, and subsequently sectioned for microscopic examination, the first portion being used in each animal as a control for the thyreoid histology.

During the experiments it was observed that in each case the thyreoid when exposed was small and comparatively avascular, but within an hour of the animal having received the injection of adrenalin, the organ was becoming hyperaemic, and in three instances there was

visible pulsation of the lateral lobes. The hyperaemia diminished inside of one and a half hours.

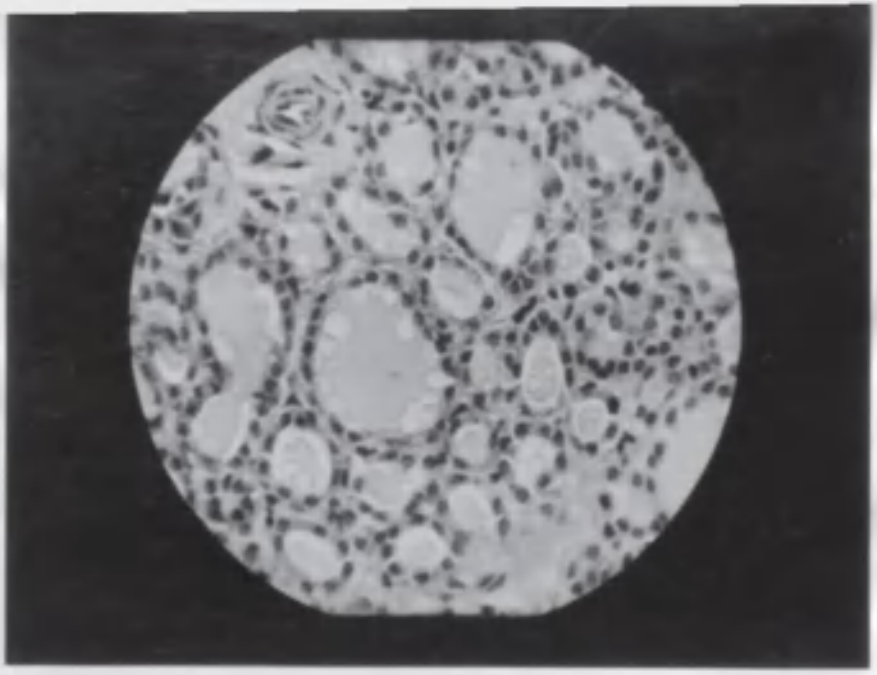
The anesthetic of choice in each case was intraperitoneal membutal with occasionally supplementary ether.

The results of the iodine estimations are tabulated...

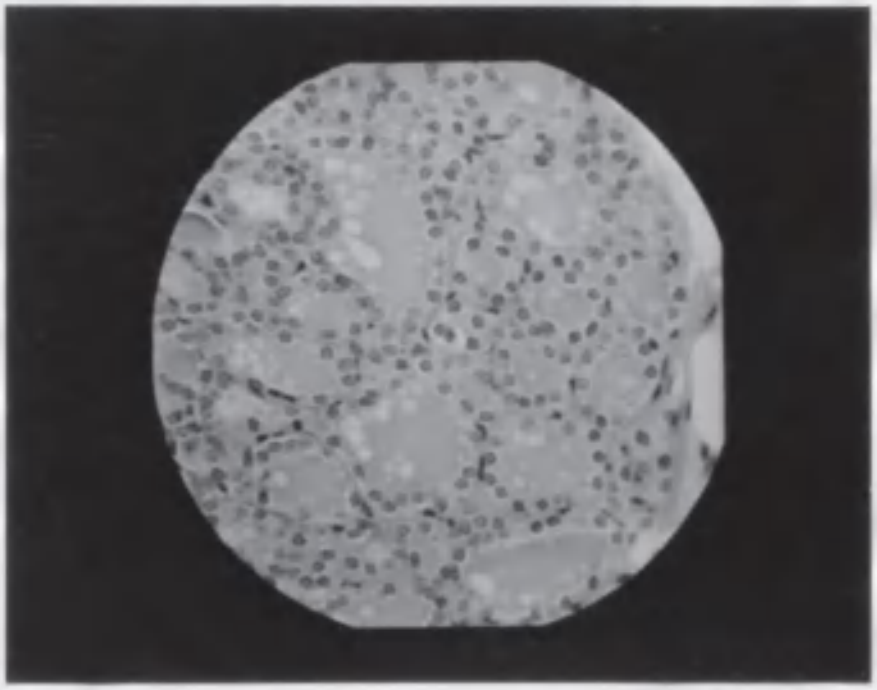
Number	Iodine content of blood before adrenalin	Iodine content of blood one hour after adrenalin
1.	9.8 gammas	124 gammas
2.	10.4 "	68 "
3.	24 "	109 "
4.	9.1 "	94 "
5.	10.6 "	78.3 "
6.	12.4 "	184.9 "
7.	11.8 "	158.2 "
8.	14.7 "	146.5 "

There is considerable variation between each animal in the initial readings, but absolute constancy in the effect of the adrenalin, there being an invariable elevation in the second estimation.

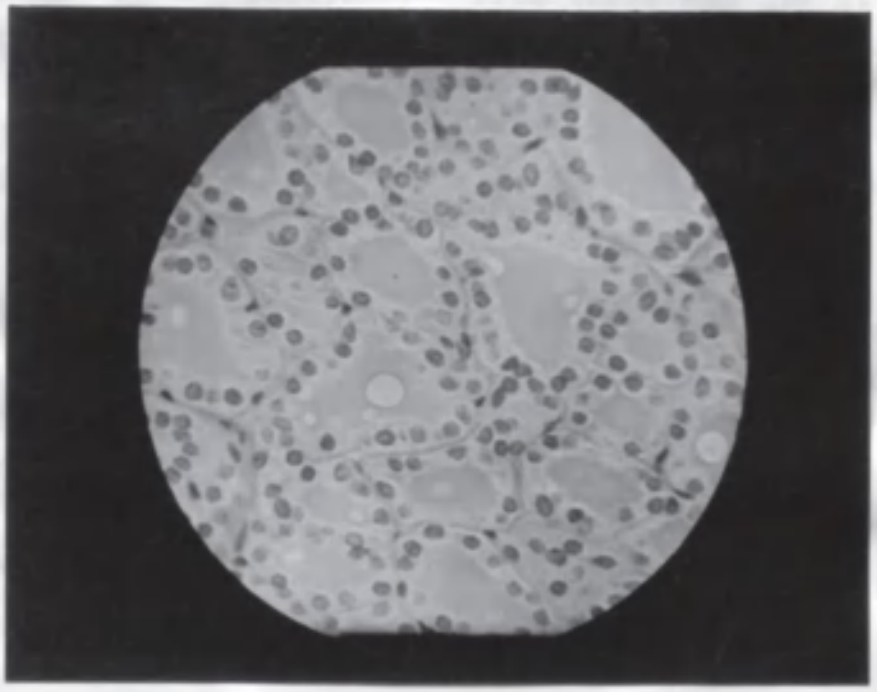
When the histology of the glands was studied, it was found, taking for each animal as control the portion of the organ first removed, that the effect of the adrenalin had been to produce a degree of hyperaemia in the thyreoid with swelling of the cells lining the acini, increased vacuolation of the colloid, and basal movement of the nuclei. These effects were not prominent in the half hour sections but were present in the hour, and definite in the two hour, although varying greatly in degree in the different animals.



Section taken prior to the injection of one and a half cc. 1/1000 adrenalin hydrochloride solution in adult male rabbit.



Section from same thyreoid gland cut one half hour later.



Third section cut at the end of one hour and three quarters from injection of adrenalin.

In one case no significant changes were observed in any of the sections. From these results it appears that the elevation in the blood iodine is associated with histological evidences of secretion within the thyreoid itself, and one may reasonably conclude that both these effects are due to the action of the adrenalin upon the gland.

In confirmation of that conclusion, the effect of adrenalin upon the thyreoid histology was further studied in other four adult male rabbits, litter-mates of two of the first series. These animals received a subcutaneous injection of adrenalin .25 c.c. twice daily for five days.

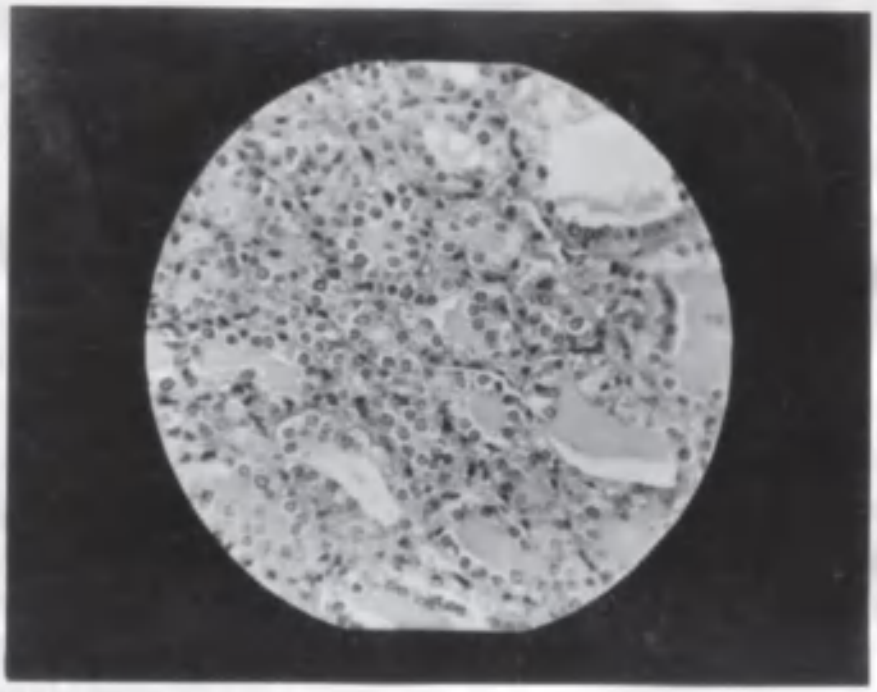
When the thyreoids were exposed the organs were markedly hyperaemic and on naked eye inspection there was a moderate degree of hyperplasia.

The glands were removed and sectioned.

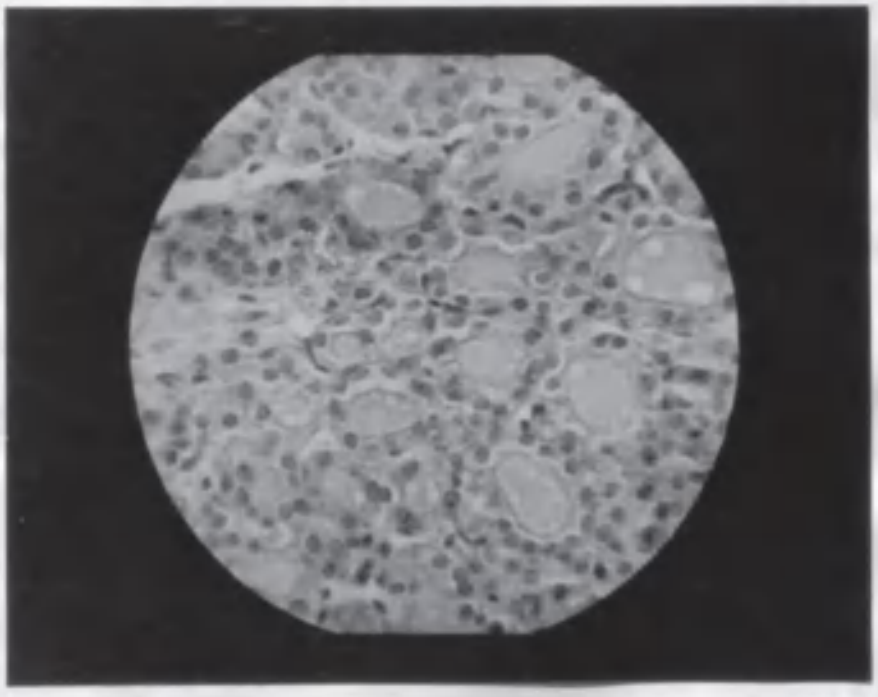
The histology of the organs was similar to that in the first series, but there was great reduction in the colloid of the vesicles, the vesicles being rather irregular in shape and the cells larger, tending to be columnar, and the nucleus staining deeply.

It is accepted by thyreoid histologists that the histology of the organ can be altered within a short time just as can that of the cells of the alimentary canal. The results of these experiments are in accord with that view, the organ being stimulated to secretion by the action of adrenalin, and the secretory evidences manifesting themselves within an hour of the initiation of the secretory processes.

When one takes into consideration the intensifying of symptoms in a person suffering from toxic goitre following upon administration of adrenalin, the elevation in the blood iodine, in the pulse rate and in the basal



Section taken from the thyreoid gland of adult rabbit, litter mate of animal from whose thyreoid photographs on previous page were taken. This animal had been subjected to a course of adrenalin injections, .25 cc. twice daily for five days.



Thyreoid section from animal treated as in case of previous photograph.

metabolic rate produced by adrenalin, and the results of the experiments detailed above, there appears to be little doubt but that the thyreoid gland is stimulated to secretion by the influence of the adrenal medulla, and it remains to be decided by what route this stimulus brings its influence to bear upon the thyreoid.

What is the mode of action of adrenalin upon the Thyreoid ?

The post ganglionic fibres of the sympathetic nervous system produce their effects by the liberation at their terminals of a substance which is indistinguishable from adrenalin [1]. (Page 84) In the case however of pre-ganglionic fibres such as the splanchnic nerves [2] to the adrenal medulla, there is liberated between the nerve terminals and the cells, not adrenalin, but actylcholine, a potent excitor of the parasympathetic division of the autonomic nervous system.

Adrenalin stimulates the sympathetic nervous system, and in the case of the post ganglionic fibres at least, the nervous impulse is transmitted from the nerve terminals to the cells by a substance indistinguishable from adrenalin, so the question arises as to whether the adrenal secretion may stimulate the tissue cells directly, or whether that stimulation can only be produced through the medium of the sympathetic.

Does adrenalin stimulate the thyreoid gland...

(1) By way of the thyrotropic hormone of the anterior lobe of the pituitary gland, that organ being stimulated through the medium of the sympathetic ?

(2) By way of a primary stimulation of the sympathetic nervous system, or

(3) By a direct influence upon the thyreoid cells of adrenalin existing in an active state in the blood stream.

1 and 2. Wright. Applied Physiology.

With a view to determining the possible influence of the pituitary gland certain experiments were performed. An effort was made to hypophysectomise a number of white Albino rats. The intention was, had the animals survived the operation, to perform the same experiments upon them as were carried out in the case of the first series of rabbits. (Page 81)

Were the same results obtained, regarding thyreoid histology in the hypophysectomised animals as in the normal, both being subjected to the same experiment, then it could have been assumed that the pituitary gland played no part in the process. Unfortunately, however, I found that in the absence of dissecting binoculars and special drilling apparatus, the successful removal of the pituitary was not possible. The operation was attempted in twelve animals, but none survived longer than 24 hours.

As an alternative approach to any possible pituitary relationship a more simple but less accurate experiment was performed.

Fifteen white mice were given increasingly larger daily doses of subcutaneous adrenalin 1/1,000 solution commencing with .05 c.c. and increasing by the end of ten days to .25 c.c. During this period the mice lost weight, the fur became dry and scanty, there was gross tachycardia, and five died between the fourth and tenth days. The adrenals, thyreoid, where possible the parathyreoid, and the pituitary glands were subsequently removed, and in four animals also the ovaries; these were all sectioned for microscopic examination. In addition, portions of liver and kidney were taken and examined for glycogen content.

It was difficult to obtain satisfactory sections of the pituitary in the mice.

Five other white mice were used as control animals

and in them the same organs were examined.

Regarding the pituitary no abnormalities of any kind were observed in the histology. The glands appeared to be quite normal.

Parathyreoids and ovaries likewise showed no significant changes.

The suprarenals in some cases showed a slight degree of hypertrophy affecting the cells of the medulla but these changes were not constant.

The thyreoid histology was unequivocal, the most constant feature being a degree of peripherial vacuolation in the colloid. The cell nuclei stained deeply.

In the case of the second series of rabbits (Page 83) the pituitary glands were also removed and examined, but again no abnormalities were noted.

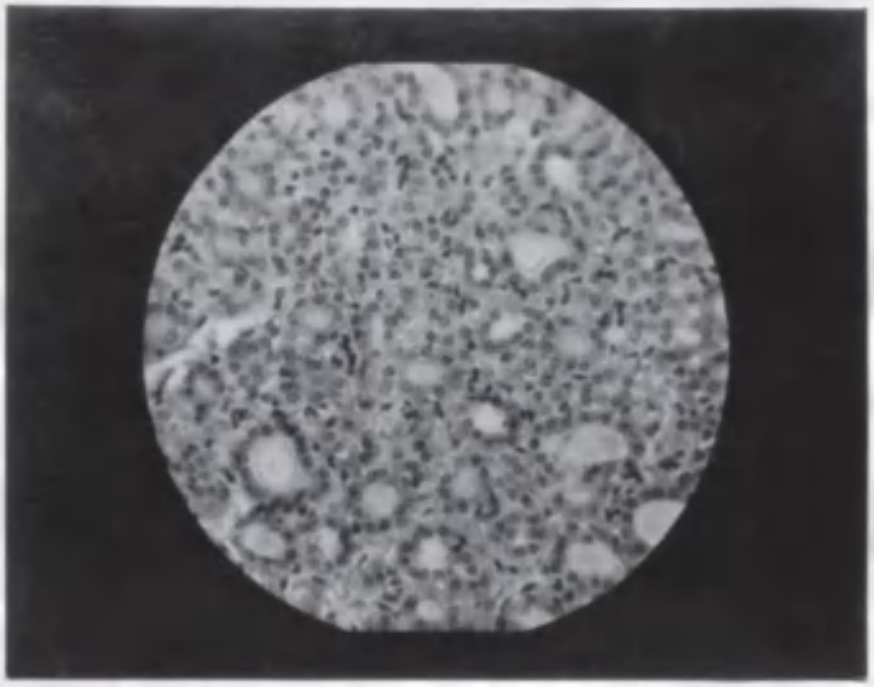
The portions of liver and kidney removed showed absence of glycogen.

The pituitary gland and its thyrotropic hormone are considered in detail in the next section...Pages 114-121 in regard to the Pituitary Theory of Etiology.

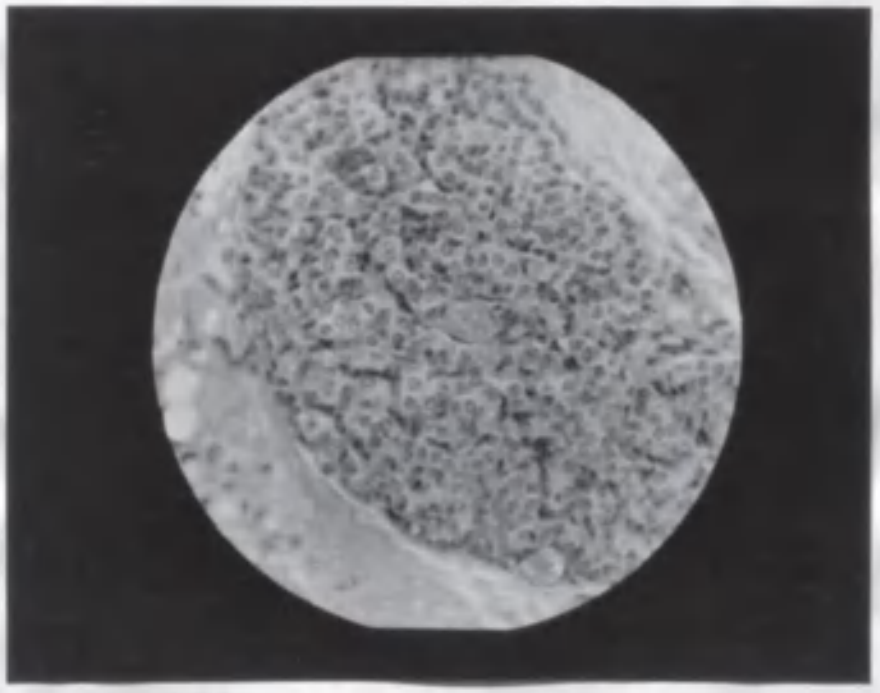
In that section of the thesis it will be observed that the thyrotropic hormone is restricted in its action, in the laboratory animal at least, and that animals treated with it over a period develop a state of refractoriness when the hormone no longer evokes a thyrotropic response.

A great deal is known about the action of the various secretions of the pituitary body, and that knowledge as it affects the subject at present under consideration is considered also in the next section, but it will be found that there is no evidence of the anterior lobe of the pituitary being influenced by the secretion of the adrenal medulla.

Even if the administration of adrenalin were capable of provoking the secretion of thyrotropic hormone



Section from thyreoid gland of mouse following upon treatment for ten days with subcutaneous injections of adrenalin 1/1000 soln., initial dose .05 cc. final dose .25 cc..



Section from thyreoid gland of control mouse litter mate of the first.

the restricted action of that hormone makes it extremely unlikely that the thyrostimulant effects noted following upon the injection of adrenalin are due to any pituitary influence. The pituitary glands of animals treated over periods of seven to ten days with injections of adrenalin show no histological changes.

When these facts are considered one may reasonably conclude that the adrenal medulla does not exert its thyrostimulant effect through the medium of that organ.

The chemical substance transmitting the nerve impulse between the sympathetic nerve terminals and the tissue cells, in the case of post ganglionic nerve fibres is probably adrenalin, and we know that adrenalin stimulates the sympathetic division of the autonomic nervous system, so there is strong presumptive evidence that in these facts lies a possible explanation of the thyreoid stimulation.

What is the nerve control of thyreoid secretion ?

The nerve supply of the gland [1] is derived from the middle cervical ganglion of the sympathetic, and blood issuing from the gland after stimulation of the sympathetic is said to contain the active principle, as shown by biological tests...precocious metamorphosis of the tadpole, but it is certain that the thyreoid can go on secreting in an apparently normal manner after its nerve supply has been destroyed.

The nerve fibres enter the gland along the walls of the blood vessels which are many in number and complex in arrangement, breaking into capillary plexuses which surround the secreting units. These capillaries have the power of rapid dilatation and contraction and the innervation of their walls is by means of post ganglionic fibres; thus the chemical transmittor is in their case that substance

1. Wright. Applied Physiology . 1936. 251.

which is indistinguishable from adrenalin.

Adrenalin acts peripherially and not upon the sympathetic nerve centres, nor does it act upon the anatomical nerve endings and will still stimulate organs after these nerve endings have degenerated. Loss of the sympathetic nerve endings appears actually to intensify the cell to the action of adrenalin, and thus it is concluded that the action is exerted upon some point between the nerve endings and the tissue cell...that is at the cell-neural junction where the chemical transmittor is liberated by the sympathetic impulses.[1]

The denervated heart is sensitive to concentrations of adrenalin even in a dilution of 1/400 million, [2] and it is further known that the thyreoid can continue to secrete even when it has been completely denervated.

In such cases it is possible that adrenalin is exerting an effect at the cell neural junction.

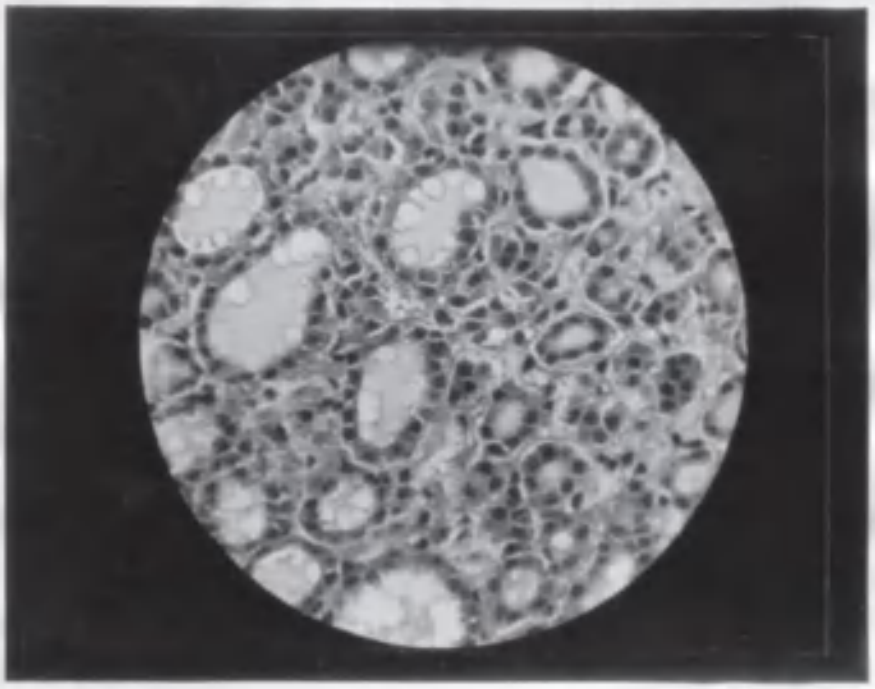
The following experiment was performed with a view to determining the direct effect of adrenalin upon the thyreoid histology.

The animals chosen were adult Chinchila rabbits.

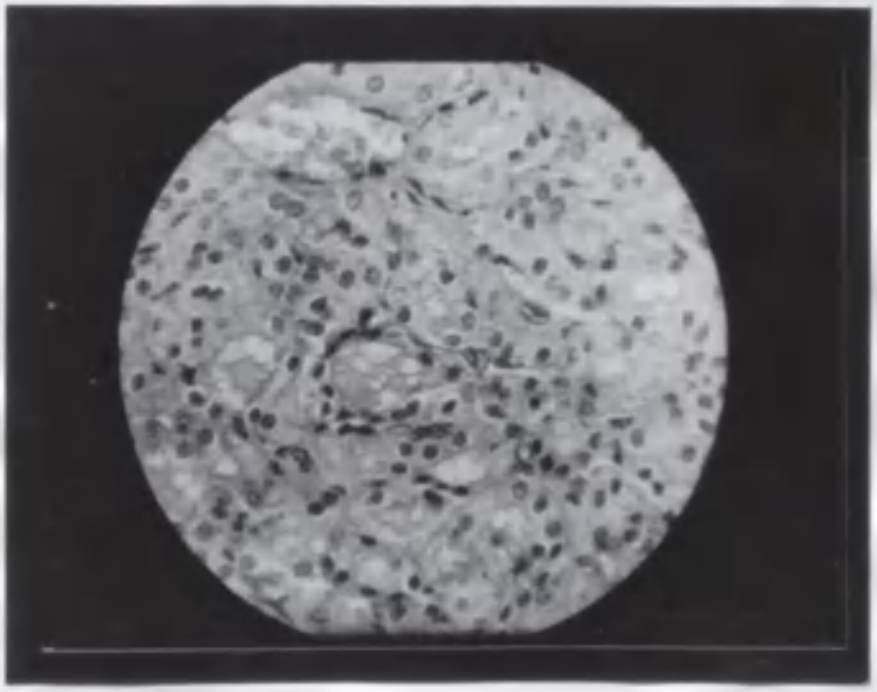
Each animal was anaesthetised by ether and the thyreoid exposed. The organ was removed intact and placed at once in Ringer Locke solution at blood heat.

The animal was then bled and the serum removed from the collected blood, the whole being maintained as near to blood heat as possible. Some hours were required for sufficient serum to have separated, but as soon as practicable the separated serum was taken and various dilutions of serum and adrenalin made up, one for each animal. In all six animals were treated after this fashion, the dilutions being in two cases 1/10,000, in two 1/100,000 and in two 1/1,000,000. Three specimens of

1 and 2. Wright. Applied Physiology. 1936. 175.



Section from thyreoid of rabbit following upon incubation for two hours in the homologous serum at blood heat in dilution 1/1,000,000 with adrenalin hydrochloride.



Section from thyreoid gland of control animal following upon incubation for two hours at blood heat in the homologous serum .

each dilution were used, and a fourth specimen taken of serum alone as control. One quarter of the isolated thyreoid was placed into each specimen and all were incubated at blood heat, the first for one half hour, the second for one hour, the third and the control, for two hours.

At the end of the periods of incubation the tissue was fixed in Sousa's Reagent and later sectioned for microscopic examination.

The same experiment was performed in a second series of six animals with the following modification; dilutions of adrenalin and Ringer Locke solution were taken in place of serum. The dilutions for this series were 1/1,000, 1/100,000 and 1/10,000,000. The incubation periods were as before, and again the tissues were examined histologically.

The histology was of interest.

In the majority of cases the control sections showed acini well filled with deeply stained colloid, but showing comparatively little vacuolation. The cells of the epithelium lining the acini were flat and contained a small, central, clearly stained nucleus. There was little distinction between the cell granules.

In two cases the colloid was fragmented.

The observations upon the 'serum adrenalin' and 'Ringer Locke adrenalin' series were similar.

Half hour Sections. Histology closely resembled that of controls. Little change detected.

One hour Sections. Some heightening of the cells lining the acini was noticed with a degree of enlargement of the nuclei. A number of nuclei show an eccentric position. No alteration noted in intensity of staining reactions. Colloid as in controls.

Two hour Section. The epithelium lining the acini was, in most sections columnar in type. Majority of cell nuclei were enlarged and eccentric, tending to occupy a basal position. Colloid was less deeply stained, often fragmented and showed increased vacuolation.

The histology is that of a gland at first inactive, but later showing evidences of secretory activity.

As regards the dilutions used, the results were unequivocal, there being little difference between the 1/10,000 and 1/10,000,000 sections. From these observations it was concluded that the thyreoid gland is susceptible to the action of adrenalin directly, apart from any sympathetic nerve innervation, and that this susceptibility can be demonstrated when the gland is incubated in dilutions of Ringer Locke solution and adrenalin, the temperature being that of blood heat. Under such conditions, at the end of two hours the greater proportion of sections examined from a series of twelve rabbits showed evidences of secretory activity.

In the case of the series of thyreoid-ectomised rabbits the animals were killed not earlier than six weeks and not more than sixteen after operation. Portions of liver and kidney were removed and examined for glycogen.

Of animals killed earlier than the eighth week there was no alteration in the glycogen content which could be regarded as significant. Three animals were killed at the sixteenth week when sections of liver and kidney showed diminished glycogen.

A certain amount of evidence has been submitted in support of the hypothesis that the thyreoid gland is stimulated by the action of the secretion of the adrenal

medulla. Should this be so one would expect that removal of the thyreoid gland would promote secretory activity on the part of the adrenal medulla with a resulting increased adrenalin concentration in the tissues.

The fact that thyreoidectomised rabbits show diminished glycogen in the liver and kidneys is evidence in support of the existence of this increased adrenalin secretion, and may be regarded as supporting the possibility of the thyreoid being stimulated through the medium of the adrenal medulla.

It is appropriate at this point to recall the more important facts accepted with regard to the physiology of the supra renal glands and to observe what evidences may be obtained from these facts in support of the hypothesis that the adrenal organs play a leading part in the production of toxic goitre.

The adrenal medulla is developed from a mass of cells which lie at first close to the posterior root ganglia, and later migrate out to differentiate into sympathetic nervous system and the chromophil tissue [1]. The function of its active principle, adrenalin, is as closely related to the sympathetic nervous system as is the gland developmentally.

The adrenal medulla through its secretion reinforces the sympathetic nervous system in times of stress, but Wright considers that some secretion also takes place even under resting conditions [2], and it is certain that a considerable secretion of adrenalin is evoked by emotional stimuli such as rage, fear, pleasure or even worry. [3.4.]

1. Wright. Applied Physiology. 171.
2. " " " 177
3. " " " 178
4. Simpson. Physiology of Adrenal Gland. B.M.J. 30.1.37

The gland is also stimulated by asphyxia [1], by exposure to cold, by physical stress, fall of arterial pressure and by cerebral anaemia [2].

Many authorities doubt the validity of claims made that adrenalin exists as such in the blood, but it has been proved beyond reasonable doubt by means of cross circulation experiments in animals that such is the case [3].

By the same means Wright maintains that rigid proof has been obtained that in the splanchnic nerves... from the sympathetic...lies the secretory innervation of the adrenal medulla. He also considers, however, that there may be a higher control centre in the brain stem whose activity may be modified by afferent impulses, especially along the sinus and aortic nerves. [4]

It is not unreasonable to infer that if a higher control centre exists, then it will respond to emotional disturbances, stimulate the adrenal medulla through the medium of the sympathetic nervous system and lead to a hypersecretion of adrenalin with resulting general sympathetic hypertonus, and hyperadrenomedullarism.

This sympathetic hypertonus will affect all organs under sympathetic control, and amongst these the thyreoid gland. At the same time there will be produced a relative vagal and adrenocortical hypotonus. Under such circumstances the normal neuroendocrine balance is destroyed, and around this neuroendocrinopathy centres the theory that from it springs the syndrome of toxic goitre.

The physiological properties of adrenalin have

1. Wright. Applied Physiology. 178
2. Simpson. Physiology of Adrenal Gland. B.M.J. 30.1.37
3. and 4. Wright. Applied Physiology. 176-177.

been discussed in the text (Page 80), and its effect upon patients suffering from toxic goitre noted.

Within recent years Crile has claimed to cure recurrent cases of toxic goitre following upon subtotal thyreoidectomy by denerving the adrenals [1]. His observations are based upon only a few cases but he claims that his results have been good.

This is in accord with the possibility at present under discussion. If emotion stimulates the secretion of adrenalin through the medium of the splanchnic nerves, and if that stimulation is capable of exerting an effect upon the thyreoid to produce an excess of thyroxin in the organism then the operation of denerving the adrenals is legitimate, heroic though it may be.

Cameron [2] amongst others in the literature, cites a case of a patient who at autopsy was shown to have an adenoma in her left supra renal medulla. She suffered from attacks of hypertension, nausea, vomiting and vasomotor disturbances, the attacks setting in with pallor and shivering, rapid pulse, perspiration, and cyanosis of the extremities, the temperature rising during the attack. During the illness she developed a degree of nitrogen retention, and albuminuria. Eventually she died of pulmonary oedema.

Such an example of gross medullary stimulation shows in an exaggerated form, certain features which may sometimes be found in the crises of toxic goitre.

The writer has seen one such patient who had a succession of 'attacks' setting in with gross weakness, sweating, pallor of the face, tachycardia, and cyanosis of the finger and toe nails, with fluctuating temperature

1. Crile. Annals of Surgery. 1934. 667.
2. Cameron. Recent Advances in Endocrinology. 1934. 203.

and a consistently high blood pressure. She had the classical signs of toxic goitre, a basal metabolic rate varying between plus 70 and plus 95% above normal, gross exophthalmos and cardiac complications. Medical treatment failed to improve her condition, and on three occasions the thyreoid was injected with boiling water. After a lengthy illness during which, for about three weeks, she was expected to die, she began to improve, and after another three months in bed she was sent home in reasonably good condition for a holiday prior to further treatment being undertaken.

The adrenal cortex is mesoblastic in origin.

Its function appears to be the regulation and maintainance of a normal volume of fluid within the vascular system. There is evidence that the adrenal-ectomised animal dies from circulatory failure due to insufficiency of circulating fluid, there being a progressive fall in the blood pressure, paralleled by a steady decrease in the blood volume. This is in keeping with the clinical picture of extremely low blood pressure, collapse, and circulatory failure found in the terminal stages of Addison's Disease, and has also points in common with the crises of toxic goitre.

A striking clinical feature of hypocorticoadrenalism is pigmentation of skin and mucous membranes.

In five cases of Addison's Disease examined by the writer the colour varied from a pale discolouration to a dusky negroid hue and was distributed over the bony prominences, dorsum of hands, knees, shoulders, and to a less definite degree under points of constriction. There was also a general darkening of the skin of face and palms of hands. Brown mottling was observed in the mucous membrane of the mouth. This corresponds with the description of pigment distribution given in text books,

but it also resembles a proportion of cases in the present series, 36% of whom had pathological areas of skin pigmentation noted upon clinical examination.

In these patients the pigment assumed one of four types.

1. General darkening of skin of thorax, abdomen, face, arms and hands, the colour varying from pale to deep brown. The areas were irregular in outline. 25%
2. Darkening over points of pressure alone. 8%
3. Darkening of skin over areas of exposure, face hands and forearms, resembling a mild degree of vagabondismus. 17%
4. Cases of Addisonian distribution. No mucous membrane pigmentation. 50%

In each instance the patient recognised that the pigmentation had developed during the course of his illness, and that it was a departure from normal.

It was invariably a late sign to appear.

The pigmentation is so definite an entity, and so generally remarked by varying authors that it would be unwise to neglect its possible significance. The sign would appear to indicate that in toxic goitre there is, in a considerable proportion of cases, a degree of hypo-activity in the supra renal cortex. The cause for this is as obscure as its existence is obvious.

One feature common to Addison's Disease and to toxic goitre is a liability to crises in the severe case, and Shapiro, quoted by Cameron [1], believes on the basis of results obtained by treating the crises of toxic goitre with adrenal cortical extract, that there is foundation for a belief in the initial disturbance being within the adrenal cortex.

1. Cameron. Recent Advances in Endocrinology. 1934. 389.

Zondek [1] also comments upon the resemblance between the coma of toxic goitre and that of Addison's Disease, from his experience in Palestine. He has treated the former condition, which appears to be comparatively common in the Near East, with adrenal cortical extract plus Lugol's iodine, and obtained good results.

The anterior lobe of the pituitary is credited with possessing an adrenocorticotropic hormone [2], and the results of experiments made by Nicholson [3] suggested to him that supra renal cortical atrophy might be due to changes in the anterior lobe of the pituitary. In this connection it may be remarked that one of the criteria of complete hypophysectomy is atrophy of the adrenal cortex [4].

The pituitary appears to exert some sustaining influence over the adrenal cortex but the precise significance of that relationship has not yet been established. It is unlikely however that the cause of toxic goitre depends upon an adreno pituitary relationship.

In page 84 of the text it was stated that the splanchnic nerves, which are the secretory nerves of the adrenal medulla, are pre-ganglionic, and that the chemical substance connected with the liberation of the impulse between the nerve endings and tissue cell is acetyl choline, a substance which acts as a potent stimulant to the parasympathetic system. Wright [5] notes that such chemical transmittors, while exerting their effects locally may yet escape into the general circulation and produce remote results.

In this statement lies a possible explanation of these phenomena attributable to vagal stimulation which are

1. Zondek. Europ. Med. 1936. June-July.
2. Cameron. Recent Advances in Endocrinology. 1934.
3. Nicholson. Bull. John Hopkins Hosp. 1936. 58. 405.
4. Hertz and Oastler. Endocrinology. 1936. 20. 520.
5. Wright. Applied Physiology. 1936. 175.

found in toxic goitre.

The state of the pupils, occasional alimentary symptoms, and the pallor of the face may be regarded as vagal effects.

It is accepted that emotion, physical trauma, infection, or other stimulus may stimulate the sympathetic nervous system and through the splanchnic nerves provoke adrenalin secretion. In the course of the impulse being transmitted to the secretory cells of the adrenal medulla a small quantity of acetyl choline is liberated, some of which may, in a proportion of cases escape into the general circulation, and, according to the amount present, so shall be the degree of remote vagal stimulation.

At the same time adrenalin is secreted into the general circulation causing a condition of general sympathetic hypertonus.

Stimulation of the post ganglionic fibres of the sympathetic thyreoid secretory nerves evokes the secretion and liberation of thyroxin, and promotes hyperaemia of the gland. Thyroxin is then absorbed into the circulation and promotes an increased rate of tissue oxidation with elevation in the basal metabolic rate.

Under such circumstances there is complete upset in the neuroendocrine balance, the adrenal medulla and sympathetic system are in a state of excitation and hyper activity, while the adrenal cortex and parasympathetic nervous system are in a condition of relative quiescence and relative hypo activity. The thyreoid is stimulated to a higher level and its secretion exerting an effect upon the cells throughout the organism.

Should this sequence of events find a place in the life of a person endowed with the Graves' Constitution then the effects are more likely to be serious than in the normal subject. Under such circumstances the existing

neuroendocrinopathy is accentuated, and while in the normal person, with the removal of the provoking stimulus be it emotion, physical strain or any other factor, the glands and nervous system revert to normal, in the person constitutionally liable the effects may be more prolonged. This stimulus, to such people, appears actually to sensitize their neuro endocrine systems to respond even more emphatically to the action of other future stimuli and so a vicious circle of events is initiated which progressively weakens any resistance there may have been until the balance of the neuro endocrine system is completely destroyed, the thyreoid gland continues to hyperfunction and the level of tissue combustion remains elevated, while within a short time the signs and symptoms of toxic goitre are recognised.

This sequence of events, however, can only follow when there is a constitutional deficiency in the neuro endocrine system, that is to say when there is present a constitutional liability to develop the disease.

Section V.

Theories regarding the Etiology...Thyrogenic... Intoxication...Sympathetic... Bulbar... Thymus... Parathyreoid... Gonad... Pituitary... Adrenal... Psychical or Neurogenic... Crile's... Eason's... Neuroendocrine.

Many theories have been propounded regarding the possible etiology of toxic goitre, and of these a considerable number have been discarded with progressive increase in knowledge, but some are still held by competent authorities, and it is of advantage to discuss the more important of them.

A study of the endocrine bodies has caused each in turn to be implicated, and attention has also been drawn [1] to the nervous and autonomic systems, especially by Eppinger and Hess, who considered that there may exist between the para and sympathetic divisions an upset in the normal balance, favouring a preponderance of the one over the other, relative or absolute.

This evolution of ideas has served to bring into prominence an association between the endocrine and the nervous systems, and more recently it has been recognised that it is fallacious to regard one division of the nervous system, or one particular organ of the endocrine system as being responsible. The two are interdependent, and a harmonious interassociation is essential for bodily well being. When one ductless gland is abnormal the whole system is thrown out of balance and the resulting effects come from many sources, while at the same time, in certain cases it is possible that the autonomic system is also involved. With a recognition of that fact progress began to be made in the elucidation of many problems, and in

1. Eppinger and Hess. Vagotonia. Translated by Krauss and Joliffe. 1915.

particular with regard to those connected with toxic goitre.

These varying theories shall now be discussed in turn.

1. Thyrogenic. This suggests that there is taking place within the thyreoid, changes which lead to an alteration in the secretion, either qualitative or quantitative, and, that the symptoms and signs are due to this departure from normal.

The theory is based upon the known differences between the symptoms of myxoedema and toxic goitre, the mitigation of the signs and symptoms of myxoedema by the administration of thyreoid extract, and the aggravation of signs and symptoms of thyrotoxicosis by thyreoid extract; the improvement following upon partial thyreoidectomy, the frequent occurrence of a goitre, and the effect in Man and animals of overdoses of the thyreoid extract. Lastly, the theory is sponsored by those who claim the existence of characteristic changes in the thyreoid histology typical of toxic goitre. It is however based upon premises which are false.

There is no doubt that the histological changes in the thyreoid gland in disease are not constant, even in the highly active organ there may be areas of absolute inactivity, and Marine [1], states, on the basis of a series of 137 cases of toxic goitre where the gland was examined post mortem or after operation, that active hyperplasia was present in only 60%, and that the symptoms were not associated with constant changes in the gland. This is in opposition to the view held by Wilson [2] and later by MacCarty [3] that the amount of

1. Marine. Jrnl. Amer. Med. Assoc. 1912. L. IX. 325
2. Wilson. Amer. Jrnl. Med. Sc. 1908
3. MacCarty. ditto 1909

hyperthyreoidism runs parallel to the extent of cell proliferation in the gland; conclusions which are based upon faulty control and deduction and which may be dismissed as incorrect.

It is a known fact that an endocrine organ may not produce an abnormal secretion. It may be altered in quantity but never in quality [1], although there has been a good deal of discussion in the literature during recent years regarding the possibility of an abnormal secretion, and even Joll hints that a dysthyreoidism is a possibility worthy of consideration. Samson Wright however, regards toxic goitre as being associated rather with an excessive secretion on the part of the gland, a view which is probably correct.

As against the possibility of the thyreoid being per se directly responsible there is the known fact that partial thyreoidectomy fails to effect in all cases a complete cure, although a considerable improvement may result. In my series of seventy-eight, twenty cases were examined not earlier than one year after operation and of these 20% stated they were cured, 70% were much improved and 10% worse; while of eight patients treated medically over one year prior to re-examination all stated that, while a temporary improvement had followed their dismission from hospital the old symptoms had since returned with varying degrees of intensity. On analysis, it was found that the symptoms which remained were in each case those referable to the nervous and metabolic systems... nervousness, inability to increase substantially in weight, easily provoked tachycardia, undue sweating and occasional periods of weakness, while the chief

1. Cameron. Recent Advances in Endocrinology. 1934.1.

clinical signs which persisted were those of the eye phenomena.

In McEwan's series [1] 67% were able to do a full day's work, and of the remaining 33% a number were constitutionally weak persons whose thyreoid condition had been cured, but who were now left with their formerly debilitated state; there was a group of the aged who would not work again, a group with associated diseases, heart and arthritic etc., those who returned to work after a too speedy convalescence because of economic pressure and a miscellaneous group of varying conditions preventing work.

The figures however, show that partial thyreoidectomy is not certain of effecting a cure, and even when the patients were able to lead a normal life and do a full day's work signs of the condition still remain in a great many cases, showing that the disease is not local, a conclusion arrived at by Marine and Lenhart [2] so long ago as 1911 and based upon the pathological findings in the gland.

Against the possibility of the disease being due to a hyperthyreoidism is the fact that it may coexist with symptoms and signs of hypoactivity, and, as was remarked in the editorial to Endocrinology Vol. 1, № 4, "Thyreoid secretion cannot be augmented and depressed at the same time".

Gautier in 1885 suggested a theory which has been called by Bram [3] the Thyreoid Insufficiency Theory, advanced with a view to explain the association of myxoedema and toxic symptoms at the same time. This supposes that in myxoedema there is defective utilisation of the iodine assimilated in the food,

1. McEwan. B.M.J. May 14th, 1938. 1042.
2. Marine and Lenhart. Arch. Int. Med. Sept. 15th, 1911.
3. Bram. Exophthalmic Goitre, 3.

it being metabolised in the liver or elsewhere; toxic goitre on the other hand being due to iodine getting into the blood stream and being insufficiently metabolised.

In many cases which are associated with superadded signs of myxoedema it will be found on examination and by careful taking of the case history that a toxic goitre was present in the first instance, and that the myxoedematous changes were secondary. This phenomenon is explained by Marine who states that there takes place in the normal thyreoid a cycle of events whereby the gland does not work as a whole but in sections, so that there is always a considerable portion of the organ at rest, one part functioning for a time then resting while another takes over. When more than usual activity is required then the area at rest is correspondingly smaller and the functioning part is working at a correspondingly higher pitch. In pathological conditions placing an excessive strain upon the gland a state of exhaustion may ensue in the working area, placing more demands upon the resources of the remaining portion, which in turn becomes exhausted until the gland has 'burned itself out'.

Certain signs of the disease however, such as exophthalmos, sweating and tremor, are notoriously difficult to remove completely and so it is possible for certain symptoms and signs characteristic of toxic goitre to persist while the person may be actually suffering from the effects of an exhaustion atrophy of the organ and myxoedema.

In one of my cases this explanation cannot explain the sequence of events.

Case History.

Unmarried woman aged 38 complained of extreme weakness and giddiness, several weeks duration.
During the past nine years been in poor health following operation for appendicitis at that time. Operation and convalescence uncomplicated, but thereafter says she has "Never been well", although never confined to bed except on a few occasions during these years. For past six years weakness, asthenia, slight breathlessness and later huskiness of the voice were the only symptoms, but for the past two she has also complained of becoming stout, the face becoming bloated and of falling out of the hairs of head and eyebrows. Recently the periods have been scanty. During the past four weeks she has experienced gross weakness and giddiness following slightest exertion.

She was put on a regime of thyreoid extract grains, one tablet daily for a fortnight, then two tablets daily for many months. There was no appreciable improvement in any respect excepting that the voice regained something of its former tone. The dose was increased to three tablets per day, and after one fortnight her friends declared that she was becoming 'jumpy and nervous'. She herself was not aware of this but she did feel more weak and more easily tired than usual.

Examination.

Patient slightly built but inclining to be stout, sits nervously in chair. Face coarse featured, pale, typically myxoedematous, no hair on eyebrows, hair of head dry, scanty and brittle. Eyelashes normal. Skin thick and coarse and dry over face and hands, but moist in the axiallae and trunk. Pulse regular in all respects soft, poor quality, frequent, rate 153.
Heart area of dullness normal. Sounds frequent, poor quality, pure, regular in all respects.
Blood pressure 140/85.
Thyreoid gland right lobe just palpable. Systolic hum heard on auscultation over the organ.
Nervous system. Reflexes slightly exaggerated. Eye reflexes normal.
Tremor. Marked fine tremor of outstretched fingers.
Renal. Urine daily output normal. Physical and chemical examination normal.
Respiratory. Normal.
Alimentary. Patient oedentulous. Tongue clean but with fine tremor.
Eyes. No exophthalmos or other phenomenon.
Basal Metabolic Rate. Plus 12%
Blood Iodine. 6.8 gammas per 100 c.c. blood.

This is an example of a person who suffered from gross long standing myxoedema, and who with moderate doses of thyreoid extract not only failed to improve, but who further developed a picture of mild hyperthyreoidism.

It is also a fact that the toxicity of the thyreoid appears to depend upon its iodine content, and, since the hyperplastic organ contains less iodine than the normal [1] the hyper theory appears to be untenable.

Thyreoid medication is one of the most frequently adopted modes of treatment for the purpose of weight reduction, both in hospital and in general practice at the present time. There must be many thousands of people taking the dry extract daily over comparatively long periods, and yet only a very few of these develop toxic goitre.

The whole situation depends upon the fact that it is only when there is an inherent predisposition to the disease that such stimuli will provoke its onset.

It has been tritely remarked that in toxic goitre it is the body which makes the gland ill. This statement is worthy of consideration because there is no doubt but what the role of the thyreoid in the etiology is merely secondary to a stimulus acting upon it from another source, and existing with the predisposition which is so insisted upon as being present in the vast majority of persons afflicted.

2. Intoxication.

This is one of the older theories and is based on the accepted physiological fact that the thyreoid can act as a detoxicating agent, and that in a proportion of cases of toxic goitre there is an association with some septic focus, commonly the teeth or the tonsils. In the present series sixteen per cent were associated with such a focus, and of that number almost half improved upon removal of the source of sepsis.

1. Cameron. Recent Advances in Endocrinology. 83.

The good results sometimes obtained are encouraging, but the infection acts as the provoking stimulus only where the stage is set ready for the production, and is almost always associated to a greater or a less extent with the stigmata of the Graves' Constitution.

It is assumed that sepsis stimulates the thyreoid to hyper activity through the undue demands made upon its function as a detoxicating agent.

Against infection being the prime cause is its comparatively low incidence in the different series mentioned in the literature.

Joll [1], with his wide experience, merely says that certain cases were noted where the origin was traced to an attack of influenza or tonsilitis, while Farrant [2], on the contrary, states that infection plays an important part, that the organisms are the B. Catarrhalis and the mutants of the B. Coli, and are found in the nose, lungs and intestines.

Before dogmatizing in such a manner, it would be necessary to prove that there is an increase in the numbers of these organisms in the majority of persons suffering from toxic goitre from the numbers present in the healthy subject... a task which would be well nigh impossible.

It is extremely doubtful if there is a higher incidence of focal sepsis in toxic goitre than there is in any other disease.

The effect of focal sepsis is generally temporary, and the prognosis comparatively good in those cases which are treated early and energetically by removal of the local lesion.

1. Unmarried female aged 19. Complained general nervousness, weakness and slight swelling in front of neck of one year's duration, but increasing progressively in degree. One year ago had slight sore throat and at that time it was noted that the

teeth were grossly carious with mild pyrhorroea alveolis.
Examination.
Patient thin, pale, restless, nervous and emotional.
Pulse. Frequent and irregular in all respects. Rate 108
Heart. Not dilated. Sounds soft irregular in all respects. Soft blowing mitral systolic murmur.
Thyreoid. Characteristic bilateral enlargement.
Eyes. Slight exophthalmos.
Respiratory System. Normal.
Alimentary System. Pyrhorroea alveolis and gross carious changes in all teeth.
Renal. Normal.
Nervous System. Reflexes all exaggerated.
Tremor of fingers and tongue marked.
Basal Metabolic Rate. Plus 6%.
Treatment.
Blaud's pill grains 3 t.i.d. Total teeth extraction.
When examined one year later the cardiac symptoms and signs were nil. Pulse 80 and regular.
Thyreoid enlargement greatly improved. No exophthalmos and patient able to lead a perfectly normal healthy life.

2. Unmarried female aged 30. Complains of nervousness, sweating and undue breathlessness upon exertion.
Twelve years ago she noticed presence of slight swelling in front of neck, perspired profusely and became rather nervous. At that time she had several carious teeth which were removed and the symptoms improved. For the past six months she has complained of a return of the nervousness and sweating, with in addition some breathlessness.
Examination.
Pulse regular in all respects, good quality. Rate 96.
Heart not dilated. Sounds regular and pure.
Thyreoid. Palpably enlarged, characteristic with systolic murmur.
Teeth. Five upper, seven lower teeth grossly carious.
Eyes. Pupils react to light and accommodation, equal. Slight bilateral exophthalmos.
Nervous System. All reflexes normal. Slight tremor of fingers.
Other systems. No abnormality detected.
Basal Metabolic Rate. Plus 10%
Treatment.
Extraction of all remaining teeth.
Re-examination one year after treatment.
Patient states that she enjoys perfect health, all of former symptoms have cleared up. Gland is not now palpable.
Basal Metabolic Rate by formula. Plus 3%.
Blood Iodine. 21 gammas per 100 c.c. blood.

It is stated that toxaemias of infectious origin seem to have a special tendency to stimulate the autonomic nervous system [1] and so, it is evident, that when a person is endowed with a nervous system which is functionally below par that such an influence will have a more profound effect than in the normal subject, being liable to upset the neuroendocrine balance and increasing the risk of toxic goitre.

3. Sympathetic Theory.

It was recognised in a comparatively early stage of the study of toxic goitre that many of the symptoms and signs were similar to those developing upon stimulation of the sympathetic nervous system.

Evidence was put forward in favour of this statement by Cannon [2] who was able to produce in cats, by fusing the phrenic and cervical sympathetic nerves, a syndrome closely resembling Graves' Disease.

In the animals so treated the thyreoid was rendered hyperplastic and the adrenal cortex greatly hypertrophied. Means states that Cannon [3] now believes the sequence of events to be first a nervous stimulation of the pituitary, and secondly thyreoid stimulation via the anterior lobe of the pituitary. This opinion was expressed at the time when the thyrotropic hormone had been discovered, and when Professor Means and his co-workers were engaged upon its study, so that it may have been, on Cannon's part a hasty adaptation of his original view to meet the requirements of advancing knowledge.

It is an opinion which has no basis upon any fact observed in regard to the pituitary body. There is no mention in the literature of the pituitary being influenced by sympathetic stimulation to produce thyrotropic hormone, on the other hand, the secretory innervation of the adrenals is by way of the abdominal sympathetic cord through the

1. Bram. Exophthalmic Goitre. 43.
2. Cannon. Binger and Fritz. Amer.Jrnl.Physiol. 1915. 36. 363
3. Means. Thyreoid Gland and its Diseases.

medium of the aplanchnic nerves [1], it may well be then that the correct interpretation of Cannon's experiment is an initial stimulation of the adrenal medulla with resulting excess of adrenalin in the blood, stimulating in turn the myoneural junctions of the whole sympathetic nervous system with especial regard to the thyreoid gland and so leading to the characteristic findings of these classical experiments.

Should that be the case it is further evidence in support of the theory that the cause of toxic goitre lies in part, in an excessive secretion of the adrenal medulla stimulating the thyreoid gland and effecting a condition of general sympathetic hypertonus, with upset in the neuro-endocrine balance and the development of the disease.

The symptoms of toxic goitre are not those of a pure sympathetic hypertonus, not are the signs; the pupils are not constant, they may or may not be enlarged, yet the sympathetic dilates the pupils; sweating is a marked feature, yet the sweat glands are not under the control of the sympathetic [2]; hyperaemia of the gland is the rule at operation and yet to cause that in the experimental animal section of the sympathetic is necessary [3], although the writer has watched in the rabbit the thyreoid become hyperaemic following a large dose of adrenalin hydrochloride 1/1,000 solution, when it may be assumed that a sympathetic effect was being produced. There is no doubt but that the sympathetic plays an important part in the etiology of toxic goitre, but only in association with certain other factors, notably the adrenal glands, the influence of environment, external stimuli and heredity.

4. Bulbar Theory.

The belief in a Bulbar origin has now been

1. Wright. Applied Physiology. 177. 1936.
2. do do
3. Bram. Exophthalmic Goitre.

universally discarded. It probably evolved because of the gross nervousness and excitement, exaggeration of the superficial and deep reflexes, and association with psychic trauma which have so constantly been mentioned by authors all through the literature.

There are no constant changes found at autopsy in the central nervous system in cases of thyreoid disease and such as are found are constant neither in nature nor in site.

5. Thymus Theory.

There is a general concensus of opinion amongst those who have studied the thymus that its function is related to growth [1], and since toxic goitre is definitely a catabolic disturbance a lesion in the thymus has been suggested as a possible cause.

Bram, quoting Adler[2], states that pregnant guinea pigs fed on large doses of thymus abort and have haemorrhages into their adrenals. When smaller doses are given the embryo develops much faster than usual and pregnancy is shortened. The association here with the adrenals is noteworthy, but the evidence is not enough to suggest an association with toxic goitre.

On the other hand Blackford and Fry [3], following examination of a hundred fatal cases of toxic goitre found that a hypertrophic thymus was present in all under forty years of age and in half of those over forty. They also stated that the menopausal group had little or no thymic involvement. They arrived at the conclusion that the thymic hyperplasia should be regarded as a result and not as a cause of thyreoid hyperplasia.

The writer noted the presence of enlargement of the

1. Cameron. Recent Advances in Endocrinology. 1934. 380.
2. Bram. Exophthalmic Goitre.
3. Blackford and Fry. Collected Papers of the Mayo Clinic. 1916. 8. 507.

thymus in five of a series of fifteen white mice treated over a period of ten days with injections of adrenalin. The mice were fully grown adults. At the end of the course there were obvious signs of loss of weight, emaciation and falling out of the hair with considerable tachycardia and increased body activity. The full results of this investigation are detailed in page 85 , but at present it is sufficient to note that the thymus was found to be enlarged in five instances.

6. Parathyreoid Theory.

One of the classical signs of toxic goitre is tremor of the outstretched fingers, and Gley, quoted by Bram [1] regards the tremor as indicating a parathyreoid derangement.

There is also in toxic goitre an alteration in the calcium metabolism of the body [2] which points to some parathyreoid influence, but it does not follow of necessity from these observations that within the parathyreoid bodies lies the cause of the disease itself.

Stengel in 1902 [3] was one of the first directly to lay the onus upon the parathyreoids and his reason for so doing was based upon the histological findings in the central nervous system following removal of the glands in eight dogs.

In the light of all that is now known it is certain that these bodies have little or nothing to do with either etiology or pathogenesis of toxic goitre.

7. Gonad Theory.

Many isolated facts have been observed by various workers regarding an association supposed to exist between the ovaries and the thyreoid.

1. Bram. Exophthalmic Goitre. 31.
2. Aub. Tr. Assoc. Amer. Physic. 1927. 42. 344.
3. Stengel. Progressive Medicine Volume 2. 1902.

Attention may have been drawn originally to the ovaries because of the fact that toxic goitre is so much more common in females than in males...seven to one in the present series, while in the Mayo Clinic, as quoted by Joll there were 85% females to 15% males. Campbell [1] carries this connection a little further and says, "It is well known that Graves' Disease is most likely to occur in women who are not married or who have not borne children". Eason [2] remarks that probably no disease is so influenced by sex, and according to him the explanation lies in the basal metabolic rate which he says is, in the adult male, five to ten times more steady than in the adult female.

In amplification of Eason's statement it may be said that there is a much greater complexity and finer adjustment of emotional structure in the female than in the male, and that in the female endocrine system, especially in the pituitary and reproductive glands, there is a continual ebb and flow of activity taking place.

Such being the case it is easy to understand how much more easily upset that finely balanced mechanism may be than in the more stable male.

The age incidence of toxic goitre is of interest in this connection. In the present series the figures were as follows.

Decade	1	2	3	4	5	6	7	8
Age Groups	-	8	19	21	16	12	2	-

Two of the cases in the second decade developed before puberty and six following some years after puberty; sixty-two cases of the seventy-eight developed during the period of active sexual life, and of these, fifty-eight were females. Of the seventy-eight patients sixty-nine were females, five of whom developed the disease during the

1. Campbell. Quart. Jrnl. Med. 1924/25. xviii. 191.
2. Eason. Exophthalmic Goitre. 127.

menopause and five during pregnancy, but in no instance did it appear within two years of puberty either before or after the onset.

The figures published vary in actual percentages occurring during the times of unduly active sexual life, pregnancy, puberty and the menopause, but in none of the papers consulted was there a significant increase at those times.

From experiments upon animals however, it appears that there is taking place in the thyreoid very definite changes during these so called 'critical' periods. According to McCarrison [1] the mode of growth of the thyreoid is a spurt in earlier life and a retardation later, the gland weight being maximal at puberty.

It is of interest that the time of greatest weight of the gland corresponds with a period of hyper activity on the part of the ovary, but that is one of the periods of maximal growth and activity of the body as a whole and the thyreoid is only demonstrating what is going on in almost every other tissue to a greater or a less degree.

There is, however, a belief that size is related to function, and so it is not unreasonable to suppose that puberty is the period of greatest activity in the normal thyreoid; that fact is not significant as regards the etiology of the disease in that only a very small proportion of cases are found occurring at that time.

The truth of the matter as regards the Gonad theory is expressed by Gardiner Hill who says that "Menstrual upset does not seem to play an important part in the cause of most adolescent Graves' Disease". [2]

1. McCarrison. Recent Researches into Etiology of Goitre. Verhandlungsbericht. 354. 1935.
2. Gardiner Hill. Quart. Jrnl. Med. January, 1929.

8. Pituitary Theory.

At various times in the literature there have been described cases of acromegaly with associated Graves' Disease, and the writer has personally seen and examined one woman who, with gross signs of acromegaly, and who upon X-ray examination of the skull was found to have considerable distortion of the sella torcica with erosion of the anterior clinoid processes, by what was diagnosed by Mr. J. Eric Paterson as being most probably an adenoma of her pituitary gland, and yet, who had in addition, definite signs and symptoms of hyperthyreoidism. The basal metabolic rate was plus 110%, the pulse elevated to 109, there was a considerable degree of nervous and emotional upset, tremor of the finger and some fullness over the thyreoid. The case responded well to deep X-ray therapy directed towards the adenoma and when last seen, her basal metabolic rate, as calculated by formula had dropped to plus 48%, there being an associated improvement in the signs and symptoms of both the hyperthyreoidism and the acromegaly.

Such a state of affairs raises the interesting question as to what relationship, if any, may exist between the anterior lobe of the pituitary gland and the thyreoid.

Crile [1] states that the thyreoid is outstandingly primordial among the endocrines, and that its function is fundamental, but that with the progress of evolution the anterior lobe of the pituitary has come to hold all the other glands in subjugation, controlling their function.

Loeb and Kaplan, quoted by Means [2], stated in 1924, on the basis of animal experiment, that in mammals thyreoidectomy was followed by an enlargement of the anterior lobe of the pituitary, and that this enlargement could be prevented by the administration of thyreoid extract.

1. Crile. Tr. Amer. Med. Assoc. 1934. 23.
2. Loeb and Kaplan. Jrnl. Med. Research. 1924. 44. 557.

This suggestion that thyreoid insufficiency stimulated the pituitary to activity verified the observation made by Cushing [1] in 1912, that after complete removal of the pituitary in dogs there followed a transient hyperplasia followed by involution of the thyreoid, implying that the latter organ requires for its normal activity some sustaining influence derived from the pituitary.

Completely successful and total removal of the pituitary is rare in Man, but a syndrome closely resembling it is found in Simmond's Disease which amounts to a natural and uncomplicated complete hypothysectomy in the human subject. In this condition the thyreoid is definitely hypofunctioning, presumably because the sustaining pituitary influence has been removed. In 1922 weight was added to this theory by the work of I. P. and P. E. Smith [2] who, by experiments upon tadpoles proved that the pituitary does exert a sustaining and stimulating influence upon the thyreoid through the secretion of its anterior lobe.

In 1930 Loeb and Bassett [3] carried this research a step further and proved that in guinea pigs stimulated by extract from the anterior lobe of the pituitary there developed a train of symptoms and signs closely resembling those of toxic goitre, and that the changes in the thyreoid were those of hyperplasia resembling those in the toxic goitrous human subject.

In 1931 Verzar and Wahl, quoted by Means, found that injections of the anterior pituitary raises the basal metabolic rate of guinea pigs, that this is not found in the thyreoidectomised animal and that the administration of iodine prevents the basal metabolic rate from being raised under such circumstances. On the other hand, Cameron [4]

1. Cushing. The Pituitary Body and its Disorders. Lippincott Co., Philad.
2. I. P. & P. E. Smith. Jrnl. Med. Research. 1922. 43. 267.
3. Loeb and Bassett. Proc. Soc. Exper. Biol. and Med.1930. 27
4. Cameron. Recent Advances in Endocrinology. 1934. 341. (490

states that extirpation of the pituitary, in part only, causes a lowering of the basal metabolic rate with resulting subnormal temperature.

Okkels [1] in 1932, examining the problem from the point of view of the physiological histologist, noted upon examination of thyreoid sections that twenty minutes after the injection of anterior pituitary extract the Golgi apparatus was swollen and hypertrophied, the acinal colloid was becoming vacuolated and that there was hyperaemia of the gland with elevation of the basal metabolic rate. Since the Golgi apparatus does not hypertrophy except during secretion it may be assumed that the effect of the injection was to cause initially an increased absorption and then an increased rate of secretion. In 1930 Aron, quoted by Means, conducted an investigation into the problems of the thyreoid-sustaining substance of the anterior pituitary, approaching the problem from the possible excretion of such a principle in the urine. The urine first used was that from persons suffering from hyperthyreoidism. Injection of such urine or its extracts into animals failed to produce any noteworthy changes in the thyreoid. When however urine from hypothyreotic subjects was used for the experiments definite changes followed, the thyreoids being stimulated to increased activity. The results from urine of normal subjects were unequivocal.

Accordingly it is seen that in toxic goitre there is a diminished output of the thyrotropic principle, while its excretion is increased in cases of hypothyreoidism. The effect of thyreoid atrophy is thus to stimulate the secretion of the anterior lobe of the pituitary, and as we have seen, removal of that organ promotes subnormal activity on the part of the thyreoid. A definite relationship was thus proven to exist between the two glands.

1. Okkels. Acta. Path Et Microbiol. Scand. 1932. 9.1.

The thyreoid-sustaining principle has been called thyrotropic hormone, and since its presence was first assumed an extraordinarily large amount of work has been devoted to ascertaining its properties.

One of the first observations to be made was that in animals treated by it over a period while the initial response is one of thyreoid hyperplasia and stimulation with elevation of the basal metabolic rate and other symptoms resembling those of toxic goitre...hyperaemia of the thyreoid, and even exophthalmos, [1] these effects are not maintained, but that the calorigenic action wears off leaving the final basal metabolic rate even lower than formerly.

There are several possible explanations of the phenomenon. It may be that there is an exhaustion involution of the thyreoid...the cycle of Marine. It may be due to a tolerance to the effect of the injections just as a tolerance may be developed to certain drugs, it may be due to the formation of immune substances within the organism as takes place upon the introduction of foreign proteins into the circulation, or lastly, as suggested by Collip, it may be due to the formation of antihormones.

As regards the possibility of an exhaustion insufficiency, that may be looked upon as a possible explanation, but not as the probable; and for this reason. Toxic goitre is not as a rule a self limiting disease, and its occurrence with signs of myxoedema very unusual. In such instances it may well be that the exhaustion theory of Marine may find a place, but there is a constancy about the restricted effect of thyrotropic hormone which impels one to look elsewhere for the explanation.

One may acquire a tolerance for morphia, for arsenic, or for practically any drug, but so far it has

1. Cameron. Recent Advances in Endocrinology. 1934. 360.

not been suggested that a tolerance may be acquired against a normal body secretion, and that is what thyrotropic hormone may be regarded as being. It is secreted constantly, and, under normal conditions in very small quantities, merely sufficient to satisfy the body requirements. Why then should a tolerance be developed ? The only differences are that in the one case the substance is introduced by an artificial route into the blood stream, while in the other it reaches the tissue directly from the gland itself; and secondly the chemical constitution of the hormone may be altered from that of the freshly secreted substance according to the particular preparation used. The idea of a tolerance may be dismissed.

Cameron [1] states there is some evidence to suggest that the serum of myxoedematous patients may contain an antithyrotropic substance, a substance which is truly antithyrotropic rather than antithyreoid, because it prevents thyreoid hyperplasia in response to thyrotropic treatment, yet it does not prevent a metabolic response on giving thyreoid preparations. He also observes that "Its solubility appears to distinguish the antithyrotropic substance from the immune bodies ordinarily evoked by injections." The same author also notes that Collip [2] is inclined to believe that such antihormones do not merely appear in experiments, but are normally present in the circulation, in other words that there is a maintained normal balance in the organism between the hormone and the antihormone, a balance which may be deflected in one direction or another, either experimentally or in pathological conditions, and suggests that the response of an animal to a given dose of hormone varies inversely with the

1. and 2. Cameron. Recent Advances in Endocrinology. 1934. 396.

quantities of antihormone already in the circulation.

Most of that evidence is in the realm of theory, but one excellently controlled series of experiments has brought forward strong evidence in support of the hypothesis that the antihormone is in the nature of an immune body response.

Sidney Werner [1] conducted a series of experiments upon guinea pigs. One hundred animals were used for the purpose, the work being properly controlled throughout. The basal metabolic rate and the iodine content of the gland were taken as the indices of thyreoid activity.

Two different preparations of anterior pituitary extract were used, one prepared by the sodium sulphate method, the other by the flavinate. The flavinate preparation rarely caused any refractoriness to develop in the animals treated, while the sulphate preparation invariably did, and it was observed that the refractoriness of the animal to the sulphate preparation was overcome when an animal immune to that preparation still evoked a response to the flavinate. He concluded that the preparation is acting as an antigen resulting in a neutralising antibody.

There is now on the market a preparation which claims to be the thyrotropic hormone in a more or less pure state, but so far it has not been used, to the best of the writer's knowledge, in the clinical treatment of any thyreoid condition.

In its preparation some form of standardization was needed, and Cuyler, Stimmel and McCullagh [2] evolved a method for its biological assay depending upon the influence it exerts upon the iodine content of the thyreoid gland. They define one unit as being that amount which, when injected into the peritoneal cavity daily on three successive days

1. Werner. Endocrinology. March 1938.
2. Cuyler, Stimmel & McCullagh. Jrnl. Pharmacol. and Exter. Therap. 1936. 58. 286.

causes a 50% decrease in the percentage iodine in the thyreoid glands of normal guinea pigs whose body weight is not more than ten or less than eight ounces. .75 milligram represents about one guinea pig unit of this hormone.

It has thus been definitely established that of the many hormones produced by the anterior lobe of the pituitary body there is one which exerts an important influence upon the thyreoid gland. It may further be assumed that this hormone is normally produced in very minute quantities, and that in persons in whom thyreoid activity is below par, there is a stimulating effect upon the pituitary causing an increased production of the thyrotropic hormone with its resulting excretion in the urine. The object presumably, is an endeavour on the part of the pituitary to restore the thyreoid to its former efficiency.

The fact has also been established that, in the experimental animal at least, the thyrotropic hormone has a self limiting action in that the thyrotropic response is not maintained, and it is not unreasonable to suppose that the same self limiting effect is present in Man, always assuming that thyreoid hypofunction produces hyperactivity on the part of these cells in the pituitary which produce the thyrotropic hormone.

From the available evidence it appears certain that even were the pituitary thus stimulated to produce an excessive quantity of thyrotropic principle, and that even were the thyreoid being constantly stimulated by it, the result would not be toxic goitre but more probably an initial degree of mild hyperthyreoidism followed by a mild degree of myxoedema.

Accordingly, the position with regard to the pituitary body seems to be that the anterior lobe normally exerts a controlling and subjugating influence upon the thyreoid, an influence which may be extended to stimulate

the latter gland when it is working at a subnormal level, but that it probably has nothing to do with the actual production of toxic goitre.

One other fact of interest is that while there is abundant evidence proving the influences of the pituitary upon other cells and glands in the body, there is extraordinarily little written about the other side of the picture, namely, what influences if any have a directly stimulating effect upon the pituitary itself.

9. Adrenal Theory.

This maintains that a deranged structure and function of the suprarenal glands are responsible.

One notable fact with regard to the adrenals is that their name is constantly cropping up in association with other theories regarding the cause, and there are many references in the literature to points observed in connection with their pathology in toxic goitre.

One other equally noteworthy feature is that there is no constancy in the structural changes described [1]. In this connection Joll observes that it is doubtful if there is any firm basis for the theory of an adrenal origin for toxic goitre, and says that even the exponents of that theory are at variance among themselves as to the nature of the processes at work. Be that as it may, there is no doubt but that a vast amount of evidence has accumulated to point out while even if adrenal dyscrazia may not be per se the actual cause of the disease, that at least it has a good deal to do with the cause and also of many aspects of the pathogenesis.

It has long been apparent to the writer that many of the signs and symptoms of toxic goitre can be divided into two main groups, those resembling suprarenal cortical hypofunction, and those resembling suprarenal medullary hyperfunction.

1. Joll. Thyreoid Gland.

Hyperactivity of the medulla is evidenced by the increased nervous tension, elevated basal metabolic rate, tachycardia, the not infrequent glycosuria, hypertension, and possibly also by the exophthalmos.

Cortical hypoactivity, on the other hand, is manifested by the asthenia, loss of weight, occasional presence of skin pigmentation, uric acid retention and by gastrointestinal upset; many of the aspects of Addison's Disease resemble toxic goitre very closely.

Swiecicki [1] also inclines to the view that a hypermedullarism is a possible explanation of many of the symptoms, especially those of vasomotor origin, and Marine, quoted by Bram [2], states "My own view of the fundamental lesion in exophthalmic goitre is that of an exhaustion insufficiency of the adrenal system."

These opinions are arrived at by consideration of the clinical picture of the disease, but a study of the adrenal pathology presents a less conclusive argument.

Holst, quoted by Means, states that there is at times hyperplasia of the adrenals, particularly of the cortex, but that it is not constant. In certain of Means' cases there was pigmentation of the cortex, and in one, the cortical cells were vacuolated. That last fact is of interest in respect that in one of the writer's cases there was also vacuolation of the cortical cells, with in addition, small adenomata encroaching upon the medulla.

The writer examined the reports of all autopsies performed on cases of toxic goitre in the Victoria Infirmary between the years 1927 and 1937, and found no constancy in lesions described. In only one instance had the adrenals been sectioned, and the findings were vacuolation of cortical cells, small cortical adenomata encroaching upon the medulla, and in addition some medullary hyperaemia.

1. Swiecicki. Presse. Med. Paris. 1921. 10. 686.
2. Bram. Exophthalmic Goitre. 31.

In a personal communication Dr. John Anderson, pathologist to the Victoria Infirmary, stated that he had rarely in toxic goitre noted the presence of adrenal pathology, but that in his experience the lesions most commonly found were cortical adenomata, generally small and noticed only when the organs were cut open. Hypertrophy, he said, was in his experience rare.

Such findings are in keeping with the histological picture of the thyreoid itself. There, while signs of activity may be noted... hyperaemia peripheral vacuolation of or diminution in the colloid content, swelling of cells and displacement of nuclei, the fact remains that there is no description of the thyreoid in toxic goitre which may accurately describe the histology of even the majority of cases. Nor are the lesions in pituitary or ovary constant. That being the case, it is quite to be expected that the adrenal histology will be in keeping with the confusing pictures presented by other glands.

Since it is accepted that the pituitary holds almost all other glands in subjugation, and that their functional integrity is dependent upon the anterior pituitary [1], it is necessary at this point to determine what is the adrenal pituitary relationship.

Long [2] observes that in pituitary basophil adenomata, hypertrophy of the adrenal cortex is common. The autopsy reports on cases of pituitary adenomata performed in the Victoria Infirmary during the years 1927/37 were examined. In no instances were the supra-renal glands examined microscopically, but in each case the microscopic appearances were normal.

The fact appears to have been established that the anterior lobe of the pituitary secretes an adreno-corticotropic hormone, but there is no evidence of the

1. Long. Ann. Int. Med. 1936. 9. 1619.
2. do do

pituitary affecting the adrenal medulla in any way. Further, the effect of this hormone upon the adrenal cortex appears to be more intense than that of the thyrotropic hormone upon the thyreoid in that complete atrophy of the adrenal cortex follows hypophysectomy while the thyreoid yet continues to function, although at a subnormal level.

In Addison's Disease it is stated that there are changes in the basophil, and slight reduction of the eosinophil granules contained within the chromophil cells of the anterior pituitary, but so far it has not been proved that the adrenal-cortical hormone has any influence upon the function of the pituitary, in spite of that evidence.

In section IV of this thesis the thyreoid adrenal relationship has been discussed in some detail and the outstanding features of both glands have been noted as regards the production of toxic goitre. There is no doubt but that the supra renal bodies are intimately connected with the etiology of this disease, but only in so far as they are related to the thyreoid and to the autonomic nervous system. It is quite in error to consider that the primary lesion is an intra adrenal pathology, and so the Adrenal theory is untenable as it is understood at present. The lesion is one of adrenals, thyreoid and autonomic nervous system acting in combination.

10. Psychical or Neurogenic Theory.

This lays emphasis upon the known fact that there is a frequent association between shock of one kind or another causing a strain upon the nervous system and the onset of toxic goitre. Such psychic trauma or emotional strain may take one of many forms, may centre round home worries, domestic incompatabilities, unsatisfactory sex life, financial worry, and the strain of nursing relatives over a long period, or may take the form of a severe physical shock such as an accident in train, car or other conveyance, while not infrequently there is a combination of several.

It has been said with truth, that there is a close resemblance between the effects of immediate terror and signs of chronic toxic goitre. The heart beats violently, there is palpitation, trembling of all the musculature of the body, the eyes start forward and the eyeballs may become fixed, there is flushing of the face, vasomotor upset and profuse perspiration.

Such a picture is that of gross sympathetic hypertonus, and in the case of terror, in the vast majority of cases those effects wear off within a short time; but there have been recorded cases when the terror initiated a train of symptoms and signs which ended in the development of true toxic goitre. Such can occur only when the nervous system fails to recover its equilibrium after the initial shock, that is where there is an unstable neuroendocrine system. Such a dramatic onset is found in very few cases, although the writer has seen one such as a result of the Castlecary rail disaster. Vidi.

Male patient aged 56.
Past history. Three years ago patient was operated upon and a gastro enterostomy performed on account of a chronic gastric ulcer. Patient states that he has always been

inclined to worry too much, that his operation worried him very considerably and that for several months after the operation he was nervous, and lost almost six stones in weight during the subsequent year. For the past two years he has enjoyed indifferent health, but has always been able to attend to his business. The main complaints were a degree of nervousness, emotional instability, and asthenia with some breathlessness upon exertion. One year and a half ago he had a course of deep X-ray therapy to his thyreoid gland. with some resultant improvement in his general condition. During the period of treatment a slight degree of exophthalmos developed and has remained since.
Present history. Patient was in the Castlecary rail disaster. He had been asleep at the time of the accident and awoke to find himself in a wrecked carriage in which many people were killed and others seriously injured. He sustained a profound mental shock and an immediate exacerbation of his nervous symptoms. The following morning his wife commented upon his appearance and sent him to the doctor, who diagnosed acute toxic goitre.
Condition upon Examination. Patient a sparely built man, gray hair, pale complexion, restless, very nervous and showing a moderate degree of bilateral exophthalmos.
Patient highly irritable.
Pulse. Of fair quality and regular in all respects. Rate 98.
The heart not dilated to percussion. Sounds soft at all areas and a soft apical systolic murmur was present.
Blood pressure. 142/76.
Respiratory System. Nothing abnormal detected.
Alimentary System. Upper right paramedian incision scar present.
There is some slight epigastric abdominal tendencies and deep palpitation.
Renal System. Nothing abnormal.
Nervous System. All tendon reflexes are brisk. No other abnormality noticed.
Skin. There is a considerable degree of perspiration. Pigmentation under the eyes is marked.
Thyreoid Gland. Slight characteristic enlargement, both visible and palpable affecting both lobes and isthmus.
Basal Metabolic Rate. Plus 42%.
Blood Iodine. 114 gammas per 100 c.c. blood.

That is a good example of severe psychic trauma and terror being productive of the disease in a suitable subject. When however, a less dramatic state of emotional upset is maintained over a prolonged period in a similar subject, then the same sympathetic hypertonus is produced, and with the same end result.

This theory supposes that emotional traumata and the like are exciting causes and that the struma of the disease is secondary. Of the association with such emotional upheavals there can be no doubt whatever. The fact is admitted by most writers, although the figures for its incidence vary greatly from 90% in Bram's series to 25% in Means', and 50% in Joll's to 96% in Eason's. In the present series it was clearly present in 78%.

Eason goes so far as to say [1] that failure to elicit this evidence of nerve strain is usually due to inadequate or unskilled enquiry, but Joll maintains that it is not possible to assess the value of these histories of psychic traumata since he says that nowadays it would be difficult to find a person in whom by assiduous questioning it would not be possible to elicit such a history, and that furthermore it must be proved that there is a greater incidence of psychic traumata among persons with toxic goitre than amongst the general population before the theory can be of value.

The point raised by Joll is apt and legitimate.

It is agreed that with the stress of modern times it would be difficult to find many who lead an absolutely untroubled and placid life with no care as to health, money, relatives, or business, but the fact remains that it is because of this stress of modern life that toxic goitre does exist and is actually increasing in its incidence.

Bram [2] says that toxic goitre is a part of the price that is paid by the human race for the delights of participation in the rapid march of civilisation towards... we know not what. Marine also wrote [3] that "The incidence

1. Eason. Exophthalmic Goitre. Page 40.
2. Bram. Exophthalmic Goitre. Page 41.
3. do do do Page 36.

of the disease is increasing in all industrial countries", while authors throughout all of this present century have drawn attention to the prime importance of psychic trauma in the etiology. [1.2.3.]

Such evidence cannot lightly be ignored. It is significant. In no other disease is the importance of emotional strain so insisted upon by clinicians as in toxic goitre, and although actual statistics may not have been compiled to prove a greater incidence amongst those persons with toxic goitre than in the general public, such is almost certainly the case. One important amendment must be made, however, these influences provoke the onset of the disease because the persons who are subjected to them are inherently susceptible to its development; the ordinary healthy person endures with impunity, but one with Graves' Constitution develops toxic goitre in a length of time varying inversely with the degree of constitutional disability present.

11. The Kinetic Theory of Crile.

This is based upon the hypothesis that toxic goitre is due to dyscrazia of the kinetic system, that is to say the thyreoid, adrenals, brain, and sympathetic nervous system, and supposes that the symptoms and signs take origin outwith the thyreoid, changes in that organ being the result and not the cause.

Crile's view closely resembles those of Eason and Bram, indeed all three have much in common. All realise that there is more than one organ implicated, and that the main cause lies outwith the thyreoid, they admit the importance of emotional traumata and note the presence of

1. Murray. Lancet 1902. Vol. 2. 1612.
2. McKenzie. Allbutt and Rolleston. System of Medicine. London, 1908. Part 1. Vol. 4. Page 359.
3. McCarrison. Thyreoid Gland in Health and Disease. London, 1917.

a constitutional liability.

The kinetic theory stresses particularly the importance of our intense mode of life, and emphasises the psychoneurotic element in the etiology [1].

12. Eason's Theory.

This maintains that a liability to toxic goitre is unlikely in those who have inherited a stable autonomic nervous system and that it is prone to occur in families of a neurotic tendency. It furthermore notes that the disease is uncommon in persons of a strong physique. The importance of the emotional element as the provoking stimulus, with or without the presence of other stimuli such as infection, is remarked with emphasis as being the prime factor concerned, providing that the 'soil is suitable'.

Eason [2] says that individuals respond differently to these emotional upsets, those who develop toxic goitre having essentially an inborn or acquired diathesis, which renders them more liable than the average. Emotional strain he says is constant, and in the cases in which it is not admitted he suggests that probably it was present but to so trifling a degree as to be unrecognised, and taking place in the life of a person so unduly susceptible that, although trifling, yet sufficed to weigh the scales against him and produce the syndrome.

13. The Neuroendocrine Theory of Bram.

This is a combination of the neurogenic and kinetic theories and supposes that the patient suffers from an inherited neuroendocrinopathy which requires but the stimulus of psychic trauma or possibly infection to provoke the onset of symptoms.

1. Crile. Diseases Peculiar to Civilised Man. New York. 1934.
2. Eason. Exophthalmic Goitre. 38.

Absolute emphasis is laid upon the existence of a predisposing factor called the Graves' Constitution, and Bram states that this, while inherited to a greater or to a less degree may be intensified by environmental maladjustment, and notes also that the igniting stimulus may be so slight as to escape notice by the patient... such strenuous occupations as telephone operator or school teacher where there is a great expenditure of nervous energy, or an all consuming passion such as fear, hate or anger often being sufficient. In support of this contention evidence is submitted.

According to him [1] the stigmata of the Graves' Constitution are

1. Heightened cerebration.
2. Autonomic and Emotional Instability.
3. Excitable Heart.
4. Vasomotor ataxia.
5. Unduly sparkling eyes.
6. Unduly palpable thyreoid.
7. Lowered threshold of emotional excitement.

It is emphasised, however, that this constitutional susceptibility does not generally incapacitate the person but merely renders him more liable to develop toxic goitre when he is thrown by the forces of circumstance into a period of emotional or physical strain.

The description of the Graves' Constitution could be criticised on the ground that the thyreoid is not constantly palpable. If it is, then some hyperplasia has probably already taken place. As regards the heightened cerebration the subject while emotional, alert and probably vivacious is not usually above normal intellectually, in fact it would appear that no outstanding man or woman has

1. Bram. Exophthalmic Goitre. 48.

suffered from the disease during the eighty years since it became generally recognised [1].

From my own experience I would also include in this description an elevation in the basal metabolic rate, with a tendency for the children to be rather thin and of subnormal physique; in a proportion of cases the blood iodine is also elevated (Page 30).

Bram has described the Graves' Constitution and has found in case histories examples of how that was modified or intensified by environmental influences. He has brought from the literature arguments supporting his belief based upon accepted facts, physiological, anatomical and pathological, with the benefit of his own wide experience as clinician to support them. He has also recognised the existence of this necessary upset in the neuroendocrine balance which is needed to induce the response which we call toxic goitre, but although he has noted these facts and has explained convincingly how the adrenals are stimulated by emotion, yet he has not ventured an opinion as to the precise adrenal thyreoid relationship.

1. Eason. Exophthalmic Goitre.

Section VI.

The subject of toxic goitre has now been discussed from the point of view of all the varying influences which may play a part in the problem of etiology, and the more important theories held regarding that problem have been detailed.

As to the existence of the Graves' constitution there can be no reasonable doubt; the importance of this neuroendocrinopathy is considerable and it would appear that it is one of the basic factors in determining the onset of the disease. Toxic goitre is unlikely to develop in its absence, and even in those cases where evidence of its presence is not forthcoming it is probable that it is nevertheless still present. One can appreciate the difficulty of recognising it in mild degree, and it has been stated several times in the text that frequently the sufferer is not incapacitated and fails to recognise any departure from normal.

A considerable weight of opinion believes that this neuroendocrinopathy may be modified or intensified by environmental influences and that according to the degree of upset present so a longer or shorter time will be required, during which it is being strained by stimulant attacks made upon it, before the disease develops. It has been shown that an examination of the age incidence, sex incidence and geographical distribution supports the contention that the stresses of life play an important part in intensifying this constitutional liability to such a degree that toxic goitre develops, and that furthermore the disease appears to be uncommon amongst primitive peoples.

An investigation has been conducted into the iodine content of the blood and the basal metabolic rate in a series of patients treated for toxic goitre, and examined not less than one year after treatment, when the persons were satisfied that they had been cured of the disease. This investigation showed that the basal metabolic rate was still elevated and that the iodine content of the blood was, on the average, almost 100% above the average normal. The majority of these patients stated that they were enjoying health similar to that prior to the onset of the disease. These facts are further evidences in support of the existence of a constitutional liability. The patients examined had been restored to the state of health which had been their norm during the years prior to the onset of trouble. Clinical and biological tests suggested that an abnormal glandular, metabolic and nervous condition was still present.

The possibility of certain stimuli evoking the secretion of adrenalin has been discussed from the point of view of known physiological fact. There appears to be no doubt but that emotional traumata, physical stress and worry are capable of producing a flow of adrenalin, and likewise infection has been observed to have a similar stimulating effect upon the autonomic nervous system. The normal physiology of the adrenal organs and the properties of adrenalin have been noted, and there is reason for the belief that persons suffering from toxic goitre are abnormally sensitive to the action of adrenalin.

Experimental evidence suggests that adrenalin is capable of elevating the basal metabolic rate and also the iodine content of the blood, these effects being the more marked in persons endowed with the Graves'

Constitution and in cases where the toxic response has already taken place. Furthermore, on the basis of animal experiments there is evidence that adrenalin produces histological changes within the thyreoid suggestive of secretory activity, and associated with a marked rise in the blood iodine.

Such being the case it may well be that in the constitutionally liable, long continued emotional or physical strain, or other appropriate stimulus capable of stimulating the flow of adrenalin may promote a condition of persistent sympathetic hypertonus and chronic hyper-adreno-medullarism, reflecting upon the thyreoid gland and associated with relative vagal hypertonus and relative hypoactivity of the adrenal cortex.

Under such circumstances tissues are maintained at an abnormally high level of combustion, undue strain is placed upon the thyreoid gland, and within a comparatively short time the struma of disease may appear.

From experimental work performed upon animals some evidence has been submitted in support of the hypothesis that the adrenal medulla, through its secretion, stimulates the thyreoid by means of an influence exerted upon the thyro neural junction of the sympathetic nerve endings, and that this action can be demonstrated by the histological findings of glands which have been denervated, placed in their homologous sera and subjected to the action of adrenalin. The thyro-adrenal relationship appears to be a direct one and independent of the autonomic system.

As to the importance of intra thyreoid pathology in the form of previous simple goitre, adenomata or other neoplasms, these are capable of directly stimulating

the thyreoid secretion in the absence of any neuro endocrinopathy or other external stimulus. The hypersecretion which is evoked elevates the basal metabolic rate and at the same time upsets the normal endocrine balance so that symptoms of hyperthyreoidism shortly develop. This accounts for only a small percentage of all cases.

An investigation has also been carried out in regard to the iodine content of the blood. The blood iodine appears to be elevated in toxic goitre, and to a degree varying with the intensity of the disease. In a marked case it is at least 100% above normal, and in a series of thirty six cases examined prior to treatment an average reading of 35 gammas per 100 c.c. blood was obtained; the average reading in a series of eight healthy normal subjects was 13. The blood iodine galls with the basal metabolic rate in the successfully treated case, be the treatment medical, surgical or by radiation, but rises again when the condition relapses, and a good late result is associated with an iodine content approaching normal limits.

In conclusion, the words of Bram may be quoted. "Toxic Goitre, or Graves' Disease is a part of the price which is paid by the human race for the delights of participation in the rapid march of Civilisation toward... we know not what. Our intensive mode of existence, especially since the last war, and consequent unrest and vacillating standards of thought and action appear to be responsible for the undue sensitivity of the ductless glands and the involuntary nervous system. In a word, in recent years the predisposition to the disease is qualitatively and quantitatively increased."

As regards etiology, a considerable body of opinion is tending towards the conclusions expressed in

this thesis with regard to the importance of the Graves' Constitution, and the menace of emotional trauma to such persons.

Further work will be required to prove or disprove these theories, and to elucidate the problem fully and finally, but one may express the hope that, as a result of future advances in Medicine and a more clear general understanding of the condition, it may gradually become as rare as it now is common.

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