THE NATURE OF ENDOCRINE EXOPHTHALMOS.

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Introduction

In 1786 Parry noticed the association between enlargement of the thyroid gland and the development of exophthalmos. This observation was published in 1825, following his death, in a collection of his unpublished medical writings, but it did not receive general recognition. In 1835 Graves re-described the syndrome which since then has been known as Graves' disease, but it is also sometimes called Basedow's disease following the detailed description of the condition by Basedow in 1840.

The problem of the nature of exophthalmos occurring in relation to endocrine dysfunction has been studied extensively during the past century in the fields of clinical and experimental medicine, and yet, despite the mass of facts which have been presented and the many hypotheses which have been evolved during that time, there is still no true understanding of the basic nature of the exophthalmic process.

During the nineteenth century scientists regarded the nervous system as the sole co-ordinator of the functions of the body. It is natural, therefore, that the mechanism of exophthalmos should have been sought within these confines.

The dawning of the present century saw the rising of the concept of a chemical regulation and co-ordination of bodily functions. From this there has emerged the science of endocrinology which has provided a great impetus to the study of experimental exophthalmos by opening up an entirely different field of investigation.

Aim and Scope of this Study

It is the purpose of this thesis to correlate as many as possible of the observations which have been made on endocrine exophthalmos and which contribute in any way to a deeper understanding of the fundamental mechanism in the production of endocrine exophthalmos. Certain of my own observations will also be included in the relevant parts of the text. This is, in part, a review, and it is hoped that every aspect of the problem will be dealt with fairly. To this end many conflicting views will be put forward, but it may be that when they are seen in their true perspective some of the apparently contradictory pieces of evidence will help to build up a clearer synthesis of the disease pattern, so that, as stated by Haines (1950) the ultimate answer to the problem will be achieved as a result of co-operation with other observers in tolerance and understanding, and as a result of a consideration in each programme of all the varied phases of the condition.

Classification of Endocrine Exophthalmos

There is a conflict of opinion on whether the two main forms of endocrine exophthalmos, first, that which appears to be dependent solely on thyrotoxicosis (thyrotoxic exophthalmos) and, secondly, that which although sometimes associated with thyrotoxicosis is apparently unrelated to it (thyrotrophic exophthalmos), are manifestations basically of the same hormonal disturbance, or whether they represent separate entities with different mechanisms. The terms thyrotoxic and thyrotrophic exophthalmos were put forward originally by Mulvany (1944).

Endocrine exophthalmos as a unitary concept

The exophthalmos of toxic diffuse goitre and the exophthalmos of a more progressive type which usually follows anti-thyroid treatment may be considered as fundamentally similar in nature (Rose, 1952, 1953; Devoe, 1954), and such a concept has found favour by Aterman (1954a) because of his finding that experimentally induced exophthalmos may be of all grades of severity despite the fact that the same basic method is used in its production.

It has been suggested by Brain (1955) that the difference between the thyrotoxic and thyrotrophic forms of exophthalmos may depend on the acuteness of the pathological process, on the

difference in the relative activities of the various hormones concerned in the pluri-glandular syndrome all of which are influenced by a basic hypothalamic-pituitary disturbance, and on the difference in the degree of responsive activity of the thyroid gland. In this way the thyroid gland may be regarded as the controller of the pituitary gland which acts as the producer of exophthalmos (Martens, 1947), and the differences in the clinical and pathological pictures of the two forms of exophthalmos are quantitative rather than qualitative (Soley, 1942; Hedges and Rose, 1953; Lamberg, 1954) with progressive exophthalmos as a more advanced stage of the exophthalmos of thyrotoxicosis (Pochin, 1945, 1946; Dresher and Benedict, 1950), or that the two conditions are similar in nature due to a common process which acts with differing severity, mildly in the thyrotoxic type and severely in the thyrotrophic type (Rundle and Pochin, 1944). Friedgood (1941) has termed the exophthalmos of Graves' disease and the malignant form of exophthalmos as reversible and irreversible phases of the same phenomenon.

Pathologically, Falconer and Alexander (1951), Ellis and Long (1953) and Iversen (1954) have failed to find any real distinction between thyrotoxic and thyrotrophic exophthalmos, and Day and Werner (1954) have shown that there is no significant difference between cases of mild and severe exophthalmos in the rates of removal of radio-active sodium following its injection

into the orbital fat. Furthermore, although there is evidence of a difference in the intra-orbital tension in the various forms of exophthalmos of Graves' disease (Copper, 1948), this difference would appear to represent a gradual variation from one case to the other so that the cases are not amenable to a division into two clear-cut categories (Kearns, Henderson and Haines, 1953).

Endocrine exophthalmos as a dual concept

There are many protagonists of the hypothesis that there is a true and basic distinction between the thyrotoxic and the thyrotrophic forms of exophthalmos (Mulvany, 1944, 1952; Brain, 1945, 1946; Azérad, 1948; Braley, 1948, 1953; Adler, Scheie and Dennis, 1949; Johnson, 1949; Purves and Griesbach, 1949; Ruedemann, 1949; Talwalker, 1949; Hirsch, 1950; Falconer and Alexander, 1951; de Gennes and others, 1951; Reeh and Singer, 1953), a distinction which is of practical importance from a therapeutic point of view (Beierwaltes, 1948, and Schlossman, 1953). Chandler (1950) also recognises two forms of exophthalmos which he calls dysthyroid non-congestive exophthalmos and dysthyroid congestive exophthalmos, and Cordes (1954) applies the terms non-progressive exophthalmos and progressive exophthalmos; names which describe the thyrotoxic and thyrotrophic forms of exophthalmos, respectively.

There is evidence that the exophthalmos which occurs as a primary manifestation of Graves' disease is to a large extent an apparent exophthalmos due to lid retraction (Braley, 1948, 1953;

Johnson, 1949), and lid retraction would appear to be a separate phenomenon from exopthalmos. For example, it has been shown that although thyroxine administration may be followed by the development of lid retraction it is never responsible for the production of exophthalmos (Brain, 1952), and conversely, that although successful anti-thyroid treatment in Graves' disease may cause a reduction in the degree of lid retraction, it is often associated with an increase in the degree of exophthalmos (Barr and Shorr, 1945; Haines and Keating, 1946; Lederer and Hambresin, 1951). There is also evidence that lid retraction bears a direct relationship to the toxicity of the thyroid gland, whereas exophthalmos bears an indirect relationship (Copper, 1948).

It would appear that the ocular changes of the ophthalmic form of Graves' disease (thyrotrophic exophthalmos) are not only independent of the hyperthyroid state (Rundle and Wilson, 1945) but are often related to a high level of thyrotrophic hormone (TSH) in the serum, whereas the ocular manifestation of pure thyrotoxicosis (thyrotoxic exophthalmos) are directly related to the hyperthyroid state and are associated with a high level of thyroid hormone and a low level of TSH in the serum, (de Robertis, 1948; d'Angelo and others, 1949; Purves and Griesbach, 1949; Chandler and Hartfall, 1952).

Further distinctions between thyrotoxic and thyrotrophic exophthalmos may be found from a pathological point of view (Rundle, Finlay-Jones and Noad, 1953), from an estimation of the

degree of retro-ocular resistance which is considered to be normal in thyrotoxic exophthalmos but increased in the thyrotrophic phase (Doyne, 1945; Means and Stanbury, 1950; Ferguson, 1951), and from the response of the exophthalmos to irradiation of the orbit which is usually a negative response in thyrotoxic exophthalmos but a positive one in thyrotrophic exophthalmos.

It is apparent, therefore, that opinion is divided on a classification of the exophthalmos of Graves' disease. It is difficult to substantiate a purely unitary concept in view of the obvious differences which exist between certain cases of exophthalmos. On the other hand, some observers find it difficult to accept a dual concept because of the fact that many cases exhibit a mixture of the thyrotoxic and thyrotrophic effects (Copper, 1948; Dayton, 1953).

It seems reasonable, however, to put forward the view that thyroid hormone exerts a certain effect on the eye, either directly or indirectly through the intervention of the sympathetic nervous system, whereas TSH (or some other related hormone) influences the eye in a different manner. In this way a purely thyrotoxic form of exophthalmos or a purely thyrotrophic form of exophthalmos may be produced, although in the majority of cases there is a mixture of the two effects (Spaeth, 1952, 1953a), usually with a preponderance of one of the effects, so that certain features of both forms of exophthalmos may be present at the same time. Such

a concept has been elaborated by Mann (1945, 1946a and b, 1950, 1951) who differentiates between three types of exophthalmos; first, exophthalmos due to thyroxine excess, secondly, exophthalmos due to TSH excess, and, thirdly, exophthalmos due to thyroxine and TSH excess. Similarly Means (1945) recognises three forms of Graves' disease; first, thyrotoxicosis without ophthalmopathy, secondly, thyrotoxicosis with ophthalmopathy, and, thirdly, a hyperophthalmopathic type which may be associated with hyperthyroidism, euthyroidism or hypothyroidism.

In any case the separation of exophthalmos into its thyrotoxic and thyrotrophic forms, even if unscientific, gives a useful clinical division (Porter and Walker, 1955) because they represent separate phases of the disease. They will be considered separately in this thesis.

PART I. Exophthalmos Related to Thyrotoxicosis (Thyrotoxic Exophthalmos).

Effects of excessive thyroid gland secretion

In thyrotoxicosis there is an excessive amount of circulating hormone which is secreted by the thyroid gland. This hormone was isolated by Kendall in 1915, and in 1919 he termed it thyroxine. Thyroxine was synthesized by Harington(1926). The metabolic fate of thyroxine is de-iodination (Benua, Albert and Keating, 1952). Rosenberg (1951) investigated the plasma of six cases of hyperthyroidism, following administration of a therapeutic dose of radio-active iodine (I^{131}), and he found that practically all the labelled organic iodine in the plasma existed as a single substance indistinguishable from thyroxine.

A measurement of the uptake of radio-active iodine by the thyroid gland may be regarded as a sensitive measure of thyroid gland function (Paschkis, Cantarow and Peacock, 1948), an increase in uptake indicating a hyperfunction and a decrease in uptake indicating a hypofunction, but Albert, Tenney and Ford (1952) considered that the amount of thyroid hormone secreted by the gland is a more accurate measure of function than the amount of hormone accumulated in the gland. Myant, Pochin and Goldie (1949) measured the amount of plasma cleared of iodine per minute, and they regarded this as a measure of thyroid function; in thyrotoxic states there is an increased clearance rate.

Ruedemann and Corrigan (1953) have emphasised that the measurement of the basal metabolic rate is not necessarily a true indication of thyroid function because it is a measurement of total gland function. They found that if a Geiger counter is applied to the surface of the thyroid gland, following the administration of radio-active iodine, small islands of hyperactivity may be found even when the basal metabolic rate is not unduly raised, and they considered that these islands may be of significance with regard to the relation of thyroid gland function to the occurrence of exophthalmos.

There are very few reports of pure thyroid administration being connected with the production of experimental exophthalmos, although Grobstein and Bellamy (1939) induced marked exophthalmos in this way in sexually immature fish (platypoecilus). Kunde (1927) produced slight exophthalmos with widening of the palpebral fissure in rabbits following administration of thyroxine. Similar experiments in the dog, however, gave negative results. Smelser (1937) showed that thyroxine causes exophthalmos in guinea-pigs, and Pochin (1944) demonstrated that this recession of the globe is due to a loss of orbital tissue. An interesting type of exophthalmos was found occurring spontaneously in certain young trout-fry (Hamre and Nichols, 1929). It was associated with marked hyperplasia of the thyroid gland, muscular weakness and emaciation. The condition could be prevented by the administration of iodine, and the primary upset appears to have been an excessive secretion

of thyroid hormone with the production of muscular weakness and exophthalmos.

Similarly in man, treatment with thyroid hormone has only rarely been associated with the production of exophthalmos. One of the earliest of such cases was described by Lawford in 1900. Brain (1936) demonstrated the production of unilateral exophthalmos and lid retraction in a woman who had been on thyroid therapy for many years. The exophthalmos subsided on discontinuing the thyroid extract. At that time Brain could only find eighteen similar cases in the literature. Justin-Besançon, Kohler and Schiff-Wertheimer (1934) found that, although thyroxine alone failed to produce exophthalmos, it did sensitise the eye to sympathomimetic drugs so that the joint administration of thyroxine and ephedrine produced some exophthalmos in a case of Graves' disease.

An excessive amount of circulating thyroid hormone appears to be responsible for the production of two main effects:-

(1) Increased excitability of the sympathetico-adrenal system (sympathicotonia).

Gellhorn and Feldman (1941) showed that in rats the administration of thyroxine causes a marked increase in the

excitability of the sympathetic nervous system. It is possible that thyroxine acts by sensitising the tissues to circulating adrenaline (Blau and McNamara, 1930), and it has been shown that thyroidectomy may be followed by a rapid diminution in sensitiveness to adrenaline (Eppinger and Levine, 1934). It is believed that thyroxine may exert this effect because of its ability to decrease the amount of amine oxidase within the liver, because it is known that amine oxidase is responsible for the destruction of adrenaline (Spinks and Burn, 1952). In this way thyroxine may potentiate the action of adrenaline. The increased excitability of the sympathetico-adrenal system is termed sympathicotonia (Barger and Dale, 1910).

A profound disturbance of the sympathetic nervous system is a characteristic feature of Graves' disease (Benedict, 1935), and, in fact, most of the manifestations of the condition, tremor, sweating, palpitations, etc., are sympathicotonic in nature (Kessel, Hyman and Lande, 1923). Evidence of some central sympathetic disturbance has been shown by a pupillographic study in 21 out of 22 cases of hyperthyroidism (Givner, Bruger and Lowenstein, 1947). Brock (1941) noted that a derangement of thyroxine secretion is followed by a derangement of other endocrine glands, particularly the adrenal medulla.

(2) Myasthenia of striated musculature.

There is considerable evidence that thyrotoxicosis may be associated with weakness of the striated muscles. Ayer, Means and Lerman (1934) demonstrated a case which developed progressive weakness of all the skeletal muscles in association with exophthalmic goitre. Thyroidectomy caused an improvement in the thyrotoxicosis and in the myopathy. In a case described by Fagin, Pagel and Sand (1944) weakness of the hands and arms was associated with weakness of the extra-ocular muscles. Starling and others (1938) reported two similar cases, in one of which there was obvious involvement of the extra-ocular muscles, with an improvement of muscular power following thyroidectomy. McEachern and Ross (1942) described three further cases of this type. An acute thyrotoxic myopathy, which is usually rapidly fatal, has also been reported as a rare complication of thyrotoxicosis (Heuer, 1916).

Lahey (1926) considered that weakness of the quadriceps femoris muscle is characteristically found in thyrotoxicosis, and he devised a clinical test to assess the power of the muscle in such cases. Shorr, Richardson and Wolff (1933) found a creatinuria in Graves' disease, and Marine (1940) reported a great reduction in the phospho-creatine content of the striated muscles. The inability

to retain ingested creatine indicates an upset in the phosphocreatine mechanism, and is further evidence of some abnormality of the striated musculature in thyrotoxicosis. The myasthenia of the striated muscles has been attributed to the direct action of excessive thyroid secretion on the muscle fibres (Brain,1938; Haines, 1939), and Haines found that the muscle weakness increases on the administration of desiccated thyroid.

Smelser (1944) suggested that the effect of thyroxine on the muscles might not be a direct one on the muscle fibres, but that it might be an indirect one dependent on the change in water content of the muscles following thyroxine administration. He found an increase in oxygen consumption of the extra-ocular muscles of the guinea-pig treated with thyroxine, but,after allowance had been made for the associated alteration in water content of the muscles, this increase was scarcely significant. This may indicate that the primary defect is an altered water balance.

Rundle and Pochin (1944) showed that in thyrotoxicosis there is an increased fat content of the extra-ocular muscles and of the levator palpebrae superioris muscle. This increased fat content occurs in direct proportion to the normal fat content of the muscles, and this suggests that the underlying mechanism

is an abnormal regulation of normal fat metabolism rather than a generalised deposition of abnormal fat. Similar fatty changes occur within the skeletal muscles although to a lesser degree of intensity. More recent work (Pochin and Rundle, 1949) has shown that the increased adipose tissue is a new tissue increasing the total bulk of the muscles and not merely a simple replacement of degenerated muscle fibres. These fatty changes which occur in thyrotoxicosis are particularly striking when one remembers that it is a wasting disease with loss of much general adipose tissue, a finding which has also been reported experimentally in rats (McKay and Sherrill, 1941).

The muscle weakness in Graves' disease is not due to any failure at the myo-neural junction, as in myasthenia gravis, and the weakness does not improve with prostigmine therapy, although, of course, myasthenia gravis may co-exist with thyrotoxicosis (Fraser,1937). Brody (1941) produced experimental evidence which conflicts with the concept of a normal myo-neural junction because he found that the ingestion of thyroxine in rats caused a decreased level of neuro-muscular activity. It is difficult, however, to assess the significance of this finding because

Brody obtained a similar decrease in neuro-muscular activity as a result of thyroidectomy. Thorner (1939) considered that Graves' disease and myasthenia gravis are mutually antagonistic. He based this conception on the improvement which occurred in the muscle weakness, following the onset of thyrotoxicosis, in a case of myasthenia gravis, and also on the fact that he found some improvement in cases of uncomplicated myasthenia gravis treated with thyroid extract. This see-saw balance between the two conditions has been shown also by McEachern and Parnell (1948) and by MacLean and Wilson (1954), because they found that the successful treatment of the hyperthyroidism which co-existed with myasthenia gravis caused a deterioration of the latter condition.

Mechanism of thyrotoxic exophthalmos.

It has been shown, in the discussion on the classification of endocrine exophthalmos, that it is difficult to establish a purely thyrotoxic form of exophthalmos, as distinct from the thyrotrophic form of exophthalmos which will be discussed in the next part of this thesis. In fact it may be that the only true thyrotoxic ocular manifestations are those associated with the eyelids (lid retraction, etc.), as suggested by Bonamour and Rougier (1951) and Philps (1953), and that exophthalmos has a uniform hormonal basis irrespective of whether it occurs in a hyperthyroid or a hypothyroid phase, so that lid retraction and exophthalmos may have entirely different mechanisms (Brunton, 1949). It is certainly significant that there is seldom any correlation between the degree of exophthalmos and the height of the basal metabolic rate (McCullagh, Ruedemann and Gardner, 1946).

This part of the discussion is concerned, however, with the ways in which exophthalmos may occur as a result solely of thyrotoxic influences.

There would appear to be three possible mechanisms in the occurrence of exophthalmos in thyrotoxicosis:-

(1) Exophthalmos due to smooth muscle overaction.

This theory is based on the known sympathicotonic effects of thyrotoxicosis.

It is interesting to recall that an upset of the sympathetic nervous system was the basis of the earliest theory of exophthalmos production, following the demonstration by Claud Bernard (1852) that section of the cervical sympathetic nerve trunk in the dog causes enophthalmos and ptosis, whereas stimulation of the cephalic end of the cut nerve produces exophthalmos and lid retraction. This observation has been repeated many times since then using different animals, for example, by Marine and Rosen (1934) in the rabbit, and by Cannon, Binger and Fitz (1915) in the cat. Code and Essex (1935) enucleated the eye of the dog and then fixed a rubber balloon within the socket. On cervical sympathetic nerve stimulation an increased pressure was recorded within the balloon. Essex and Corwin (1936,1937) demonstrated a fallacy in certain aspects of these experimental findings. Many of the anaesthetics used in

the experiments produce an enophthalmos. The exophthalmos which occurs on nerve stimulation is, therefore, to a certain extent a recovery of the eye from the enophthalmic position although there is also a small amount of true exophthalmos.

There is little doubt about the mechanism of this experimental exophthalmos in animals. It is closely related to the action of the smooth musculature found in the region of the eye, and innervated by the sympathetic nervous system. There are several smooth muscles to be considered.

Orbital muscle of Müller -

In 1858 Müller described an orbital smooth muscle which on contraction can produce exophthalmos. Müller described this muscle in man although he mentioned the fact that it is better developed in the lower mammals. It is now recognised that Müller's orbital muscle is only properly developed in animals which have an incompletely formed bony orbit and, therefore, require a powerful orbital muscle to help to maintain the eye in its normal position. In man the orbital muscle is a vestigial structure lying in the inferior orbital fissure. It cannot affect the position of the eyeball either directly following contraction of its muscle mass, or indirectly by impeding

the venous outflow from the orbit (Whitnall,1932). Foster Moore (1923) dissected a large series of orbits without finding any significant evidence of Müller's orbital muscle. Brunton (1938) examined this muscle in six cases of Graves' disease and found no evidence of any hypertrophy. There is no justification, therefore, for the view (Kravitz and Moehle, 1941) that exophthalmos in hyperthyroidism is due to contraction of Müller's orbital muscle.

Peribulbar smooth muscle -

This is an ill-defined mass of smooth muscle fibres surrounding the anterior half of the globe and closely associated with Tenon's capsule. This muscle band was described in detail by Hesser (1913). Some of the fibres are attached anteriorly to the orbital septum and others come into association with the superior and inferior palpebral muscles of Müller. Posteriorly the fibres fade away indefinitely, although a few fibres blend with the fascial expansions given off by the recti muscles at their points of attachment to the globe (Sappey,1869).

Landström (1907) believed that the peribulbar smooth muscle is capable of causing protrusion of the globe. Morley (1936) has suggested that in Graves' disease these bands of smooth muscle may combine to form a catapult so

that the eyeball is projected forwards. Mulvany (1944) believed that the muscle is capable of exerting an effect on the globe when associated with weakened extra-ocular muscles. Normally the recti muscles have a retracting influence on the globe.

On the other hand Whitnall and Beattie (1933) dismissed Landström's muscle by merely attributing to it the function of retraction of the conjunctiva during movements of the eye in a horizontal plane. Code and Essex (1935) showed that in the dog Tenon's capsule plays no part in the production of exophthalmos following stimulation of the cephalic end of the cut cervical sympathetic nerve.

Periorbital smooth muscle -

Russell (1936) has claimed that there is a moderate amount of smooth muscle within the periorbita, especially on its lateral aspect. The muscle fibres run in a circular direction parallel to the equator of the globe. She thought that there may be sufficient muscle in this situation to produce a certain degree of exophthalmos. The periorbita was examined histologically in 9 cases of Graves' disease but there was no evidence of hypertrophy of the muscle fibres.

There is, therefore, no conclusive anatomical evidence of any smooth musculature capable of producing and sustaining exophthalmos in man, and there are no grounds for accepting the Editorial Comment (Jour. Amer. med. Assoc., 102, 2188. 1934) that exophthalmos is simply the result of hypertonicity of orbital smooth muscle. This is in keeping with observations which have been made in man following stimulation of the cervical sympathetic nerve. Benedict (1938) stimulated the

cervical sympathetic nerve electrically during operations on the neck, and found no change in the position of the eye as shown by exophthalmometric recordings. A similar negative result was obtained by Pochin (1939a) and Friedgood (1941).

On the other hand there are smooth muscle fibres within the periorbital tissues which may be implicated in the exophthalmic process. It is interesting that Friedgood (1941), although he did not produce exophthalmos in normal subjects by cervical sympathetic nerve stimulation, found that exophthalmos, already present in a case of hyperthyroidism, increased by 3-4 mm. on similar stimulation. This may be evidence that there is more than one factor responsible for the production of exophthalmos in thyrotoxicosis.

A rapid reduction in exophthalmos in Graves' disease following bilateral cervical sympathectomy has been reported (Jonnesco, 1897), but some of this improvement may have been due to a decrease in the degree of lid retraction, and Juler (1913) did not obtain any dramatic reduction in exophthalmos in a case treated in a similar way. Labbé and others (1933) have shown that yohimbine, a sympatholytic agent, may lessen exophthalmos in certain cases, and they concluded that there is a sympathetic element in exophthalmos, although they stressed the presence of a hyperthyroid component which is not influenced by the sympathetic nervous system.

It has been suggested (Massoud, 1946) that sympathetic stimulation may cause exophthalmos by producing a state of venous dilatation within the orbit. This is an unlikely mechanism, however, in view of the different directions in which venous blood may drain from the orbit; forwards into the facial veins, downwards into the pterygoid venous plexus and backwards into the cavernous sinus. There is no doubt that venous congestion plays a part in the elaboration of the progressive type of exophthalmos (thyrotrophic exophthalmos) which will be dealt with in the next part of this thesis, but venous dilatation is not the initiating force.

(2) Exophthalmos due to striated muscle weakness.

This theory is based on the known weakness of the striated muscles in thyrotoxicosis.

The extra-ocular recti muscles exert a retracting influence on the globe, and, if this is weakened, it is natural that there may be a tendency towards the development of exophthalmos. This idea was put forward originally by Dalrymple (1834). The recti muscles have been likened by Greene (1955) to the wires which maintain a champagne cork in position, so that exophthalmos may follow a reduction of their normal tonicity.

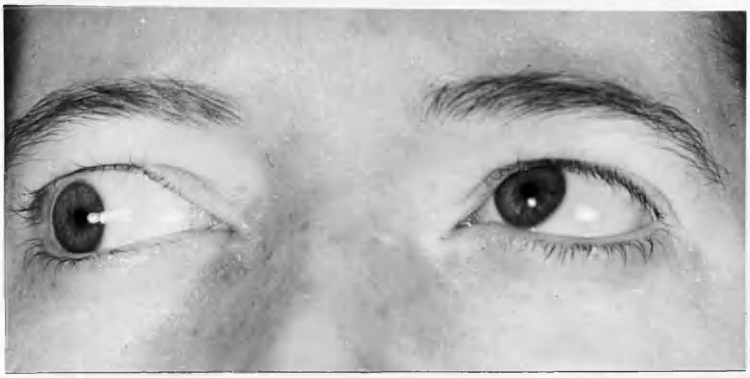
The lids also exert a restraining influence on the globe so that even the normal eye moves forwards about one millimetre when the lids are widely opened (Dayton, 1953), and it is possible that this effect will be even more marked if there is an associated lid retraction.

Parker (1922) reported a case of hyperthyroidism in which complete luxation of both eyes occurred beyond the lids. Severe manual labour appears to have been a contributing factor in this case, but there must also have been a marked degree of hypotonia of the ocular muscles. Rundle and Wilson (1944a) have demonstrated by careful measurement that varying degrees of ophthalmoplegia occur in nearly half of all cases of thyrotoxicosis. Wilson (1935) examined at autopsy the extra-ocular and thigh muscles of eight cases of Graves' disease, and he found that the muscles were all small and degenerate.

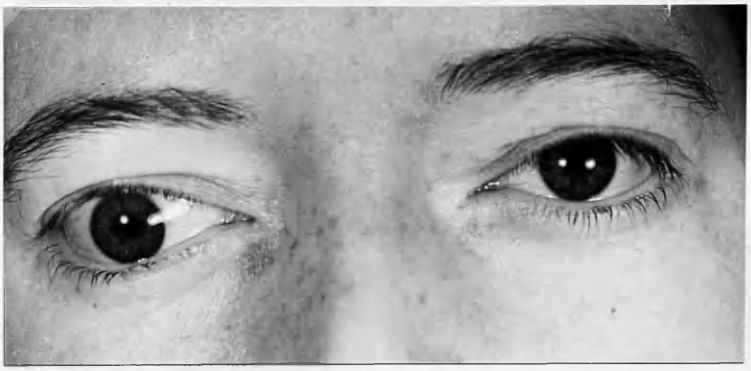
He postulated that weakness of the ocular muscles may be a factor in the production of exophthalmos. Plummer and Wilder (1935) also suggested that weakness of the ocular muscles may allow some forward displacement of the globe, and it is interesting that they found a positive correlation, in a series of cases of Graves' disease, between loss of power of the quadriceps femoris muscle and the presence of exophthalmos. Smelser (1938a) found a decrease in size of the extra-ocular muscles in guinea-pigs treated with thyroxine.

Figs. 1 and 2 illustrate the occurrence of ophthalmoplegia in two cases of thyrotoxicosis. In the case shown in fig. 1 there was complete paralysis of the right superior rectus muscle with overaction of the contralateral synergist (left inferior oblique). There was also some paresis of the right inferior oblique. In the case shown in fig. 2 there was an identical affection of the left eye. In both cases there was an improvement in the systemic condition following thiouracil treatment, and also some improvement in the ophthalmoplegia. It may be concluded, therefore, that to some extent these cases exhibit an ophthalmoplegia of thyrotoxic origin, although it must be remembered that in the majority of cases of ophthalmoplegia associated with thyroid dysfunction the condition is of a thyrotrophic type. This latter type of ophthalmoplegia is not relieved by anti-thyroid treatment (Zondek, 1951), and it will be discussed in detail in the next part of this thesis.

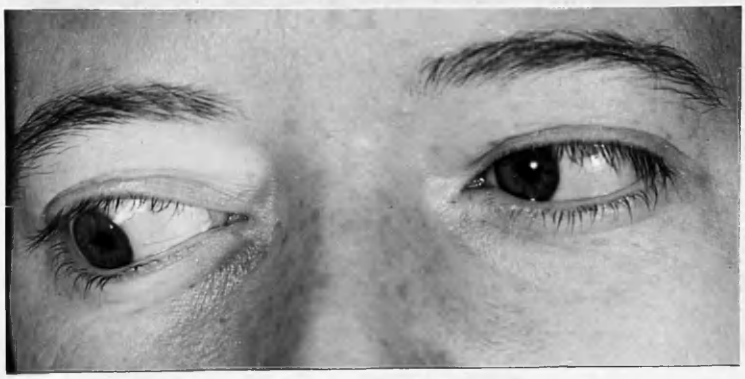
FIG.1.



Eyes in dextro-elevation.



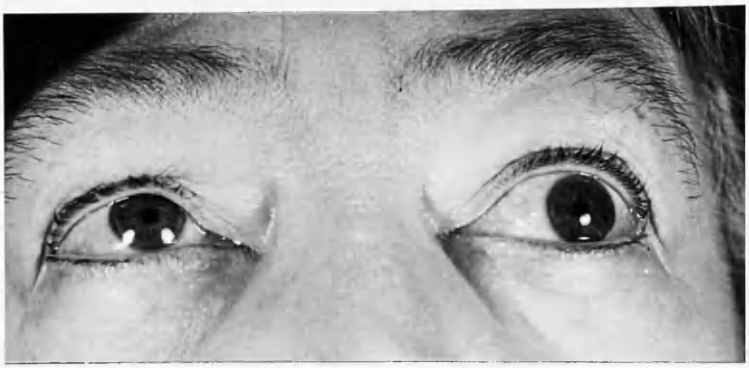
Eyes in primary position.



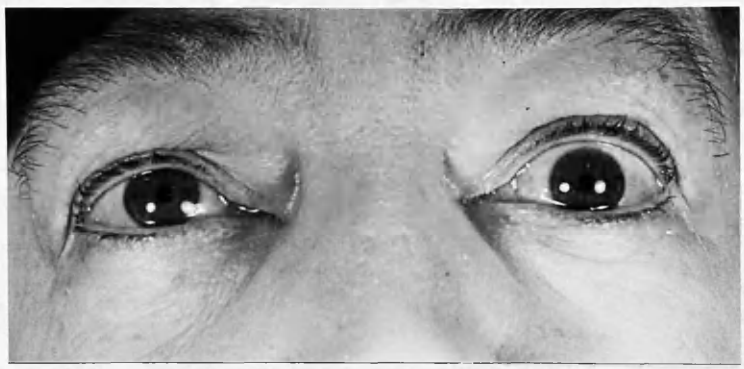
Eyes in dextro-depression.

Case of marked thyrotoxicosis showing complete paralysis of right superior rectus with overaction of contralateral synergist, left inferior oblique, and homolateral antagonist, right inferior rectus. There was also some paresis of right inferior oblique. Slight upper lid retraction (R>L.) Some exophthalmos of right eye (Hertel exophthalmometer, R= 21mm., L= 18mm.). No sense of abnormal retro-ocular resistance.

FIG.2.



Eyes in laevo-elevation.



Eyes in primary position.

Case of moderate thyrotoxicosis showing complete paralysis of left superior rectus with overaction of contralateral synergist, right inferior oblique, and of homolateral antagonist, left inferior rectus. There was also some paresis of left inferior oblique. Some upper lid retraction (L > R). Slight exophthalmos of left eye (Hertel exophthalmometer, R=17 mm., L=19 mm.). No sense of abnormal retro-ocular resistance.

A cardinal feature of thyrotoxic exophthalmos is the comparative ease with which the eye may be compressed backwards into the socket (Crawford, 1952), an effect first noticed by Cooper (1849). This has been accurately demonstrated by Copper (1948) using an orbitonometer. Ease of compression of the eye is consistent with the concept of a mechanism based on extra-ocular muscle weakness, and it explains the disappearance of exophthalmos in some cases after death. It may also help to explain the quite rapid fluctuations which may occur in the degree of exophthalmos (Bristowe, 1886) because such fluctuations would be unlikely if exophthalmos is determined solely by the presence of some new tissue within the orbital cone.

There are reports of the ophthalmoplegia in thyrotoxicosis benefitting from prostigmine therapy (Critchley and Cameron, 1948; Greene, 1949; Hatch, 1952), but such cases usually exhibit a co-existent myasthenia gravis.

It is convenient to note at this point that in spite of the abundant evidence that a weakness of striated musculature may be a characteristic feature of thyrotoxicosis, the opposite point of view has been put forward by Daniel (1938) and Essex (1938) who postulated that there is an increased tone of the striated muscles in Graves' disease. Daniel (1938) suggested that this increased muscle tone may lead to a rise of venous pressure within the orbit with the production of congestive oedema and exophthalmos. It is difficult, however, to

substantiate this theory in the light of the other known features of the striated musculature in thyrotoxicosis.

(3) Exophthalmos due to increased orbital fat.

It has been shown that in certain cases of thyrotoxicosis there is a persistence of exophthalmos after death (Woods, 1946), even when allowance is made for the normal post-mortem recession of about 2.5mm. An increase in the amount of orbital fat has been demonstrated in some cases of thyrotoxicosis (Rundle and Pochin, 1944; Pochin, 1945, 1946; Rundle, 1951). This is quite apart from the fatty changes which occur within the extra-ocular muscles and which are more marked than the purely orbital fat deposits. The increased fat within the orbit provides an explanation for the cases which show a degree of persistent exophthalmos after death.

In an interesting experiment Pochin (1949) showed how the adipose tissue found in the orbit may be purely secondary to the forward protrusion of the eye. He introduced a small perspex frame into the subcutaneous tissues of a rabbit. This formed a cavity which could not be occluded by a mere displacement of the surrounding tissues. The cavity became filled with fluid, presumably due to the low hydrostatic pressure within the space, and later the fluid became replaced by a solid tissue. Pochin postulated that a similar process may occur within the orbit following forward displacement of the eye as a result of the weakness of the extra-ocular muscles. It may be, therefore, that any fat which is deposited in the orbit in thyrotoxicosis is the result and not the cause of the exophthalmos, and this

concept is supported by the fact that the fat deposit is merely an exaggeration of the normal adipose tissue within the orbit, and not a deposit of some abnormal tissue unrelated to the normal orbital fat (Pochin and Rundle, 1949). On the other hand, it has been suggested that the laying down of fat within the orbit may be determined by some lipotropic hormone (Rundle, Finlay-Jones and Noad, 1953).

The three possible mechanisms in the production of a thyrotoxic type of exophthalmos have been detailed under their separate headings, but it is more than likely that the exophthalmos is the result of a combined action of all three mechanisms so that the hypertonus of the orbital smooth muscles acts in conjunction with the hypotonus of the extra-ocular striated muscles (Spaeth, 1937; Mulvany, 1944) thereby causing some forward protrusion of the eye, and that this is followed by a fatty deposit within the orbit.

Other Clinical considerations of thyrotoxic exophthalmos.

Exophthalmos in thyrotoxicosis is commonly bilateral and symmetrical (Rundle and Wilson, 1945), although Hedges and Rose (1953) have found a difference of over 3 mm. in the degree of exophthalmos in 9 out of 19 cases, and exophthalmos may even occur as a unilateral phenomenon (Spaeth, 1937; Covitz, 1941; Dixon, 1941; Vail, 1948). Unilateral exophthalmos has been reported at an early stage of the disease before the appearance of any systemic manifestations (Kisner and Mahorner, 1947), despite the fact that in general it is rare for exophthalmos to precede the more general signs of the disease (Saltzman and Mellicker, 1951). There is evidence, however, that unilateral exophthalmos is rare if careful measurements are made of the other eye (Naffziger, 1948; Drescher and Benedict, 1950), and Copper (1948) has shown that examination with an orbitonometer may reveal early involvement of the apparently "unaffected" eye. In certain cases a long interval may elapse between the early general manifestations of the disorder and the onset of exophthalmos (Dayton, 1953).

There is no doubt that, provided a careful distinction is drawn between true exophthalmos and apparent exophthalmos (lid retraction), exophthalmos is not a universal feature of Graves' disease; in fact it only occurred in 19 out of 134 cases (Eden and Trotter, 1942), in 6 out of 17 cases (Rundle and Pochin, 1944), and in 18 out of 57 cases (Donoso, 1953). Exophthalmos is seldom a marked feature of thyrotoxicosis, although Stokes (1954) described a case of severe exophthalmos in a girl in which the exophthalmos

subsided following the successful medical and surgical treatment of the underlying Graves' disease. This response of the exophthalmos to anti-thyroid treatment suggests that the exophthalmos was determined by the thyrotoxicosis, and was not, therefore, of the thyrotrophic variety which is the more common form of severe exophthalmos, and which is not under discussion in this part of the thesis.

Mechanism of lid retraction in thyrotoxicosis

There is no general agreement on the mechanism underlying the occurrence of lid retraction in Graves' disease, and two main theories have been put forward; first, that it is due to an overaction of the smooth palpebral muscles, and, secondly, that it is due to an overaction of the striated levator palpebrae superioris muscle. An earlier theory (Stellwag, 1869) that the primary cause of lid retraction is a weakness of the orbicularis oculi muscle has never found much favour and has been disproved by Pochin (1939b) who found a complete absence of any lid retraction in 15 cases of unilateral facial palsy.

There is, of course, a certain degree of lid retraction in all cases of true exophthalmos as a result merely of the mechanical effect of the protruding globe on the eyelids, and care must be taken to exclude exophthalmos before arriving at an assessment of lid retraction (Dayton, 1953). This discussion is concerned only with lid retraction which occurs as an independent phenomenon from exophthalmos.

(1) Hypothesis that lid retraction is due to overaction of the smooth palpebral muscles of Müller.

The theory that overaction of the smooth palpebral muscles is instrumental in the production of lid retraction was put forward originally by von Graefe (1864), and has been restated by many others since then (Marine and Rosen, 1934; Seitchik, 1942; Mulvany, 1944; Azerad, 1948; Klotz, 1948c; Braley, 1948 and 1953; Dayton, 1953.) It is based on the following premises:-

(a) The fact that there are smooth muscles in the upper and lower lids - the superior and inferior palpebral muscles of Müller.

The superior palpebral muscle of Müller arises between the striated fibres of the levator palpebrae superioris muscle and passes downwards to be inserted by fine fibres into the upper surface of the tarsal plate of the upper lid.

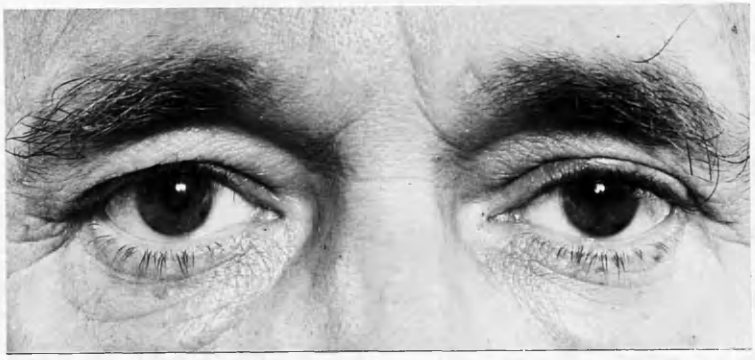
The inferior palpebral muscle of Müller is less distinct than the corresponding muscle of the upper lid. It arises from the fascial sheet of the inferior rectus muscle and passes forwards as two lamellae one of which is inserted into the bulbar conjunctiva whilst the other is inserted just behind the lower edge of the tarsal plate.

These smooth muscles are innervated by the sympathetic nervous system, and their presence in the upper and lower lids accounts for the fact that the narrowing of the palpebral fissure on the affected side in a case of Horner's syndrome is due, not only to a drooping of the upper lid, but also to a slight elevation of the lower lid (fig. 3). This narrowing of the palpebral fissure may also be produced temporarily by a blockage of the cervical sympathetic nerve by local anaesthesia (Miller, 1953). Conversely, it has been shown that stimulation of the cervical sympathetic nerve in man causes an obvious retraction of the upper lid and a slight retraction of the lower lid (Pochin, 1939a).

(b) The fact that lid retraction is a phenomenon which may affect both the upper and the lower lids.

There is no doubt that lid retraction is an effect primarily apparent in the upper lid, but Mulvany (1944) has shown that retraction of the lower lid may occur and, in fact, may be the earliest ocular manifestation of thyrotoxicosis in about 75% of cases. Holloway, Fry and Wentworth (1929) also found that, although retraction of the upper lid is the outstanding feature of thyrotoxicosis, retraction may occur to a lesser extent in the lower lid. This has been investigated in a series of cases of Graves' disease.

FIG. 3.



Case of Horner's syndrome of left eye showing narrowing of left palpebral fissure due to slight depression of upper lid and slight elevation of lower lid. Note slight miosis on affected side.

Examination of lid retraction in thyrotoxicosis.

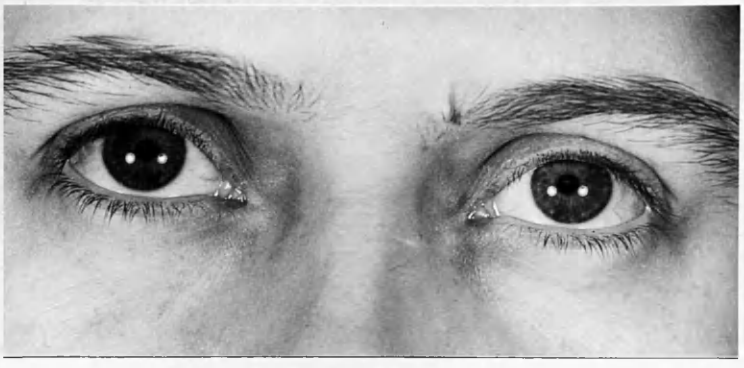
In most normal individuals, with the head held erect and eyes directed straight forward, the lower lid just borders on the lower corneal limbus. Lower lid retraction causes a disturbance of this relationship and an area of conjunctiva becomes visible between the limbus and the lower lid margin. This visible conjunctiva is termed the lower scleral rim, and it is illustrated in figs. 4-7 which show the phenomenon of lower lid retraction as it occurs in cases of mild thyrotoxicosis. In fig.4 there is retraction of both lower lids, although the retraction is more marked on the left side than on the right side. In fig. 5 there is an equal degree of lower lid retraction in the two eyes. An interesting feature of these cases is the fact that the size of the lower scleral rims did not always remain constant and that fine twitching movements could be seen sometimes along the length of the lower lids which caused an alteration in the extent of the lower scleral rims, evidence surely of some active muscular disturbance.

It would appear that lower lid retraction, when it occurs, may be only a transitory phenomenon. When retraction of the upper lid becomes effective there is a raising of the whole level of the palpebral fissure of that eye and a consequent masking of any lower lid retraction. Upper lid retraction is, therefore, a more powerful and dominant force than lower lid retraction. Figs. 6 and 7,

FIG. 4.

Case of early thyrotoxicosis showing retraction of both lower lids (L > R). No upper lid retraction. No exophthalmos.

FIG. 5.



Case of early thyrotoxicosis showing retraction of both lower lids. No upper lid retraction. No exophthalmos.

FIG.6.

FIG.7.

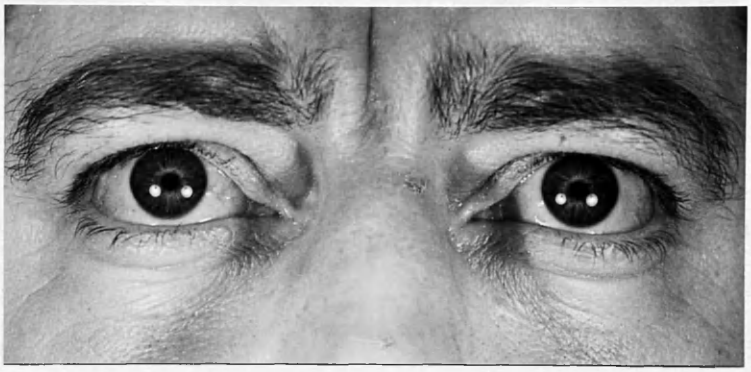
FIGS.6 and 7.

Cases of early thyrotoxicosis. Each case shows retraction of left lower lid with appearance of scleral rim between cornea and lower lid. No obvious retraction of right lower lid, but this effect is probably masked by slight raising of level of right palpebral fissure due to retraction of upper lid. No retraction of left upper lid. No exophthalmos of either eye.

showing cases of early thyrotoxicosis, illustrate this point. In each case the left lower lid is retracted as compared with the right lower lid but on the right side there is the additional feature of upper lid retraction and it may be this which has caused the difference in levels of the lower lids.

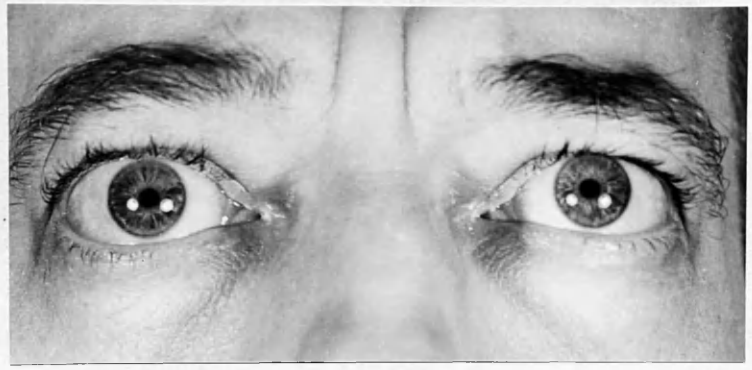
It is important in determining the presence of lower lid retraction to exclude any true exophthalmos. When an eye becomes proptosed an area of conjunctiva becomes exposed between the lower corneal limbus and the lower lid margin quite independently of any lower lid retraction. Figs. 8, 9 and 10 illustrate this occurrence, the lower scleral rims being determined by the presence of exophthalmos. It is also important to exclude any structural anomaly of the lids before attaching undue significance to the presence of lower scleral rims. In certain normal individuals the lower lid margin shows a pronounced curve downwards in its lateral two-thirds, and this produces the appearance of obvious lower scleral rims. Figs. 11 and 12 illustrate this point.

FIG.8.



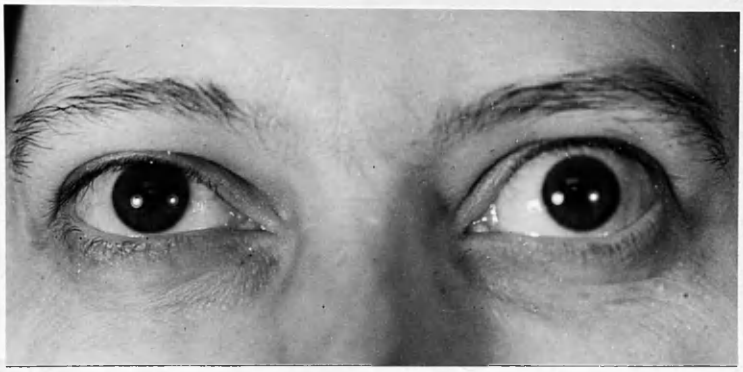
Case of established thyrotoxicosis showing appearance of lower scleral rims, but in view of the occurrence of exophthalmos (Hertel exophthalomometer, R = 21 mm., L = 20 mm.), no conclusion may be reached regarding lower lid retraction. There is some upper lid retraction of both eyes.

FIG. 9.



Case of established thyrotoxicosis showing appearance of lower scleral rims, but in view of the occurrence of exophthalmos (Hertel exophthalmometer, R = 23 mm., L = 21 mm.), no conclusion may be reached regarding lower lid retraction. There is some upper lid retraction, particularly on the right side.

FIG.10.



Case of established thyrotoxicosis showing appearance of obvious lower scleral rims. There is, however, exophthalmos, (Hertel exophthalmometer, R = 19 mm., L = 21 mm.), and this has determined the appearance of visible lower scleral rims.

FIG.11.

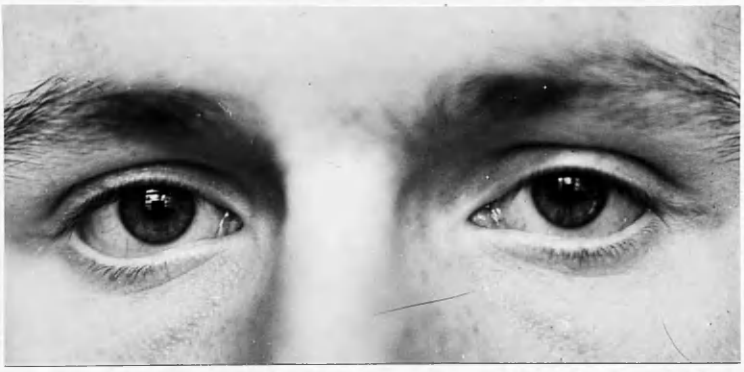
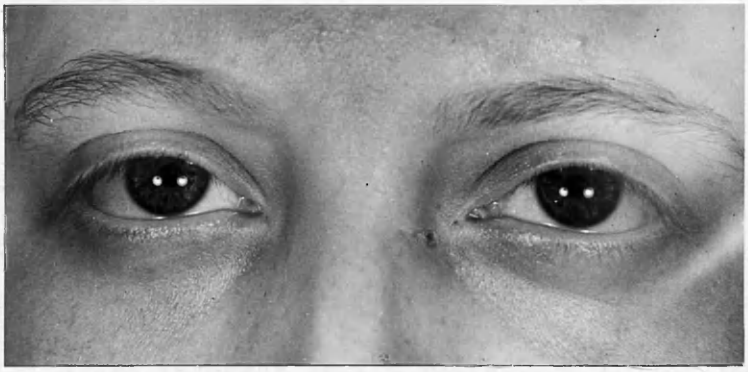


FIG.12.



FIGS.11 and 12.

Normal healthy individuals. The lower scleral rims are determined solely by the peculiar curve of the lower lid margins.

(c) The fact that lid retraction may be lessened by a reduction in sympathetic tone.

It has been shown in certain cases of Graves' disease that cervical sympathectomy causes a diminution in the degree of lid retraction (Edmunds, 1900; Jonesco, 1903; Shaw, 1929; Keynes, 1952), and in fact, Brain (1952) has recommended this operation in patients who are distressed by the persistence of the staring appearance despite the successful completion of the usual anti-thyroid therapeutic procedures.

The cervical sympathetic nerve may be blocked by local anaesthesia, and this causes a marked temporary reduction in lid retraction (McCullagh, 1953). A reduction in sympathetic tone may be achieved also by the use of sympatholytic drugs, and Givner, Bruger and Lowenstein (1947) have noted that ergotamine causes a narrowing of the palpebral fissure in cases of lid retraction during the period of its administration.

The effect of hexamethonium iodide, a sympatholytic drug, has been noted on the positions of the lids in thyrotoxicosis. It has been shown by Paton and Zaimis (1951) that hexamethonium may block the retraction of the nictitating membrane in the cat which normally follows cervical sympathetic nerve stimulation, and an investigation has been carried out also on the influence of this drug on experimentally induced lid retraction in the monkey. These investigations will be reported now.

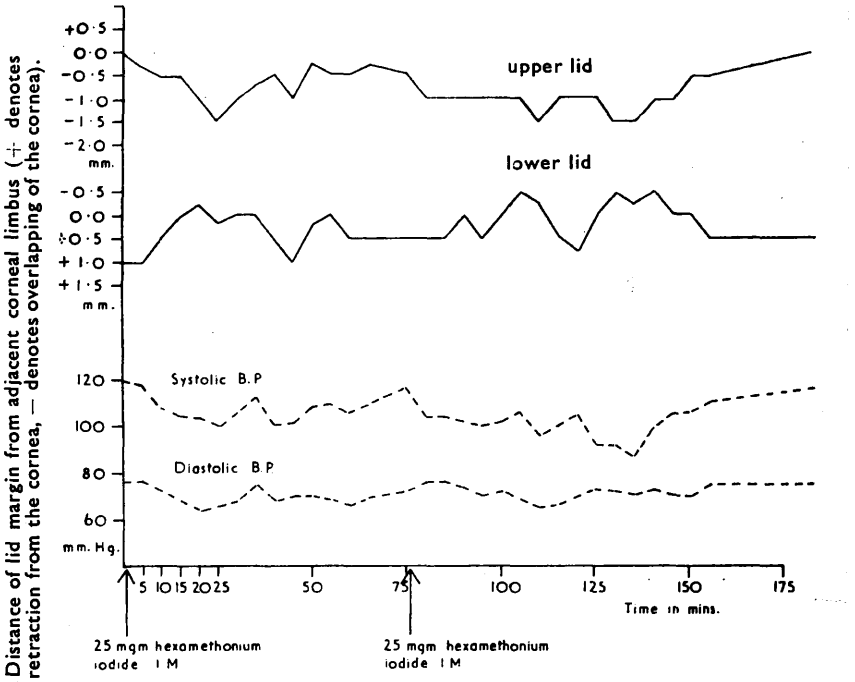
Examination of influence of hexamethonium iodide on lid retraction in thyrotoxicosis.

An investigation has been conducted on the effect of a sympatholytic drug, hexamethonium iodide, on the degree of lid retraction in three cases of early untreated thyrotoxicosis. In two cases the effect of the lid retraction was predominantly on on the lower lids, but in the other case retraction of the upper lids was the outstanding feature, and there was no retraction of the lower lids. There was no true exophthalmos in any of the cases.

The position of the lids was determined at five minute intervals before and after the administration of 25 mgm. hexamethonium iodide by intramuscular injection. The distance of each lid margin from the adjacent part of the corneal limbus was measured in millimetres, a positive value indicating retraction of the lid from the cornea, a negative value indicating overlapping of the lid by the cornea. Great care was taken to ensure that each measurement was made under standard conditions, with the patients' head in an upright position and the eyes in the primary position, so that it was possible to obtain a comparable series of readings. A recording of the blood pressure was made simultaneously in order to give further evidence of the effectiveness of the drug.

Figs. 13 and 14 show the effect of hexamethonium on the upper and lower lids of the right and left eyes, respectively, of one of the cases showing retraction of the lower lids. It is apparent that within 10 - 15 minutes of the administration of the sympatholytic

FIG.13.



Right Eye.

Diagram to show the influence of hexamethonium iodide on the position of the upper and lower eyelids of the right eye and on the arterial blood pressure in a case of mild thyrotoxicosis showing lid retraction particularly affecting the lower lid.

FIG.14.

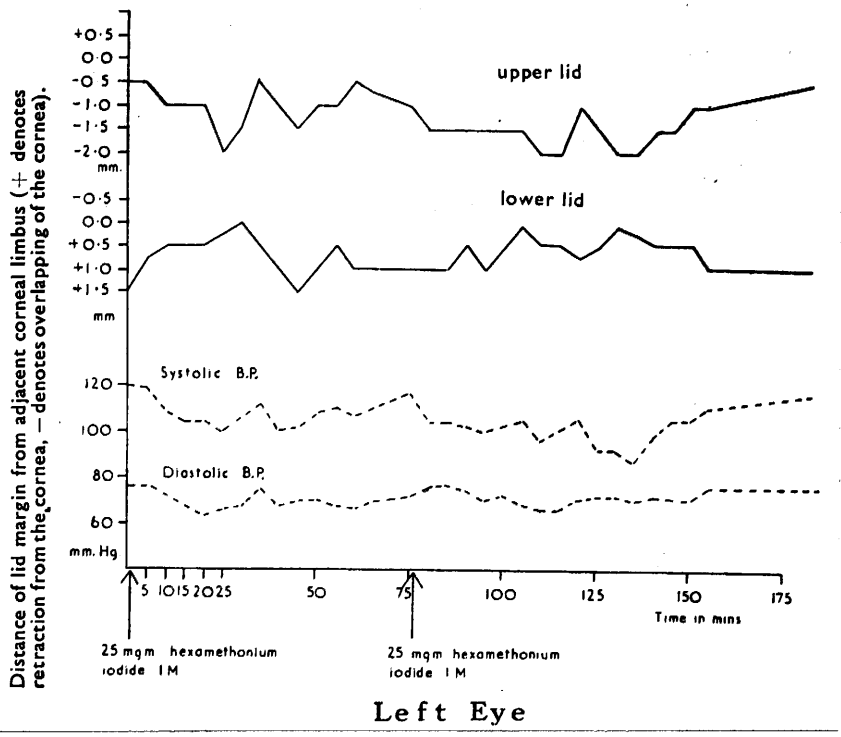


Diagram to show the influence of hexamethonium iodide on the position of the upper and lower eyelids of the left eye and on the arterial blood pressure in a case of mild thyrotoxicosis showing lid retraction particularly affecting the lower lid.

drug there was a decrease in the degree of lid retraction of both lids, and that this reached a maximum within 30 - 40 minutes followed by a gradual return of the lids to their original position. It may be noted that the blood pressure recordings fluctuated in a similar manner to the changes in lid position. The other case showing lower lid retraction gave a comparable result.

Figs. 15 and 16 show the effect of hexamethonium on the upper lids of the right and left eyes, respectively, of the case showing obvious upper lid retraction, and it is clear that the drug brought about a gradual reduction in the degree of upper lid retraction for a period of about 40 minutes. The lower lid is not recorded in the charts because its position did not alter to any significant degree during the period of observation.

It is suggested that the absence of any dramatic effect on the lower lid in this case is not evidence against the existence of a mechanism within the lower lid capable of being associated in the process of lid retraction. If it is accepted that upper lid retraction is the more powerful mechanism and that when it becomes effective there is a raising of the whole level of the palpebral fissure, then any reduction of lower lid retraction due to the administration of hexamethonium may be masked by the dropping of the level of the palpebral fissure following the reduction of upper lid retraction.

FIG.15.

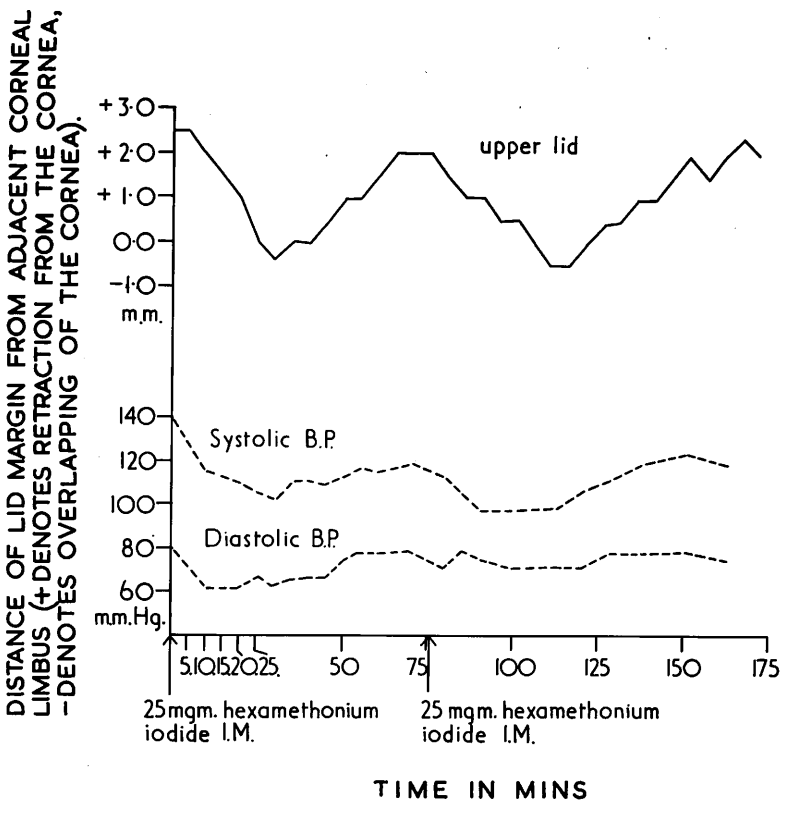


Diagram to show the influence of hexamethonium iodide on the position of the upper eyelid of the right eye and on the arterial blood pressure in a case of thyrotoxicosis showing obvious retraction of the upper lid.

FIG.16.

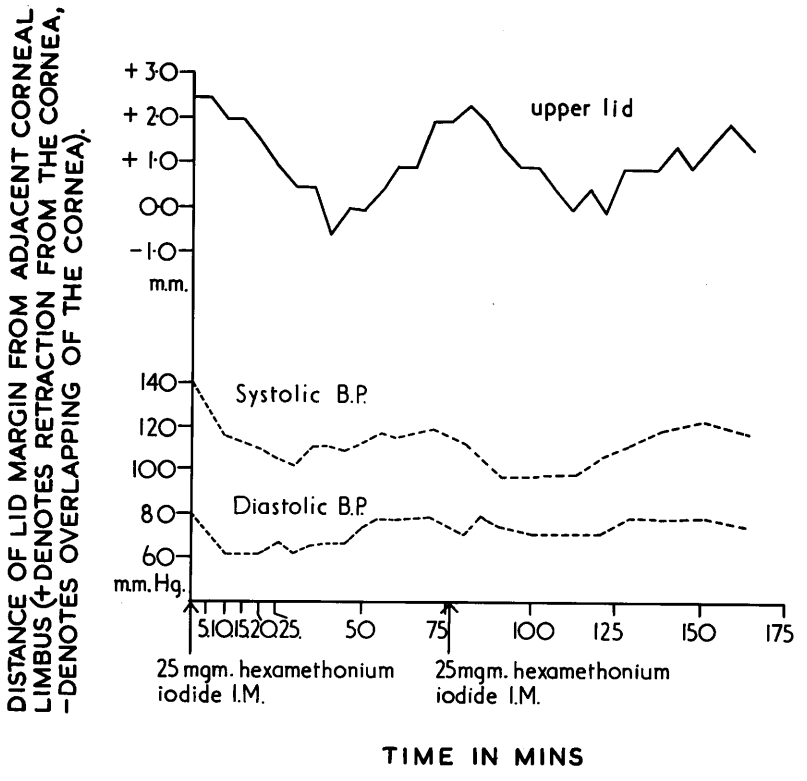


Diagram to show the influence of hexamethonium iodide on the position of the upper eyelid of the left eye and on the arterial blood pressure in a case of thyrotoxicosis showing obvious retraction of the upper lid.

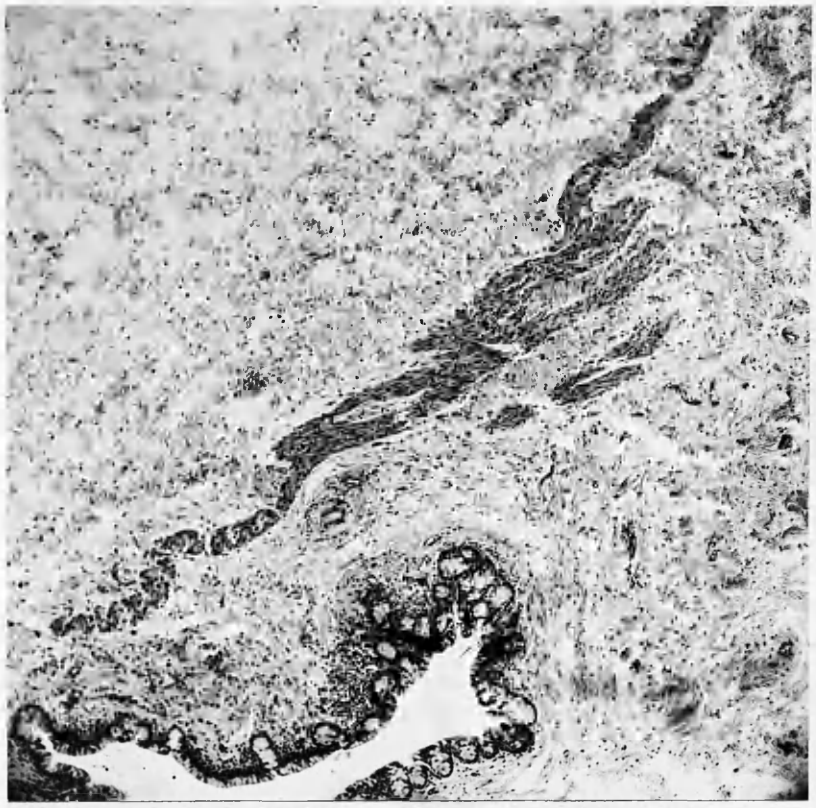
Examination of influence of hexamethonium iodide on lid retraction induced by sympathetic stimulation in the monkey

Three monkeys were used in the experiment and it is known that both lids of the monkey contain smooth muscle which is capable of exerting a retracting influence on the lids. The smooth palpebral muscle of the upper lid is shown in fig. 17.

A moderate degree of anaesthesia was produced by exposing the monkey to ether vapour, and then anaesthesia was completed by injecting chloralose through a cannula inserted into the femoral vein. The chloralose was dissolved in water at a temperature of 55°C (10 mgm. chloralose per ml. water), and it was administered in a dose of 100 mgm. chloralose per Kg. body weight. If the experiment was prolonged an additional 100 mgm. chloralose was given supplemented, if necessary, by 3 ml. of a nembutal solution (1/10th gr. nembutal per ml. water). The nembutal was also given intravenously.

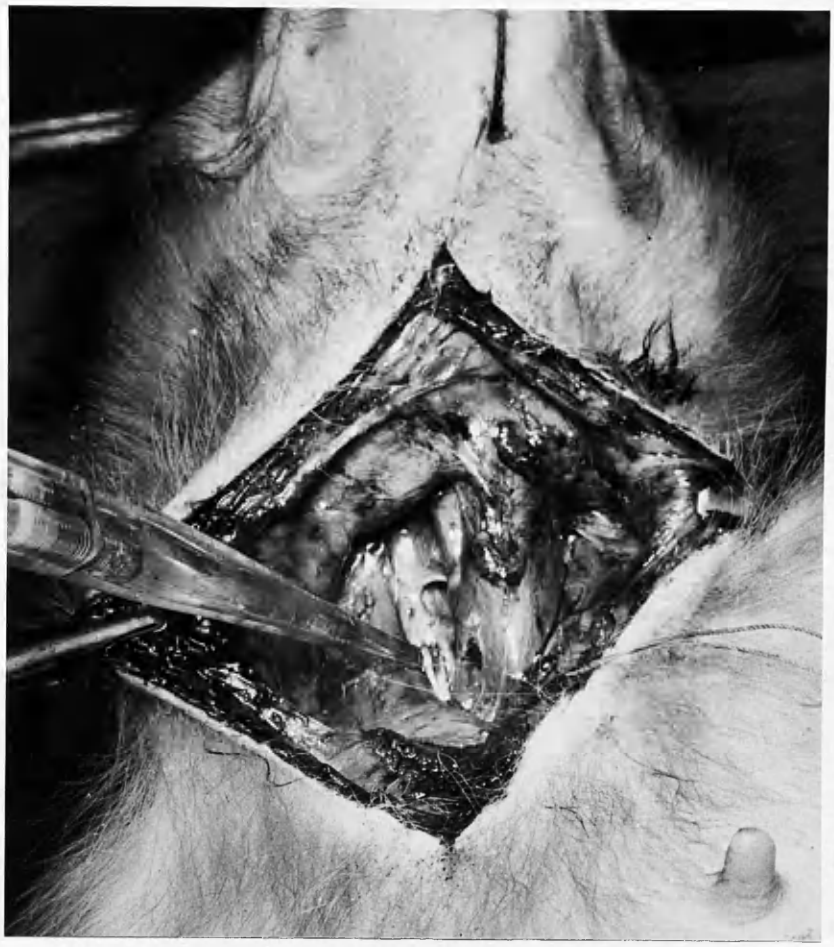
The anaesthetised monkey was placed in the dorsal position with the head extended, and the right side of the neck was dissected through a paramedian incision to expose the carotid sheath with its constituent vessels and nerve. This sheath was carefully lifted to reveal the underlying cervical sympathetic nerve which was placed on the groove of a stimulator, great care being taken to prevent any undue stretching of the nerve (fig. 18). The stimulator was designed to administer a current of 15 volts with a frequency of

FIG.17.



Photomicrograph of a section of the upper eyelid of a monkey to show the presence of a smooth palpebral muscle in the lid adjacent to the superior fornix. X48.

FIG.18.



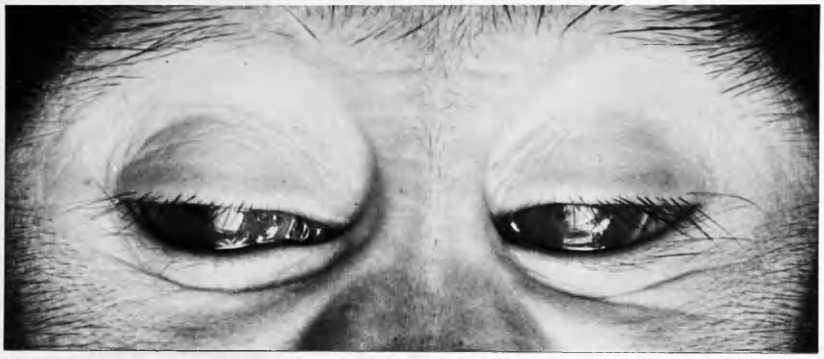
Photograph of a dissection of the right cervical region of the monkey to show the right cervical sympathetic nerve lying on the curved end of a stimulator.

20 cycles per second and a range of one millisec. Each stimulation persisted for 10 seconds. Before each period of stimulation the nerve was carefully dried and covered by a dry swab, but at all other times its integrity was maintained by being moistened with normal saline. The effect of stimulation of the cervical sympathetic nerve on the eye is shown in fig. 19, and it is apparent that it causes a well marked retraction of both lids, particularly the lower one, with an associated mydriasis.

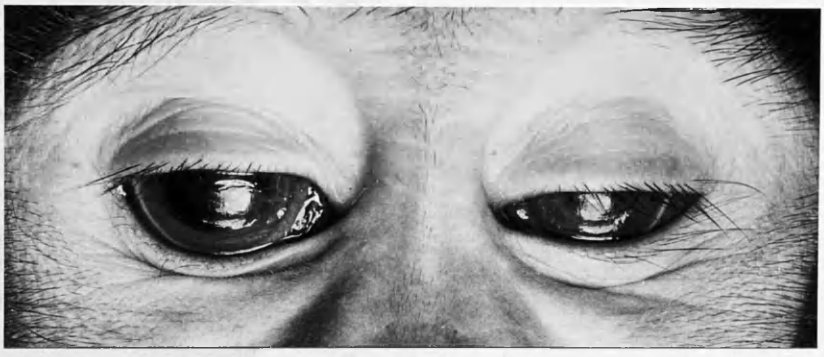
During the period of observation the animal's head was placed in a clamp designed to maintain the head in a set position. The upper or lower lid margin of the right eye was attached to an isotonic lever by means of a fine suture which passed from the lid in a horizontal plane so that it caused slight tension on the lid. Any retraction of the lid resulted in a pulling on the suture with a corresponding movement of the recording lever. This lever was placed against a kymograph, set at a speed of 2 F so that 7 mm. of the tracing was equivalent to one minute of time.

Figs. 20 and 21 show the effect of the administration of one ml. hexamethonium intravenously (10 mgm. hexamethonium per ml. water) on the degree of lid retraction following stimulation of the cervical sympathetic nerve, and it is apparent that hexamethonium greatly reduces the ability of the stimulated nervical sympathetic nerve to induce lid retraction, although the effect is only transitory and passes off within about 10 minutes.

FIG.19.

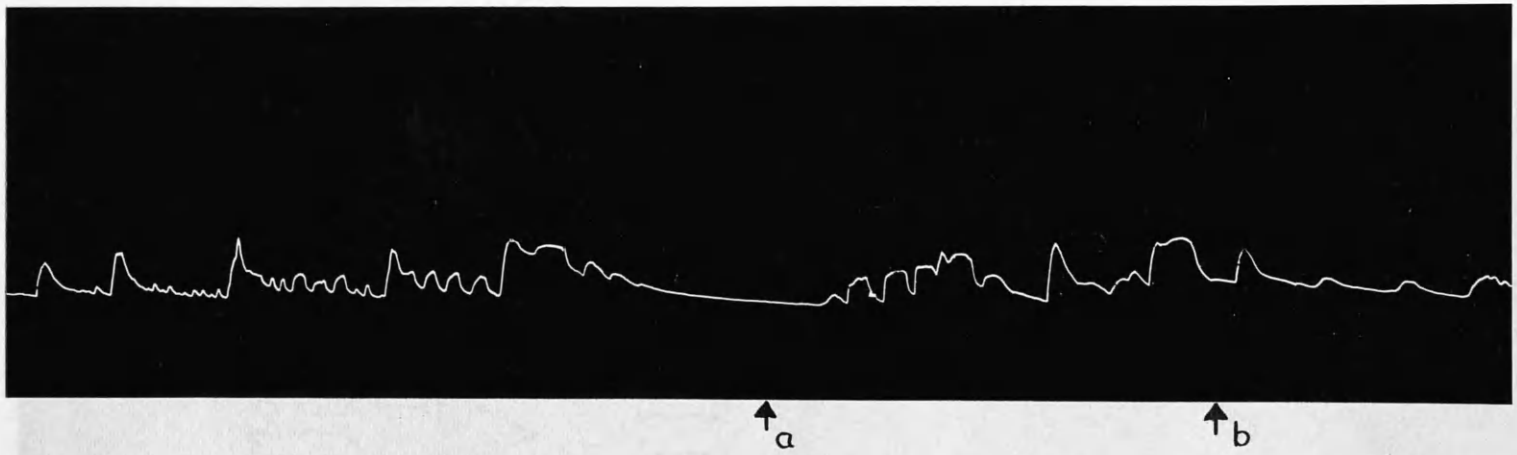


(a) The normal monkey.



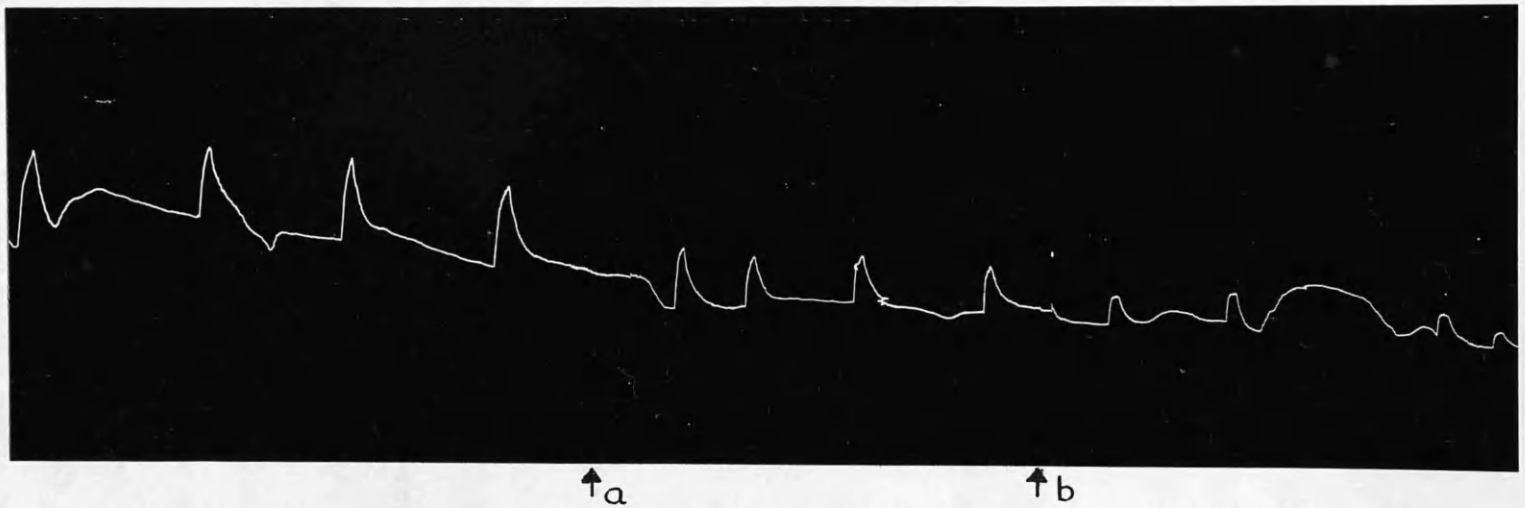
(b) The effect of stimulation of the right cervical sympathetic nerve in the monkey. Note the retraction of the lids, particularly the lower one, and the associated mydriasis.

FIG.20.



Diminished retraction of right lower lid of monkey as a result of stimulation of right cervical sympathetic nerve following administration of hexamethonium at (a) and (b).

FIG.21.



Diminished retraction of right upper lid of monkey as a result of stimulation of right cervical sympathetic nerve following administration of hexamethonium at (a) and (b).

(d) The fact that a correlation exists between the degree of sympathicotonia and the degree of lid retraction in thyrotoxicosis.

There is no doubt that many of the manifestations of Graves' disease are of a sympathicotonic nature and it is, therefore, an attractive concept to relate the occurrence of lid retraction to this mechanism, particularly as an adenoma of the thyroid gland, which is seldom associated with signs of a sympathicotonic disturbance, is also seldom associated with lid retraction (Atkinson, Lisser and Shepardson, 1928).

Furthermore, there is often a direct correlation between the extent of the thyrotoxicosis and the degree of the lid retraction, (Levitt, 1951) and, conversely, successful surgical and medical treatment of Graves' disease is usually followed by a marked reduction in the degree of lid retraction (Ruedemann, 1931; Barr and Shorr, 1945).

(e) The fact that lid retraction may occur in sympathicotonic states, quite apart from thyrotoxicosis.

It has been shown that stimulation of the distal end of the cut cervical sympathetic nerve may produce a definite elevation of the upper lid and a slight lowering of the lower lid (Pochin, 1939a). Savin (1943) made the interesting personal observation that the

sudden explosion of a nearby bomb produced typical thyrotoxic fascies with marked widening of the palpebral fissures!

Lid retraction does not occur exclusively in thyrotoxicosis. Friedgood (1930) observed some degree of retraction of the upper lid in nearly 50% of 258 cases of essential hypertension without any associated thyrotoxic element. He considered that this lid retraction is identical with that found in Graves' disease, and that a common factor is in operation, namely, spasm of the smooth muscle of the upper lid due to overaction of the sympathetic nervous system. Nevin and Kiloh (1951) noted the occurrence of lid retraction in disseminated sclerosis due to irritation of the descending spinal sympathetic fibres. Kessel and Hyman (1923) found lid retraction in a series of cases showing autonomic imbalance but without any signs of thyrotoxicosis. In a case of periodic sympathetic spasm of the pupil, the phase of pupillary dilatation was related to a widening of the palpebral fissure (Lowenstein and Levine, 1944). Rundle (1941) described the occurrence of lid retraction in a number of cases without any evidence of thyrotoxicosis, although he stated that several of the cases developed thyrotoxicosis at a later date. Jackson (1949, 1950) noted that lid lag, a phenomenon which is dependent on a hypertonicity of the retracting influence of the upper lid, occurs in 33% of persons with peptic ulceration whereas it occurs only in 10% of normal persons.

Hypothesis that lid retraction is due to overaction of the striated levator palpebrae superioris muscle.

The theory that overaction of the striated levator palpebral superioris muscle is responsible for the production of lid retraction has been put forward by Pochin (1939b), and re-affirmed by Brain (1939), Rundle (1951), Cogan (1953), and Ruedemann and Corrigan (1953). In fact, Ruedemann and Corrigan designated lid retraction as levator retraction. This theory is based on the following premises:-

(a) The fact that there is a striated muscle in the upper lid - the levator palpebrae superioris muscle.

The levator palpebrae superioris is a powerful muscle which arises at the apex of the orbit from the lesser wing of the sphenoid above the annulus of Zinn, and runs forwards under the roof of the orbit to terminate in an expanded aponeurosis, the main part of which is inserted into the skin of the upper eyelid and into the lower third of the anterior surface of the tarsal plate. It is innervated by the oculomotor nerve, and is responsible for lifting the upper lid in the expression of staring, a function first attributed to it by Dalrymple (1834).

(b) The fact that lid retraction is a phenomenon confined solely to the upper lid.

A detailed description of lid retraction has been given by Pochin (1938a) who emphasised that it is only the upper lid which becomes elevated. In such cases when the lids are closed a prominent horizontal fold may be seen lying about 6 - 10 mm. above the lid margin, and this probably represents the unduly prominent superior border of the upper tarsal plate. Pochin has declared that in association with the retraction of the upper lid there is a slight elevation of the lower lid, and this would appear to indicate the absence of any effective mechanism within the lower lid capable of producing retraction so that the lower lid becomes elevated as a direct mechanical consequence of the raising of the external canthus following retraction of the upper lid. François (1951a) has also stated that lid retraction is confined to the upper lid only.

(c) The fact that lid retraction may be relieved by tenotomy of the levator palpebrae superioris muscle.

In an isolated case of unilateral lid retraction in Graves' disease, Cogan (1953) has shown that tenotomy of the levator palpebrae superioris muscle relieved the appearance of lid retraction. Spaeth (1953b) recommended recession of the levator muscle in cases of marked upper lid retraction.

(d) The fact that pathological changes may occur in the levator palpebrae superioris muscle in thyrotoxicosis.

Rundle and Pochin (1944), in a study of the fat content of the ocular muscles in thyrotoxicosis, found an increased fat content in all the striated ocular muscles and this was most marked in the levator palpebrae superioris. This is consistent with the fact that normally the levator has a slightly higher fat content than the other extra-ocular muscles, because Rundle and Pochin found that the increase in fat was in proportion to the normal fat content of the various muscles. They concluded that the pathological change within the levator is responsible for lid retraction.

(e) The fact that lid retraction may occur in a state of oculomotor nerve hyperexcitability, quite apart from thyrotoxicosis.

It has been shown that retraction of the upper lid may be associated with the phase of pupillary constriction in a case of cyclic oculomotor paralysis (Lowenstein and Givner, 1942). It may also be a feature of Parinaud's syndrome or of post-encephalitic Parkinsonism, presumably as a result of a lesion in the mesencephalic diencephalon producing a hypertonicity of the levator palpebrae superioris muscle (François, 1951a).

Conclusion regarding the mechanism of lid retraction in thyrotoxicosis

There can obviously be no reconciliation of the two opposing hypotheses which have been put forward to account for the occurrence of lid retraction in thyrotoxicosis, and, on balance, from the evidence which has been produced, it would appear that spasm of the smooth palpebral musculature is the more attractive concept. There are, however, certain difficulties in an acceptance of this hypothesis:-

(a) The fact that lid retraction in thyrotoxicosis is a feature of the upper lid, whereas stimulation of the cervical sympathetic nerve produces retraction of both lids, although to a more marked degree in the upper lid than in the lower one.

This is a serious objection to the sympathicotonic hypothesis, unless the evidence which has been put forward in an earlier part of this thesis is accepted, namely that lower lid retraction occurs in the early stages of the condition and that this becomes masked when the more dominant upper lid retraction becomes effective.

(b) The fact that lid retraction in thyrotoxicosis is not characteristically associated with mydriasis.

Brain (1939) considered that the absence of a dilated pupil in thyrotoxicosis conflicts with the idea that lid retraction is due to sympathetic overaction. The absence of mydriasis in exophthalmic goitre has been stressed by many observers (Holloway, Fry and Wentworth, 1929; Justin-Besançon, Kohler and Schiff-Wertheimer, 1934; Plummer and Wilder, 1935; Weekers and Dedoyard, 1951). On the other hand Givner, Bruger and Lowenstein (1947) examined the pupil in hyperthyroidism by a pupillographic method and found some evidence of a sympathetic disturbance although of a central type. It is interesting to note that Justin-Besançon and others (1931) showed that intravenous ephedrine in dogs causes mydriasis and a very slight degree of exophthalmos, but if thyroxine is also administered a marked exophthalmos occurs which is only rarely accompanied by any dilatation of the pupil. Similarly Labbé and others (1931) demonstrated that in a case of obesity treated with thyroxine, administration of ephedrine produced exophthalmos with only very slight pupillary dilatation. It may be that in thyrotoxicosis the absence of mydriasis is not necessarily incompatible with the presence of increased sympathetic tone.

(c) The fact that lid retraction in thyrotoxicosis may occur despite the presence of a lesion of the peripheral sympathetic pathway.

Brain (1939) reported the development of lid retraction in a case of thyrotoxicosis superimposed on an old-standing syringomyelia. The syringomyelia was associated with involvement of the peripheral sympathetic pathways to the eyes, as shown by the earlier presence of ptosis, more marked in one eye than in the other. Following the onset of thyrotoxicosis bilateral lid retraction became apparent. The eye which had shown the lesser degree of ptosis developed the greater degree of retraction. This case would appear to refute any idea of the implication of the smooth lid muscles in the development of lid retraction. On the other hand, it may be that the integrity of the sympathetic nerve pathways is not essential to the development of lid retraction, and that circulating adrenaline may act on denervated smooth muscle which has been sensitized by an excess of thyroxine in the circulation.

It is interesting to note that Brunton (1935) produced retraction of the lids in cats and dogs with intravenous ephedrine irrespective of whether the cervical sympathetic pathway was intact or not. He concluded that the effect of ephedrine is a local one on the sympathetic nerve endings or on the smooth muscle fibres. Marine and Rosen (1934) even considered that the smooth muscles of the eye are more sensitive to adrenaline after cervical sympathetic ganglionectomy, an effect which was noticed within six days of the operation in cats and dogs (Bacq and Isola, 1946). Lockett (1950) also demonstrated a similar effect on the nictating membrane of the cat, and she found that pre-ganglionic or post-ganglionic sympathetic

denervation causes a marked increase in the threshold sensitivity to adrenaline or to dl-noradrenaline. Paton and Zaimis (1951) noted that the effect of adrenaline on the blood pressure is enhanced after the administration of hexamethonium, and this may be another example of adrenaline exerting a strong influence on a temporarily denervated structure.

The case described by Brain may not necessarily be regarded, therefore, as a contradiction of the view that sympathicotonic influences motivate the occurrence of lid retraction in thyrotoxicosis.

The opposing hypothesis, that lid retraction in thyrotoxicosis is due to overaction of the striated levator palpebrae superioris muscle, is attractive in explaining the marked upper lid retraction which is a characteristic feature of Graves' disease. There is, however, a serious difficulty in an acceptance of this hypothesis because lid retraction in thyrotoxicosis has been associated with an increased fat content of the levator palpebrae superioris, and there is evidence that a similar increase of fat within the extra-ocular muscles in Graves' disease is responsible for varying degrees of ophthalmoplegia (Rundle and Wilson, 1944a), particularly as a correlation has been shown between the amount of fat within the muscle and the degree of ophthalmoplegia.

It is indeed difficult to see how fatty changes may produce spasm of one striated muscle and weakness of another similar

muscle, and, even if the pathological changes within the muscle are discounted, it is still difficult to reconcile hypertonicity of one striated ocular muscle to the exclusion of the others (Cooper, 1849; François, 1951a).

It would appear more likely, therefore, that an increased fat content within the levator may produce a weakness of the muscle thus allowing a more marked action of the smooth muscle component within the lid (Adler, Scheie and Dennis, 1949). In this way thyroxine may play a dual role in facilitating lid retraction, first, by sensitising the smooth muscle to the action of circulating adrenaline (Mann, 1946b), and, secondly, by weakening the response of the striated muscle.

In any case it is difficult to ascribe a dominant role to pathological changes within a muscle in the mechanism of lid retraction. The rapidity with which lid retraction may develop in a case of thyrotoxicosis, and the equal rapidity with which it may disappear in certain cases after successful medical or surgical treatment of the thyroid dysfunction are more consistent with the response of a nervous mechanism.

It is doubtful if the single case described by Cogan (1953), in which lid retraction was relieved by tenotomy of the levator muscle, is of significance in this discussion because, irrespective of the mechanism of lid retraction, such an operation is bound to be followed by a lowering of the lid. On the other hand, it is of interest

to note that an injection of novocaine into the region of the stellate ganglion is reported by Cogan to have caused a miosis without affecting the position of the lids. Spaeth (1953b) also described the operation of levator recession in lid retraction, but this did not deter him from ascribing the mechanism of the phenomenon to a tonic spasm of the smooth muscle of the lid.

Other clinical considerations of lid retraction in thyrotoxicosis.

There is evidence that lid retraction is a more common feature of Graves' disease than exophthalmos, and that, although there is some association between exophthalmos and lid retraction, they may occur independently or simultaneously in Graves' disease (Pochin, 1938b).

Eden and Trotter (1942) noted the occurrence of lid retraction in 72 out of 134 cases of Graves' disease, whereas exophthalmos was present in only 19 of the cases. Donoso (1953) described lid retraction in 28 out of 57 such cases, and exophthalmos in 18 of the cases. Shannon and Hunt (1947) have claimed that 50% of cases of Graves' disease exhibit lid retraction without any evidence of exophthalmos. There certainly can be little ground for the statement of Knudtzon (1949) that an exophthalmometric measurement will confirm or refute the presence of early thyrotoxicosis. Lid retraction is not only an outstanding feature of Graves' disease but it may be one of the earliest manifestations of the disease and may even precede any general signs of the condition (Werner and Spooner, 1955). Lid retraction is usually bilateral and symmetrical but it may occur as a unilateral phenomenon (Dixon, 1941; François, 1951a).

It is important to realise that lid retraction causes an illusion of exophthalmos, and that judgement of exophthalmos is often fallacious when judged solely by direct observation (Benedict, 1936; Soley, 1942). This is particularly misleading when the lid retraction

is unilateral, as illustrated in fig. 22 in which the left eye appears to show a much higher degree of exophthalmos than the right eye. In fact, exophthalmometric readings showed an identical degree of exophthalmos in each eye, and the illusion of unilateral exophthalmos is due purely to the obvious lid retraction on the left side.

This concept is important also in assessing the state of the eyes following successful medical or surgical treatment of Graves' disease. Barr and Shorr (1945) noted an apparent reduction in exophthalmos follwing thiouracil treatment, and yet the exophthalmos was ound to have increased by 2 - 4 mm. The apparent improvement was due to a dramatic decrease in the amount of lid retraction. Similar observations have been made following thiouracil treatment (Dobyns and Haines, 1946a, b; Haines and Keating, 1946) and following thyroidectomy (Dobyns, 1945; Rundle and Wilson, 1945; Dobyns and Haines, 1946a, b). Naffziger (1948) stated that, although most cases appear to show a lessening of exophthalmos following thyroidectomy, only 5% of cases show an actual reduction in the degree of exophthalmos. This emphasises the importance of exophthalmometric observations before determining the state of exophthalmos (Bartlett, 1949).

FIG.22.

Case of thyrotoxicosis with an equal degree of exophthalmos in each eye (Hertel exophthalmometer, R = 19.5 mm., L = 19.5 mm.). Left eye appears more markedly proptosed due to retraction of the upper lid of that eye.

PART II - Exophthalmos Unrelated to Thyrotoxicosis (Thyrotrophic Exophthalmos)

Introduction

This type of exophthalmos appears to be independent of any increased function of the thyroid gland. In fact most cases are associated with a state of hypothyroidism.

In 1910 Gley found that thyroidectomy in rabbits resulted in the production of exophthalmos. He clearly differentiated this type of exophthalmos from that which followed stimulation of the cervical sympathetic nerve pathway. Gley offered no explanation for the mechanism of this exophthalmos, but Poncet (1910) postulated the presence of an exophthalmos-producing factor secreted by some organ other than the thyroid gland. He made the prophetic remark that this might be the pituitary gland.

A large number of experimental and clinical observations have pointed to the thyrotrophic hormone of the anterior pituitary body as being directly concerned with the production of exophthalmos. It is proposed to consider this aspect of the problem first, and then to discuss certain other endocrine glands which may also have an important influence on the problem of exophthalmos. The exophthalmos under consideration will be termed thyrotrophic exophthalmos. This

is not a strictly accurate term, but it at least signifies a type of exophthalmos which contrasts with that relating to thyrotoxicosis.

Clinically thyrotrophic exophthalmos is commonly termed progressive exophthalmos, and this name takes account of the active proptosis which is associated with the condition. It is also sometimes called malignant exophthalmos, and this is a useful term because it emphasises the fact that, in certain cases, the ocular manifestations run a rapid and grave course. On the other hand it is unsatisfactory because strictly speaking the term malignant exophthalmos should be restricted to cases of proptosis due to malignant growths in the region of the orbit, and, therefore, unrelated to endocrine disorder.

Means (1945) has termed progressive exophthalmos the hyperophthalmopathic form of Graves' disease. This is scarcely a euphonic term but it does emphasise that the ocular involvement completely overshadows any general manifestations of the condition. Brain (1938) introduced the term exophthalmic ophthalmoplegia for a group of cases showing marked proptosis with obvious limitation of ocular movements especially those of elevation. It is noteworthy that exophthalmic ophthalmoplegia, when considered in a broad sense, need not occur exclusively in the thyrotrophic phase of Graves' disease, in so far as the combination of exophthalmos and muscle weakness is found in thyrotoxicosis but in normal usage it implies a thyrotrophic type of change.

Nature of pathological process in thyrotrophic exophthalmos

Nature of pathological changes in orbital tissues.

The changes in the orbital tissues in thyrotrophic exophthalmos may be considered under five separate headings; increase in water content, increase in mucin content, increase in fibrosis, increase in lymphocytes and change in fat content.

1. Increase in water content.

There is widespread evidence that oedema is a characteristic feature of the orbital tissues in thyrotrophic exophthalmos, both experimentally (Smelser, 1936; Paulson, 1939; Aird, 1941; Albert, 1945; Dobyns, 1946b, d, e, 1950), and clinically (Foster Moore, 1920; Benedict, 1938; Brain, 1938; Haines, 1939; Means, 1940; Zondek and Ticho, 1945; Copper, 1948; Heinbecker, 1949; Falconer and Alexander, 1951; Medine, 1951; Craig and Dodge, 1952, 1953; Cuendet and Cruchaud, 1953).

Oedema in the orbit may occur as a primary effect following the influence of the hormone responsible for the production of exophthalmos (Means, 1943), and this is suggested by the experimental finding that orbital oedema occurs even if the eye has been previously enucleated (Smelser, 1943a). There may also be a local orbital tissue hypersensitivity (Heinbecker, 1949; Rose, 1952, 1953; Hedges and Rose, 1953); a striking tendency of the orbital tissues to take

up fluid has been noted by Naffziger (1952) in exophthalmos and the hydrophilic property of the tissues may persist even after decompression. The finding of a high protein content of the oedematous fluid in experimental exopnthalmos is suggestive of an increased permeability of the orbital capillaries (Smelser, 1947). This would appear to be dependent on some basic characteristic of the orbital fat because the oedema is much less evident in fat transplanted into the orbit from other fat depots of the body than in fat transplanted into the orbit from another orbit (Smelser and Ozanics, 1949). Furthermore, the oedematous process is not distributed evenly throughout the orbit; it occurs to a much greater degree in the fatty tissues than in the Harderian gland (Smelser and Ozanics, 1955), and it is more marked in the orbital fat than in the extra-ocular muscles (Smelser,1943**b**).

On the other hand, oedema in the orbit may occur as a secondary effect, perhaps as a result of the reaction within the connective tissues (Mulvany, 1944; Dobyns,1950), or as a result of the hydrophilic properties of the mucopolysaccharides which are known to accumulate within the orbit in exophthalmos (Ropes and others, 1947; Ludwig, Boas and Soffer,1950; Nuzum, 1953; Greene,1955).

There is certainly no evidence that oedema is the result solely of a venous obstruction; the orbital veins are too well endowed with alternative pathways of drainage (Drescher and Benedict, 1950) and there is no sign of any delay in the removal of radio-active

sodium from the orbital tissues in progressive exophthalmos (Day and Werner, 1954). Furthermore, oedema may occur in the lids at a sufficiently early stage in the development of exophthalmos to exclude a venous obstruction at the orbital septum as the determining mechanism (English, 1950). Undoubtedly, however, venous obstruction plays some part in the extension of the exophthalmos in the more advanced cases (Dobyns, 1950; Poppen, 1953).

It is also unlikely that orbital oedema is the result merely of the forward displacement of the eye allowing fluid to enter the orbit because a vacuum is created therein. It is probably unwise therefore, to draw too close an analogy between the oedema of the orbit in thyrotrophic exophthalmos and the oedematous fluid which rapidly enters a space formed artificially within the subcutaneous tissues, as in the experiment of Pochin (1949).

It may be that oedema of the orbit is the main factor in the production of exophthalmos (Means, 1940; Smelser, 1947; Dinsmore, 1952) and that the accumulation of this fluid is responsible directly for the marked increase in the intra-orbital pressure which is a characteristic feature of such cases (Albert, 1945). Certainly the orbit is closed in all directions except anteriorly so that any increase in the volume of the orbital contents must give rise to a certain degree of protrusion of the eye. Means (1945) and Shannon and Hunt (1947) have emphasised the importance of the oedematous changes by recommending that all such cases should be nursed with their heads

in the elevated position to assist in the drainage of oedematous fluid. Radiation of the orbit would also appear to be effective in reducing oedema (Jones, 1951; Stallard, 1955).

It should be noted, however, that some doubt has been cast on the role of oedema in the production of exophthalmos by Rundle, Finlay-Jones and Noad (1953) because, although they found an increase in the water content of the extra-ocular muscles in cases of severe progressive exophthalmos, this did not appear to be excessive when regard was taken of the increased bulk of the muscles.

2. Increase in mucin content.

An increase in mucin content has been found within the orbital tissues in experimental exophthalmos (Ludwig, Boas and Soffer, 1950), as shown by the increased hexosamine content which is a measure of the mucopolysaccharides, and by the increase in the amount of metachromatic ground substance which is a measure of hyaluronic acid. Hyaluronic acid is an important component of the ground substance of connective tissue and is probably derived from mast cells (Asboe-Hansen, 1950). This ground substance disappears on exposure to hyaluronidase. The fact that Ludwig, Boas and Soffer (1950) have shown an absence of any increase in the dried weights of the orbital contents in exophthalmos as compared with the normal guinea-pig orbit, despite the marked increase in bulk of the exophthalmic orbit, is further evidence of the role of mucin (or oedema) in the production of exophthalmos. Asboe-Hansen and Iversen (1951) have shown that TSH

administration in guinea-pigs is followed by replacement of the retrobulbar fat by a loose connective tissue containing mucopolysaccharides and mast cells.

An increase in mucin has also been found in the orbital tissues clinically (Curtis, Cawley and Johnwick, 1949; Iversen, 1954), particularly in semi-lunar spaces which form under the sarcolemma of the extra-ocular muscles as shown histochemically (Asboe-Hansen, Iversen and Wichmann, 1952). There is, however, doubt regarding the serum mucoprotein level in post-hyperthyroid exophthalmopathy; Mancini and Garberi (1952) reported a normal level whereas Fromm, Hecker and Silva (1954) found an increase in the serum level.

Further evidence of the significance of mucin in endocrine exophthalmos is the influence which may be exerted on exophthalmos by hyaluronidase, an enzyme which causes hydrolysis of hyaluronic acid, with perhaps also an absorption of the breakdown products N-acetyl glucosamine and glucuronic acid (Grais, 1949), and a consequent decrease in the water-holding abilities of the tissue ground substance (Nuzum, 1953). In experimental exophthalmos the injection of hyaluronidase into the orbit is followed by a transient increase in exophthalmos (Nuzum, 1953; Aterman, 1954a), but this is replaced by a definite enophthalmos (Nuzum, 1953; Aterman, 1954b) which persists for a short time before exophthalmos becomes re-established.

In clinical exophthalmos a temporary decrease in exophthalmos may follow retrobulbar injections of hyaluronidase (Grynkewich and others, 1951; Danis, 1954) a line of therapy suggested by Mills and Forsey (1949), and the consequent reduction in orbital tension may be sufficient to facilitate the performance of tarsorrhaphy in cases of severe exopthalmos (Stallard, 1955). Hyaluronidase has been found to assist in the diffusion of anaesthetic solutions injected into the retrobulbar tissues without causing any obvious ballooning of the tissues (Atkinson, 1949; Key and Key, 1950), and without causing any rise in intraocular pressure (Key and Key, 1950). On the other hand, Aterman (1954b) has considered that hyaluronidase injections into the orbit may be dangerous clinically, because of the initial increase in exophthalmos which may occur, and Kadin (1950) has reported a case of thyrotrophic exophthalmos in which an increase in exophthalmos and an increase in oedema followed an injection of hyaluronidase. In some other cases retrobulbar hyaluronidase has been followed by an improvement in ocular mobility without any effect on exophthalmos (Plessier, 1954).

3. Increase in fibrosis.

Experimentally, it has been shown that there is a replacement fibrosis within the orbit of the guinea-pig in TSH-induced exophthalmos (Paulson, 1937; Aird, 1941; Dobyns, 1946d), and a similar process occurs clinically (Thomson, 1924; Thomas and Woods, 1936; Benedict, 1938; Medine, 1951; Craig and Dodge, 1952, 1953). The fibrosis within the orbit may be so marked that it prevents any recession of exophthalmos even after subsidence of the acute

exophthalmic process (Ridley, 1952) and, in fact, certain cases of endocrine exophthalmos have presented as a pseudo-tumour of the orbit (Hope-Robertson, 1947). The fibrosis within the extra-ocular muscles may also be extensive (Meadows, 1952) and may account for a marked restriction of certain ocular movements; not only in the field of action of the affected muscle due to failure of its contraction, but also in the opposite field of action due to a failure of relaxation of the fibrosed muscle (Dunnington, 1947; Ridley, 1952). It has been shown by O'Connor and Pierce (1935) and by Falconer and Alexander (1951) that the fibrotic changes within the muscle do not assume an even distribution so that a single biopsy specimen of muscle tissue may not be representative of the true pathological picture within the muscle. It would appear that the changes in the muscle are fundamental and are not merely the result of the stretching of the muscle which follows the protrusion of the eye (Grósz, 1950). It is interesting, therefore, that Poppen (1950) denied any absolute relationship between the rapidity of the development of exophthalmos and the degree of ophthalmoplegia. In fact, Poppen found that muscle palsies are more common in the cases of moderate exophthalmos than in the cases of severe exophthalmos.

The occurrence of fibrosis in the orbit in exophthalmos is one of the reasons why an orbital decompression operation must be carried out in severe cases at a sufficiently early stage so that the orbital tissues are resilient enough to take advantage of the increased space within the orbit following the operation (Craig and Dodge, 1952,

1953). It is likely that the longer exophthalmos remains untreated the greater is the risk of irreparable damage to the orbital tissues due to scar formation (Gedda and Lindgren, 1954a, b). There is evidence that this process of fibrosis is lessened by radiation of the orbit (Jones, 1951; Chang, 1953; Gedda and Lingren, 1954a, b), and it may be that hyaluronidase injections are also of value in preventing subsequent irreversible fibrotic changes particularly in view of the nature of the myxoedematous process within the orbit (Levensohn, 1950).

4. Increase in lymphocytes.

There are many reports of the accumulation of lymphocytes in the orbital tissues in experimental exophthalmos (Albert, 1945; Dobyns, 1946b, d) and in clinical exophthalmos (Curtis, Cawley and Johnwick, 1949; Heinbecker, 1949; Falconer and Alexander, 1951; Medine, 1951; Meadows, 1952; Craig and Dodge, 1952, 1953). These cells are highly radio-sensitive and this may be a factor in the improvement in exophthalmos which sometimes follows radiation of the orbit (Jones, 1951; Chang, 1953; Stallard, 1955). An increase in the number of lymphocytes in the conjunctival tissues may follow thiouracil administration (Arvy and Gabe, 1950), and this is of interest in view of the increased exophthalmos which may follow thiouracil treatment.

5. Change in fat content.

There is little evidence that the thyrotrophic form of exophthalmos is associated with an increase in the fat content of the orbital tissues, and in this respect the changes in the orbit in thyro-

trophic exophthalmos differ from those which are more characteristic of a purely thyrotoxic form of exophthalmos, as discussed in an earlier part of this thesis. It has been shown experimentally that TSH causes rapid mobilisation of fat (Dobyns, 1946c), so that there is a depletion of the fat depots (Dobyns, 1946b, d), although Mann (1950) has stated that some fat may be deposited in the orbit following TSH stimulation. Poppen (1953) considered that in the solid progressive type of exophthalmos the fat content of the orbit is low due to the absorption of the fatty tissues by the other pathological events occurring within the orbit.

Rundle and Pochin (1944b) considered that the bulging of the lids which may occur in exophthalmos is due to a protrusion of orbital fat into the lids. It is more usual to explain this prominence of the lids on an oedematous basis, but Rundle and Pochin are unable to reconcile the absence of pitting on pressure with pure oedema.

It has been shown that an important part of the pathological change which occurs in the orbital tissues in thyrotrophic exophthalmos is present within the extra-ocular muscles. An investigation has been conduction, therefore, into the vascular pattern of normal extra-ocular muscles with a view to determining any feature of the circulation which may be of significance in a consideration of the pathological events which characterise the exophthalmic process. In particular each muscle has been examined for the possible presence of arterio-venous anastomoses.

Examination of vascular pattern within normal human extra-ocular muscles.

In this investigation the vascular pattern of the extra-ocular muscles has been examined in six human eyes, and, as far as could be ascertained, each eye was free from any local ocular or orbital disease, so that it may be assumed that this study in the main represents the vascular anatomy of the normal muscle.

The eyes together with their associated orbital structures were removed at post-mortem examination through an intra-cranial approach by the following technique, which is similar to that used in a study of other parts of the ocular circulation (Ashton, 1951, 1952; Wybar, 1954a, b, c, 1956).

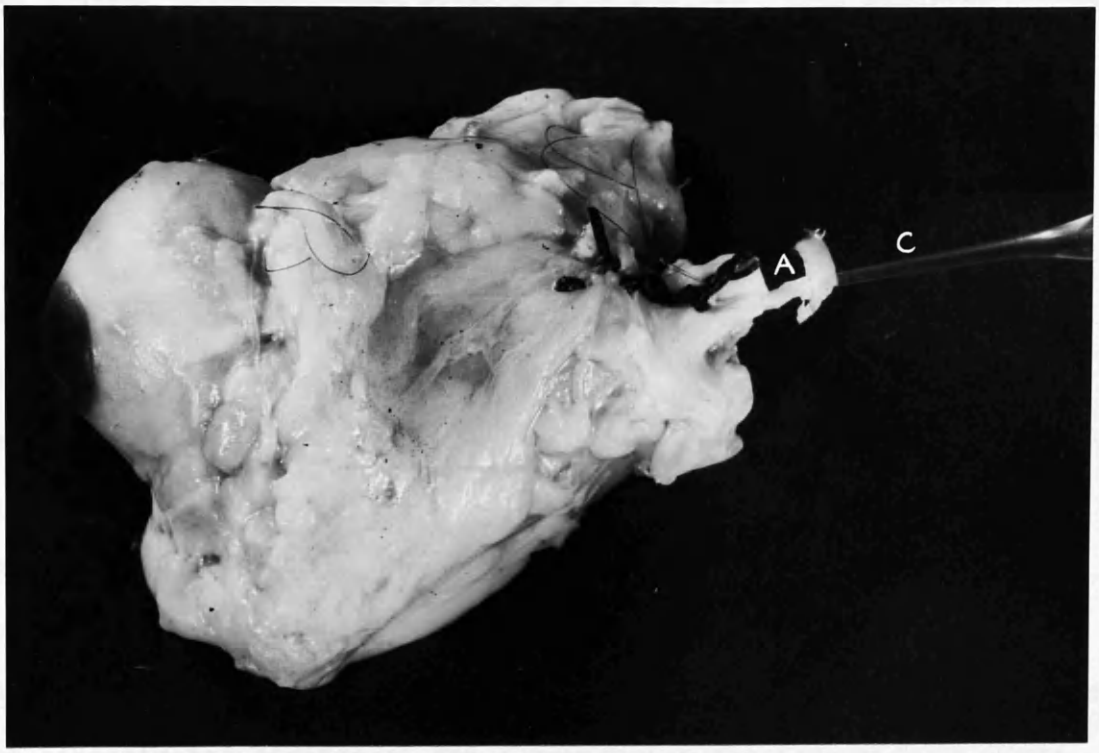
A sagittal incision was made in the scalp in the region of the vault of the skull, and, after reflexion of the scalp anteriorly and posteriorly, the bony cranium was removed by a coronal incision. The brain was then lifted out of the skull by incising the dura and arachnoid membranes and by severing the neuro-vascular connections of the brain with the extra-cranial structures. During this manoeuvre great care was taken to avoid any damage to two important structures. First, the optic nerves and chiasma which were left intact by cutting through the optic tract so that the chiasma was retained in its normal position in the base of the skull. Secondly, the internal carotid artery up to the point of origin of the ophthalmic artery and this

was left intact by cutting the artery after its emergence from the cavernous sinus at the origin of its two terminal branches, the anterior and middle cerebral arteries.

The orbital contents were then exposed by removing the anterior clinoid process, the lesser wing of the sphenoid including the roof of the optic canal, and the orbital plate of the frontal bone, and great care was taken during removal of these bony structures to avoid opening the periorbital sheath. The bulbar conjunctiva was incised round the limbus and, after severing the fibrous and muscular bands passing from the orbit to the eyelids, the whole orbital mass, including the extra-ocular muscles, the eyeball, the optic nerve, the ophthalmic artery and the cavernous portion of the internal carotid artery, was removed in one mass and placed in a container.

The ophthalmic artery, identified as it left the internal carotid artery to run under the optic nerve, was incised through half its circumference, and a glass cannula was inserted into the artery through the incision and ligatured in position (fig. 23). The vessels of the eye and orbit were then irrigated with tap water through the cannula for 60 minutes. Provided the orbital mass had been removed in a reasonably intact condition, this procedure was only associated with a gentle uniform capillary ooze, but in certain eyes when large superficial vessels were exposed it was necessary to ligate them before proceeding with the irrigation. A thorough preliminary irrigation was found to be an important step in the successful

FIG.23.



Cannula (C) used for irrigation and injection shown in position within ophthalmic artery (A).

injection of the muscular circulation. The ocular mass was then placed in the refrigerator for 12 hours. After thawing, the specimen was finally irrigated with water for 15 minutes, thus ensuring complete removal of any small residual particles of blood clot from the circulation. Two methods were adopted in the subsequent injection and examination of the muscles:-

(1) Injection of Neoprene latex (4 eyes).

Neoprene latex 572 was prepared for injection. This white synthetic rubber preparation, an emulsion of polymerised 2 chlorbutadium with a partial size of 0.1 - 1.0μ, was obtained from the B. B. Chemical Company. Neoprene was normally obtained with a consistency similar to that of milk, but sometimes it was in a more concentrated form, and it was then necessary to dilute it with a suitable amount of water. Neoprene is unsuitable for injection when too concentrated because of the tendency for the formation of clots within the smaller vessels thus preventing complete injection of the circulation in its ramifications.

The cannula in the ophthalmic artery was connected to a Woulff's bottle containing about 50 ml. Neoprene, and this was then injected into the ocular circulation under a pressure of 5 -10 lbs. using a small electric pump (Edward's rotary vacuum pump and compressor, type IV). Neoprene was found to coagulate rapidly on entry into the circulation, and it was, therefore, essential to commence the injection at a reasonably high initial pressure. This was achieved by releasing the clamps on the rubber tube connecting the Woulff's bottle to the cannula in the ophthalmic artery a fraction

of a second after switching on the electric pump. By this technique Neoprene was more likely to pass right along the whole length of the circulation including its fine terminal ramifications without causing blockage of any of the narrow vessels.

The change-over of Neoprene from a stable emulsion in the bottle to an irreversible colloid system within the circulation is probably due to a change in PH values. Neoprene is stable in the presence of alkali (as in the bottle) but precipitates in an acid medium (as in the tissues) to form a solid, resilient, acid-resisting and alkali-resisting substance. It is these properties which make Neoprene so useful in a detailed study of a densely vascular tissue.

Following the completion of the injection of Neoprene through the ophthalmic artery, the eyes were subjected to the action of digestive ferments. The injected orbital mass in its fresh state was placed in a saturated solution of pepsin in N/10 hydrochloric acid for a few days at 37°C, and then for a shorter period of time in 1% sodium bicarbonate at the same temperature. Neoprene is not susceptible to the action of digestive ferments so that a complete cast of the vessels within the muscle may be obtained but it was found to be important to stop the digestive process before it was quite complete otherwise, due to loss of all supporting structures, it was extremely difficult to identify the various vessel groups within the tangled network of Neoprene injected vessels.

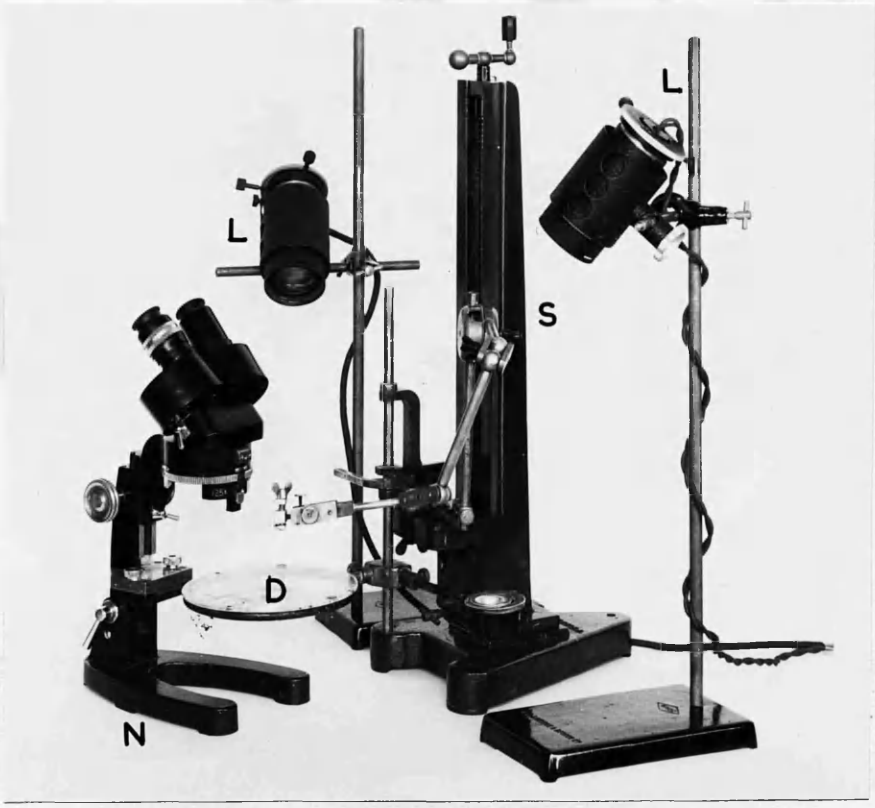
The partially digested orbital mass was dissected to reveal the individual extra-ocular muscles, and each muscle was then dissected under water in a large Petri dish which contained a thin layer of black paraffin wax. The vessel groups were identified, and where necessary pinned in position in the wax. (Fine glass pins were used in preference to steel ones because the latter cause contamination of the casts with rust particles after a few days under water). The remnants of the muscular tissue were carefully removed to complete the exposure of the pattern of the injected vessels within the muscle.

The cohesive and elastic properties of Neoprene permitted dissection of individual vessels and capillary areas from the main vascular mass, and these were studied in detail using a wide-field stereoscopic microscope with eye-piece lenses of X7 and X15, and objective lenses of X1.25, X5 and X10, giving a magnification range of X8.75 to X150 (fig. 24). Direct illumination was provided by one or two high-power low-voltage filament lamps (fig. 24). The initial stages of the dissections were carried out with ordinary plain forceps and sharp or blunt-pointed scissors, but thereafter the dissections were continued with very fine watchmaker's forceps and fine straight or curved spring scissors, so that it was possible to handle even the fine vessels individually (fig. 25).

(2) Injection of indian ink (2 eyes).

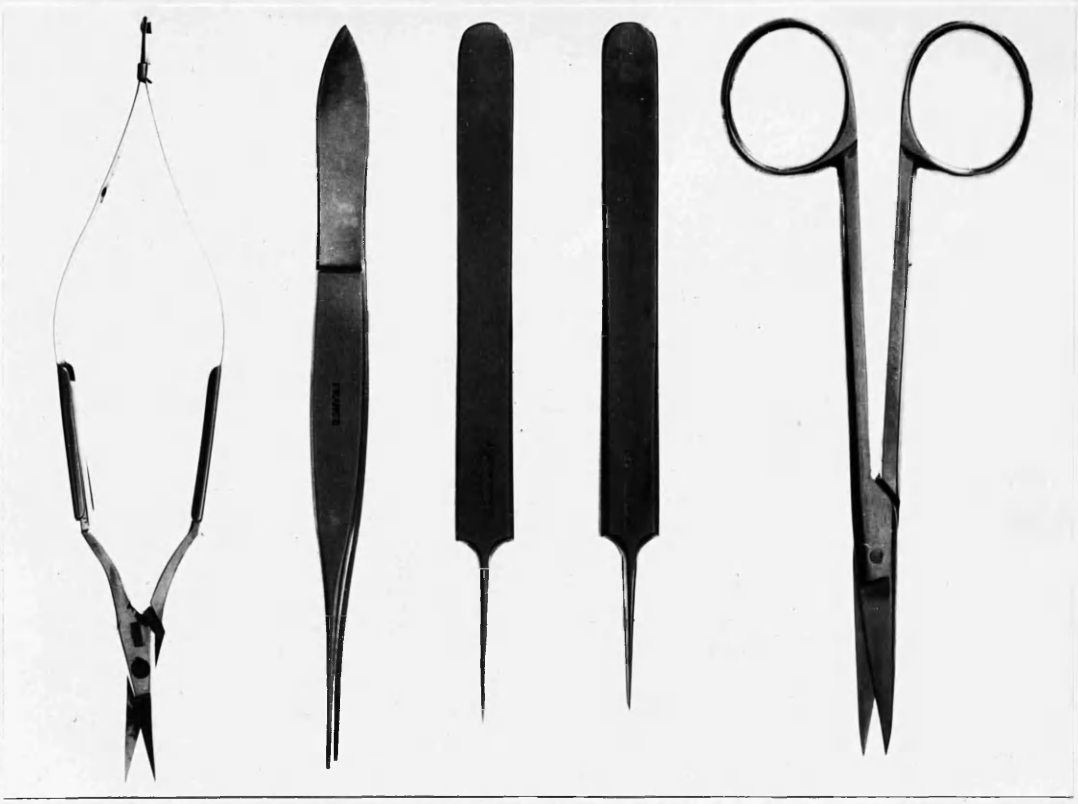
After thorough irrigation of the orbital circulation with water through the ophthalmic artery, 50 ml. indian ink was injected

FIG.24.



Wide-field stereoscopic microscope (N) with stand (S) for perspex platform (D). Direct illumination from two high-power low-voltage filament lamps (L).

FIG.25.



Dissecting instruments.

from a hand syringe. The eye was fixed in 10% formol saline, and then cleared by the Spalteholz method, a technique devised originally for the clearing of small embryos following the intravascular injection of some dye substance. In this method the eyes were dehydrated by passing them through 80% alcohol (1 day), 90% alcohol (1 day), absolute alcohol (1 day) and fresh absolute alcohol (1 day). They were then placed in a mixture of benzol and absolute alcohol, 1 part of each, (1 day), pure benzol (1 day), fresh pure benzol (1 day), and finally cleared by immersion in oil of wintergreen (3 parts of methylated spirits to 1 part of benzyl bonzoate). The specimens were maintained in oil of wintergreen during examination and storage. The injected vessels were examined through the semi-transparent muscular tissue with the stereoscopic microscope and under direct illumination.

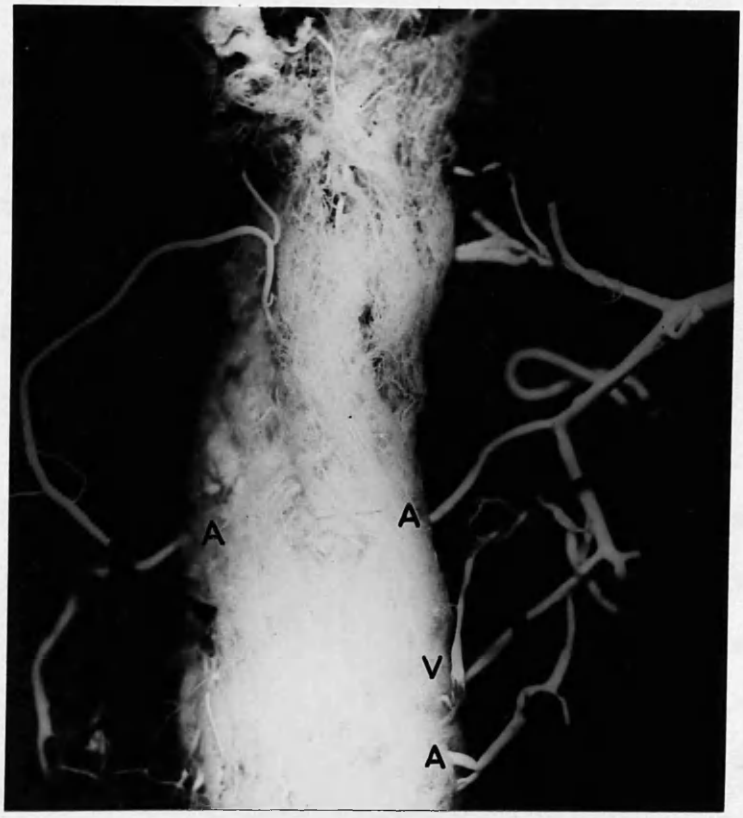
Findings.

The arteries of the extra-ocular muscles are derived from the posterior ciliary arteries within the orbit and, as a rule, each muscle is approached in both its longitudianl borders by a muscular artery near the junction of the proximal one-third with the distal two-thirds of the muscle. Each muscular artery breaks up into several branches near the muscle border (figs. 26 and 27) and these pass to the undersurface of the muscle where they enter its substance.

FIG.26.

Neoprene cast of orbital vessels showing the arteries (A) and veins (V) of the extra-ocular muscles.

FIG.27.



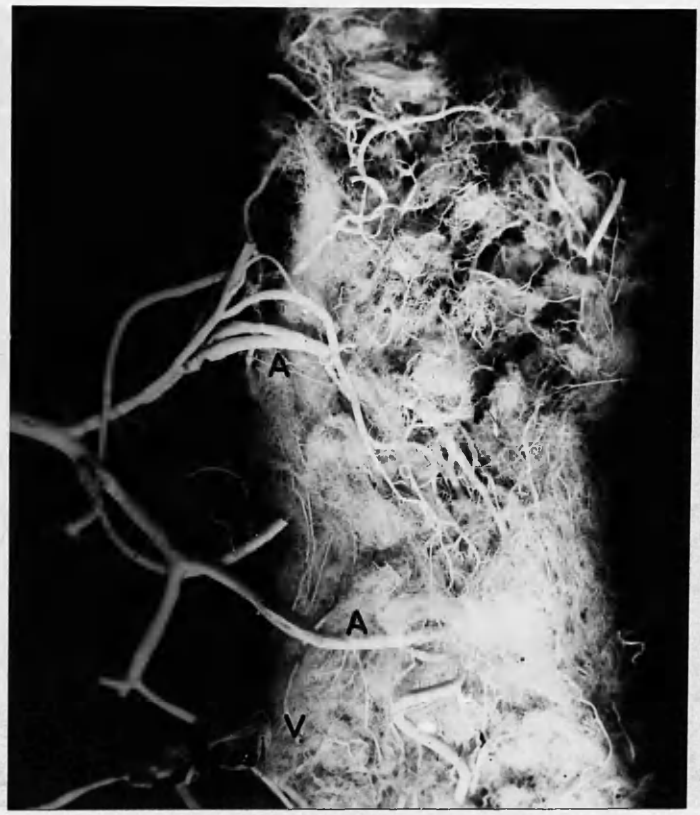
Neoprene cast of orbital vessels showing the arteries (A) and veins (V) of the extra-ocular muscles.

One large branch turns as it nears the centre of the muscle and continues its course along an axial direction towards the insertion of the muscle. This artery may divide into two or more smaller branches during its passage down the muscle, and it also gives off several smaller branches which pass in a transverse direction to the adjacent parts of the muscle tissue, but the main trunk of the artery is continued beyond the insertion of the muscle as an anterior ciliary artery. The other muscular branches also tend to turn in an axial direction towards the muscle insertion as they reach the centre of the muscle substance, but they are smaller arteries and break up into their terminal arterioles without running the length of the muscle. These smaller arteries are closely associated with the transverse branches of the main axial artery, and they provide the muscle with a dense network of arterioles and capillaries. These features are illustrated in figs. 29 - 34.

The venules take origin from the capillaries (fig. 33) and join together to form veins which run along a course corresponding to that of the arteries (figs. 26, 28 - 31), but there is no evidence, despite careful dissection of the vascular network of each extra-ocular muscle in this series, of any arterio-venous anastomosis except through the normal capillary channels.

There is no evidence, therefore, of any significant anatomical feature of the vascular circulation of the extra-ocular muscles which may be related directly to the exophthalmic process.

FIG.28.



Partial dissection of Neoprene cast showing arteries (A) and veins (V) within extra-ocular muscle. x 7.

FIG.29.

Partial dissection of Neoprene cast showing arteries (A) and veins (V) within extra-ocular muscle. x 8.

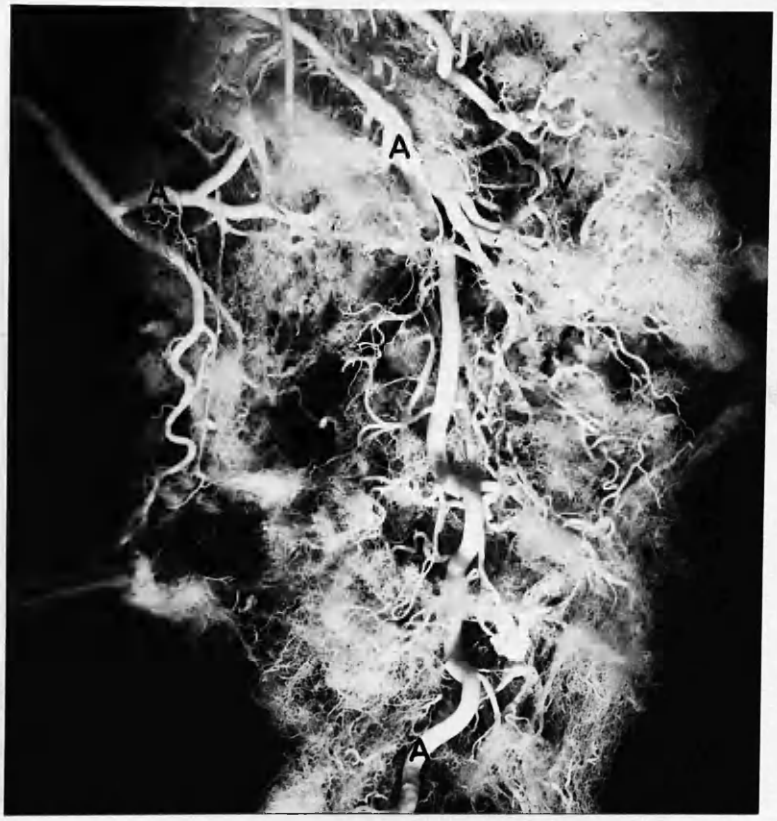
FIG. 30.

Dissection of Neoprene cast showing arteries (A) and veins (V) within extra-ocular muscle. x 9.

FIG. 31

Dissection of Neoprene cast showing arteries (A) and veins (V) within extra-ocular muscle. x 7.

FIG. 32.



Dissection of Neoprene cast showing arteries (A) and veins (V) within extra-ocular muscle. x 12.

FIG.33.

Dissection of Neoprene cast showing arteries (A) and veins (V) within extra-ocular muscle. x 12.

FIG.34

Indian ink injection of some vessels within extra-ocular muscle (Spalteholz method). x 7.

On the other hand, there is undoubtedly a very extensive network of vessels within the muscle so that it is easy to understand how readily the circulation may become embarrassed during any protrusion of the eye.

It is know that venous occlusion of muscle tissue results in necrosis, oedema, congestion and marked inflammatory reaction with a later proliferation of fibroblastic connective tissue leading to fibrosis and permanent contraction of the muscle (Adams, Denny-Brown and Pearson, 1954). It may be that a stasis within the extra-ocular muscles is responsible, at least in part, for the pathological picture which characterises thyrotrophic exophthalmos.

Effect of pathological changes in orbital tissues.

The effect of the pathological changes which occur in exophthalmos within the orbit is to produce a hypertrophy of the orbital contents with a consequent rise in orbital pressure (Brain, 1938; Mulvany, 1944; Doyne, 1945; Juler, 1945; Rundle, 1951; Craig and Dodge, 1952, 1953), an effect which has been demonstrated at decompression operation by the tenseness of the orbital fascia (Rundle and Wilson, 1945; Meadows, 1952). This increase in orbital tension has been measured accurately by Møller (1955) using a Tybjaerg-Hansen condenser manometer connected to a needle filled with fluid which is inserted into the orbital tissues. It may also be assessed by the method of Copper (1948) who used an orbitonometer to measure the extent of the retro-displacement of the eye following the application of a given pressure to the front surface of the eye.

Brain (1938) considered that the muscle weakness of exophthalmic ophthalmoplegia is due to this increased tension within the muscle cone. An attempt has been made to refute this concept by citing certain cases in which the muscle weakness preceded any sign of proptosis, for example, the cases of McGregor (1940), and of Martin and Pennell (1941), but these cases are examples of ophthalmoplegia due to thyrotoxicosis and are not, therefore, strictly relevant to the classical syndrome of exophthalmic ophthalmoplegia which is thyrotrophic in nature.

The fact that the retro-displacement of the eye decreases in direct proportion to the degree of exophthalmos (Kearns, Henderson and Haines, 1953) may be regarded as evidence that the increase in orbital tension is the immediate mechanism, or proximate cause (Brunton, 1949), of exophthalmos (Danis and Mahaux, 1951), although it has been shown by Copper (1948) that a small rise in orbital tension may occur without the production of obvious exophthalmos. It is possible that the lids exercise some effect in limiting the occurrence of exophthalmos (Rundle and Wilson, 1945) so that the degree of exophthalmos and the degree of orbital tension are not necessarily equal. The importance of the orbital tension is stressed by Naffziger (1952, 1954, 1955) who has shown that the height of the orbital tension is a more important criterion that the degree of exophthalmos in determining the necessity for a decompression operation. Furthermore, the value of orbital radiation may be primarily that it relieves orbital tension, and thereby reduces the incidence of ocular complications (Lyle, 1952).

Nature of pathological changes in extra-orbital tissues.

In a consideration of the pathological changes which occur in the orbit in endocrine exophthalmos it is important to take account of the reports of similar changes occurring in other parts of the body.

Experimentally, Dobyns (1946b, d, e) has shown that the changes which occur in the orbit of the guinea-pig following TSH administration are part of a generalised picture, with a depletion of all the fat depots in the body and a replacement of the fat by oedematous fluid, connective tissue and infiltrations of granulocytes, lymphocytes and tissue macrophages. A jelly-like appearance of the peritesticular connective tissues, resembling the changes within the connective tissues of the exophthalmic orbit of the guinea-pig, has been described by Asboe-Hansen and Iversen (1951) and by Aterman (1954a). Smelser (1939b) found a minimal amount of oedema throughout the fatty tissues of the body but, apart from the orbital changes, it was only marked in the peritoneal fat. Smelser suggested that this peculiarity of the orbital and peritoneal fat is due to their structure and not to their location in the body.

Clinically, there are a few reports of a generalised myositis in association with the typical changes in the extra-ocular muscles in progressive exophthalmos (Terplan and others, 1951), but this is not a common finding and, for example, the temporalis muscle has been shown to be entirely normal despite the presence of well-marked changes in the extra-ocular muscles (Meadows, 1952).

There is a most interesting association between progressive exophthalmos and localised areas of skin myxoedema. These areas of skin myxoedema, like exophthalmos, are part of the picture of Graves' disease (Ludwig, Boas and Soffer, 1950; Richtsmeier, 1952), and usually occur during the hypothyroid phase of the disease (Vila nova and Cañadell, 1949; Bott, 1950), particularly after thyroidectomy (Curtis, Cawley and Johnwick, 1949; Rosman, 1950), although more rarely they may occur during the hyperthyroid phase (Watson, 1946). There is certainly no evidence that they are direct manifestations of a pure hypothyroidism (Means, 1949) and, although they have been reported in a case of myxoedema, this case was complicated by the co-existence of a pituitary tumour (Degowin, 1946). There is evidence that both exophthalmos and localised myxoedema are manifestations of the same hormonal disturbance, possibly an excessive production of TSH (Degowin, 1946). This will be discussed more fully in a later section.

The cutaneous myxoedematous patches usually have a distinct outline and appear symmetrically on the body particularly on the anterior surface of the legs. They are variable in size and do not pit on pressure (Vila nova and Cañadell, 1949). They contain a colourless, sticky, gelatinous substance of a mucinous nature (Ropes and others, 1947; Grynkewich and others, 1951), probably

hyaluronic acid (Watson and Pearce, 1947), which infiltrates the collagenous tissues (Hanley and Philip, 1952). In addition to the increased hyaluronic acid within the tissues there is also an increase in the water content (Watson and Pearce, 1949).

Direct injections of hyaluronidase have proved effective in decreasing the size of localised areas of skin myxoedema (Sharlit, 1949; Bott, 1950), although the effect is only temporary unless firm pressure is applied to the area immediately following the injection (Rosman, 1950; Grynkewich and others, 1951), or unless the area softened by the injection is aspirated before the tissues become hardened again (Inch and Rolland, 1953). In some cases the lesions are prone to recur even after firm padding (Mills and Foosey, 1949). Means (1949) has reported a case of localised skin myxoedema in which the swelling dispersed following direct trauma of the affected area.

There is evidence, therefore, of a close relationship between exophthalmos and localised myxoedema (Asboe-Hansen, 1954), but because they do not always occur together and because, even when present together, they often do not occur to the same extent, doubt has been cast on whether the two conditions are attributable to the same basic mechanism (Beierwaltes, 1954). It may be, however, that the greater quantity of collagen in normal skin as compared with the normal orbit is responsible for the difference in reaction between the skin and eye lesions, because it is known that mucin is a

derivative of collagen (Curtis, Cawley and Johnwick, 1949). Furthermore, it is possible that localised myxoedema occurs more commonly than normally reported because, when present in a mild form, the skin lesions are readily overlooked (Netherton, 1949; Engel, 1953).

Nature of Hormonal Process

There are several hormones which may exert an influence on the thyrotrophic form of exophthalmos. These will be considered now.

Relation of thyrotrophic hormone (TSH) to exophthalmos.

The anterior pituitary gland secretes several hormones which are responsible for the regulation of the secretion of hormones from the peripheral endocrine organs, and one of these, the thyrotrophic hormone (TSH), is directed towards the thyroid gland.

In 1929 Loeb and Bassett found that an extract of the anterior pituitary gland causes stimulation of the thyroid gland in the guinea-pig. In 1930 they showed that this effect is due to the TSH in the extract. The thyroid gland acts as a storehouse and distributing centre for its iodine containing hormone, and TSH administration causes a reduction in the amount of colloid within the gland, with a corresponding increase in the amount of thyroid hormone in the blood (Closs, Loeb and MacKay, 1931). This closely resembles clinical Graves' disease.

Billingly, O'Donovan and Collip (1939) considered that there are two fractions of the thyrotrophic hormone, both of which have an effect on the metabolic rate, but only one of which mediates

its effect by way of the thyroid gland. Fraenkel-Conrat and others (1940) isolated a highly purified form of the hormone.

A major difficulty in the study of TSH is the absence of any biochemical test for its detection in the tissues and fluids of the body. Reliance has to be placed on biological assay. For example, Hertz and Oastler (1936) examined the histological changes within the thyroid gland in pituitarectomized rats after administration of the extract to be tested. Smelser (1938b) measured the height of the thyroid epithelium of day-old chicks. Rawson and Starr (1938) employed the same method as Smelser but using guinea-pigs. Galli-Mainini (1942) measured the change in oxygen consumption of the guinea-pig thyroid gland. De Robertis and Del Conte (1944) and Dvoskin (1947) observed the alteration in the colloid droplets within the thyroid epithelium. Purves and Griesbach (1949) examined the height of the thyroid epithelium. D'Angelo and others (1951a, b) employed the stasis tadpole technique.

These methods vary greatly in their sensitiveness to small amounts of TSH. They all have the disadvantage of requiring an elaborate technique which is difficult to control adequately. It is possible that some of the anomalous results, which have been reported, are based on a faulty assessment of TSH assay. In any case a biological test is unreliable in comparison with modern biochemical techniques (Duke-Elder and Goldsmith, 1951) and for this reason some of the conclusions regarding TSH may not be strictly valid. Further-

more, in animal experiments it is apparent that starvation alone causes a marked reduction of TSH secretion (D'Angelo, 1951) so that a change in feeding habits during the experiment may give rise to misleading results.

There is considerable doubt regarding the possible influence which TSH may have on the production of Graves' disease. It has been found fairly consistently that there is no evidence of the presence of the hormone in the urine or serum in thyrotoxicosis (Hertz and Oastler, 1936; Rawson and Starr, 1938; Purves and Griesbach, 1949), and this negative finding is difficult to reconcile with the straight-forward concept that TSH is the cause of Graves' disease.

On the other hand Marine (1935) considered that Graves' disease is due to an excess of TSH, either due to its over-production, or due to insufficient formation of anti-thyrotrophic factor. It may be that an excess of the pituitary hormone escapes detection because it becomes neutralised by the large amounts of thyroxine found in thyrotoxicosis. This possibility was shown by Rawson, Sterne and Aub (1942) by a tissue culture method in which they found that thyroid gland tissue taken from a case of thyrotoxicosis can inactivate twice the amount of TSH which is inactivated by normal thyroid tissue. Cope (1938) also considered that the absence of detectable TSH in Graves' disease is most likely to be due to its neutralisation by thyroxine. Alternatively he suggested that it might be due to the presence in the serum of large amounts of anti-

thyrotrophic factor. He found, however, that serum from a case of thyrotoxicosis did not cause depression of metabolism and, therefore, the former suggestion would appear more likely.

An interesting observation was made by Collard and others (1940). They injected TSH into two normal persons but were unable to detect the presence of the hormone in the urine. They considered however that this result cannot be due purely to fixation of the hormone by the thyroid gland, because the same result was obtained in cases which had been subjected to thyroidectomy. Cortell and Rawson (1944) considered that thyroxine could neutralise TSH and that this neutralisation occurs at an extra-pituitary level. It has been suggested that TSH is not detected in the urine in Graves' disease because iodine, which may be present in the urine in this condition, neutralises the hormone. This was investigated experimentally by Rawson and Starr (1938), but they did not find any such masking effect.

It would appear that the basophile cells in the anterior pituitary are the cells producing TSH. Severinghaus, Smelser and Clark (1934) showed that thyroidectomy in the rat causes a marked increase in size and number of the basophile cells, and a decrease in acidophile cells. Zeckwer and others (1935) confirmed this finding, and further showed the presence of large amounts of dense hyaline material within the basophile cells.

Ch'en and Van Dyke (1934) demonstrated an increase in the amount of TSH in the anterior pituitary of thyroidectomized rabbits. Zeckwer (1936b) confirmed this finding in the rat. She postulated that the accumulation of hyaline material within the basophile cells represents an increased secretion of the hormone. Zeckwer's results were criticised on the grounds that thyroidectomy causes a hypofunction of the gonads, and that, therefore, the abnormal cells in the pituitary represent the so-called "castration cells" which are known to occur in the anterior pituitary following gonadectomy. However, in further experiments Zeckwer (1936a) refuted the criticism by showing that there is a clear distinction between the "thyroidectomy cells" and the "castration cells". On the other hand Nelson and Hickman (1937) considered that the two types of basophiles are identical, although they represent different phases of a secretory cycle which reacts differently to thyroidectomy and to castration.

There is a considerable wealth of evidence to suggest that exophthalmos may be attributed to the influence of TSH. This evidence may be grouped into two fundamental types. First, evidence of a direct nature wherein the actual influence of TSH has been determined, and, secondly, evidence of an indirect nature wherein the influence of TSH has been assumed because of a change in the amount of circulating thyroid hormone.

Direct evidence that TSH causes exophthalmos.

Experimentally, there is strong evidence to suggest that TSH is responsible for the production of exophthalmos and that its effect is independent of the thyroid gland secretion (Means, 1943). Albert (1945) has shown that exophthalmos occurs rapidly in the fundulus (common Atlantic minnow) following the injection of anterior pituitary extracts of various types, and he inferred that TSH is the causative agent because exophthalmos only occurs in thosefish showing hyperplasia of the thyroid gland, evidence of thyrotrophic stimulation. This form of exophthalmos persists after death, anaesthesia or cervical sympathectomy. Exophthalmos has been produced also in guinea-pigs by the injection of pituitary extracts containing TSH (Marine and Rosen, 1933; Smelser, 1937; Dobyns, 1946a, d; Rawson, 1949; Ludwig, Boas and Soffer, 1952), and, when these extracts are incubated with thyroid tissue prior to injection there is a loss of the exophthalmic effect (Rawson, 1949; Dobyns and Rawson, 1951). This is a significant result because it is known that TSH becomes inactivated on exposure to a culture of thyroid tissue (Heinbecker, 1952). Smelser (1939a) showed that this form of experimental exophthalmos is independent of the integrity of the sympathetic nerve pathways or of Muller's orbital muscle.

Aird (1940) demonstrated that TSH-induced exophthalmos is dependent on pathological changes in the orbit and it has been suggested (Curtis, Cawley and Johnwick, 1949; Kamel and Hamdi, 1949)

that TSH is a potent factor in the formation of oedema and that this contributes in a large extent to the production of progressive exophthalmos. Mann (1950) also has considered that TSH is responsible for orbital oedema and, in addition, for increased fat in the orbit. In this connection it is interesting that Albert (1945) concluded that TSH may exert a direct effect on the orbital tissues because he found that exophthalmos develops in the fundulus after local injection of the hormone into the orbit. Heinbecker (1949), as a result of his work on dogs, has considered that TSH shares with other anterior and posterior pituitary extracts an anti-diuretic action and that this water-retaining influence is a potent factor in the swelling of the intra-orbital contents, particularly, the muscles, connective tissues and fat, in exophthalmos. It may be significant that Copper (1948) found an increased sense of orbital resistance in Cushing's syndrome, although without any exophthalmos, because it is known that this is a disease of the pituitary basophile cells which are responsible for the secretion of TSH.

Clinically, there is further evidence that TSH causes exophthalmos. Stallard (1936, 1937) described an interesting case of thyrotoxicosis in which TSH was administered at a time when the basal metabolism was subnormal and the exophthalmos was mild. This was followed by a transient thyrotoxicosis which quickly subsided but with the subsequent development of severe and progressive exophthalmos. Leiter (1950) has shown that severe exophthalmos is

prone to occur after thyroidectomy in those cases in which there are abnormally high amounts of TSH in the serum pre-operatively. This is in keeping with the finding of a high level of TSH in the serum of certain cases of progressive exophthalmos (Galli-Mainini, 1942; de Robertis, 1948; Asboe-Hansen, Iversen and Wichmann, 1952; Silvestrini, Melloni and Pasargiklian, 1953), and with the finding of a low level of TSH in the serum of other cases of Graves' disease showing an absence of progressive exophthalmos (de Robertis, 1948). In certain cases of progressive exophthalmos the increased TSH level has been noted in the urine instead of in the plasma (Klotz, 1948a).

There is an interesting association between progressive exophthalmos and a localised form of myxoedema affecting particularly the skin of the pre-tibial region (Villanova and Canadell, 1949; Grynkewich and others, 1951; Hanley and Philip, 1952), and it may be that both these lesions are due to a common factor. They tend to occur after the successful medical or surgical treatment of thyrotoxicosis and the role of TSH is their production is strengthened by the finding of an abnormally high titre of TSH in the urine (Villanova and Cañadell, 1949), particularly as this titre decreases markedly following oestrogen administration in association with a reduction in exophthalmos and in the size of the skin lesions.

The ability of ovarian hormones, particularly the natural ones (François, 1951), to suppress TSH production has been shown by Lederer (1948) and François (1951) and they considered that the fact

that these hormones also reduce exophthalmos is further evidence of the role of TSH in the genesis of exophthalmos. The role of the gonadal hormones in exophthalmos will be amplified in a later section but mention must be made here of the claim that parahydroxypropriophenone (PHP), a synthetic oestrogen, may also be of value in reducing exophthalmos because of its inhibiting effect on TSH secretion (Perrault, 1950; Chávez Montes, 1952a, b; Okie, Daley and White, 1952). Fossati, Silvestrini and Melloni (1953) described four cases of progressive exophthalmos treated by pituitary irradiation, and it is significant that the level of TSH in the blood became reduced as a result of this therapy.

Exophthalmos has been reported in newborn babies whose mothers have been treated for thyrotoxicosis by thyroidectomy (Keynes, 1952; Skelton and Gans, 1955), by thiouracil (Keynes, 1952), or by radio-active iodine (Koerner, 1954). There is evidence that the reduction in thyroid function in the mother is responsible for an over-secretion of TSH which passes across the placental barrier to influence the developing foetus. Particular support is given to this concept by the case cited by Koerner (1954) because, in addition to the marked exophthalmos and puffiness of the eyelids, the baby exhibited an enlarged thyroid gland and an abnormally high pulse rate, further evidence of TSH stimulation.

Indirect evidence that TSH causes exophthalmos.

There is evidence of a pituitary-thyroid axis whereby the pituitary and thyroid glands are able to exert an influence on one another. This concept is of great significance in a consideration of the role of TSH in the production of the exophthalmos because it indicates that a change in thyroid secretion may be responsible for an alteration in TSH secretion.

Pituitary-thyroid relationship.

It has been shown that TSH causes an increase in the uptake of radio-active iodine by the thyroid gland (Stanley and Astwood, 1949; Bogoroch and Timiras, 1951; Frederickson, Forsham and Thorn, 1952; Epstein and others, 1953), and also an increase in the rate of secretion of the thyroid hormone from the gland into the blood stream (Keating and others, 1945; Heinbecker, 1949; Albert, Tenney and Ford, 1952). In an interesting experiment Junqueira (1947) has shown that exposure of the thyroid gland of the rat to TSH in vitro results in an accumulation of intracellular colloid within the gland.

There is also evidence that thyroid hormone is able to exert an influence on TSH, and it has been shown clinically that a high level of thyroid hormone in the blood is associated with a low level of TSH (de Robertis, 1948; Purves and Griesbach, 1949; Simkin, Starr and Hancock, 1953), as demonstrated by the decreased uptake of radio-active iodine by the thyroid gland (Greer, 1951).

It is likely that this effect of thyroid hormone is directly on the TSH and not merely the result of an influence on the thyroid gland causing a decrease in its ability to respond to TSH, because when exogenous TSH is given during the phase of depressed thyroid activity following thyroxine administration, the thyroid gland responds in a normal manner by increasing its uptake of iodine (Perlmutter and others, 1952). Furthermore, when TSH is added to a culture of thyroid tissue the TSH becomes inactivated (Seidlin, 1940; Heinbecker, 1952).

This pituitary-thyroid relationship, or pituitary-thyroid axis of Salter (1940), is a finely adjusted mechanism and it has been shown (Purves and Griesbach, 1949) that when the level of thyroxine in the blood becomes reduced there is a further secretion of TSH followed by an outpouring of thyroid hormone with a consequent diminution in the output of TSH until the whole cycle occurs once more. This chain of events has been termed an example of a "servo system" by Hoskins (1949) because it is one in which variations or consequences of variations in the quantity of the output of the apparatus are fed back for the control of the system. This mutual relationship of the two hormones was clearly shown by Galli-Mainini (1941). He demonstrated in the guinea-pig that an intravenous injection of TSH produces a rise in oxygen consumption of the thyroid tissue, whereas injection of thyroxine causes a lowering of oxygen consumption. He also showed that if certain proportions of the two

hormones are injected simultaneously, there is no alteration in the oxygen consumption. The relationship leads, therefore, to a state of equilibrium or "homeostasis" (Cannon, 1929), and the functional equilibrium may be achieved by the interaction of the two hormones in the circulation (Means, 1939).

The maintenance of the pituitary-thyroid axis appears to be independent of nervous impulses. Thyroxine can affect the thyrotrophic hormone level with equal facility before and after complete pituitary stalk section (Uotila, 1940). The transmission is probably purely a humoral one.

In relation to the pituitary-thyroid axis a fine distinction has been drawn between the use of the terms thyrotrophic and thyrotropic as applied to the thyroid stimulating hormone of the anterior pituitary. "Thyrotropic" means that the pituitary secretion turns specifically towards the thyroid, whereas "thyrotrophic" indicates that the thyroid is nurtured or maintained by the trophic activity of the pituitary secretion.

It is natural that a permanent reduction in the secretion of the thyroid gland may be followed by a prolonged rise in the amount of TSH in the blood and this may be regarded as an example of a release phenomenon (Simpson, 1945). There is certainly no doubt that severe progressive exophthalmos is a relatively new disease and has followed in the wake of surgical and medical advances in the treatment of thyroid disorders (Ruedemann, 1947). It may, therefore, be regarded as one of the iatrogenic diseases.

An increased TSH in the blood may be brought about by surgical removal of the thyroid gland (Gordon, Goldsmith and Charipper, 1945; Soffer and others, 1947), and it is associated with a hypertrophy of the pituitary and with an increase in TSH within the gland. Administration of thyroid hormone restores the pituitary to its normal size (Marine, Rosen and Spark, 1935). Increased amounts of TSH may also be found in the urine following thyroidectomy (Emerson and Cutting, 1938).

An increased TSH in the blood may follow medical treatment with a goitrogen such as thiouracil (Astwood and others, 1943; Mackenzie and Mackenzie, 1943; Fralick, 1949; Purves and Griesbach, 1949) which is known to cause a depressed avidity of the thyroid gland for iodine (d'Angelo and others, 1953) and which is an effective therapeutic agent in the treatment of toxic goitre (Crile, 1947; Jackson, 1948) by producing a state of functional thyrostasis (Baumann, Metzger and Marine, 1944). Further evidence that thiouracil causes an increased production of TSH is found in the histological changes within the pituitary gland following thiouracil administration as shown by an increase in basophile cells (Salter, Cortell and McKay, 1945; Sellers, Hill and Lee, 1953), and by the fact that exposure to thiouracil in vitro not only restores the activity of TSH which has been annulled by previous exposure to iodine but also augments the activity of normal TSH extracts (Albert and others, 1947a, b; Jefferies, 1949b).

It is interesting to recall that some earlier experiments do not appear to be in accordance with the view that thiouracil increases the level of TSH because the reverse effect has been found (Gordon, Goldsmith and Charipper, 1945). Further investigation by these observers has shown, however, that the decreased level of TSH is only found when the enlarged thyroid gland is able to mop up the excess TSH, and that an increased level of TSH is found in the blood when a thyroidectomised animal is used; an excess which is greater than may be accounted for solely by the thyroidectomy. Their experiments confirm, therefore, that thiouracil facilitates TSH production. In this connection it is of interest to note that Seidlin (1940) found that TSH injected into the guinea-pig is only recovered in quantity in the thyroidectomised animal.

A hypertrophy of the pituitary gland with an increased secretion of TSH is found in rats maintained on a diet of low iodine content which failed to provide sufficient thyroxine for normal metabolic demands (Gassner, Barrett and Gustavson, 1947). This is a further sign of an inverse pituitary-thyroid relationship.

It follows, therefore, that any evidence which shows, either that a decrease in the function of the thyroid gland favours the production of exophthalmos or that the administration of thyroid hormone is in favour of the reduction of exophthalmos, may be regarded as an indirect indication of the responsibility of TSH in the genesis of exophthalmos.

Exophthalmos-producing following thyroid hypofunction.

(1) Exophthalmos following thyroidectomy.

Experimentally, there is evidence that thyroidectomy alone causes a slight degree of exophthalmos in the guinea-pig (Dobyns, 1945; Ludwig, Boas and Soffer, 1950; Williams, 1953), and that thyroidectomy intensifies the exophthalmos which follows TSH administration (Dobyns, 1946a, d; Smelser, 1947; Ludwig, Boas and Soffer, 1950; Aterman, 1952a, 1954a); in fact Dayton (1952) considered that it is essential to carry out a preliminary thyroidectomy in order to produce experimental exophthalmos by TSH. Exophthalmos may occur in thyroidectomised rats fed on a thyroxine-free diet (Leblond and Eartly, 1952).

Clinically, there is also evidence that thyroidectomy in Graves' disease may be followed by an increase in the degree of exophthalmos (Thomas and Woods, 1936; Soley, 1942; Dobyns and Haines, 1946a, b; Post, 1947; Martin, 1948; Alonso, 1949; Hunt, 1949; Netherton, 1949; Moffatt, 1951; Woods, 1951b; Richtsmeier, 1952; Wayne, 1954; Bergfelt, 1955), particularly when in the pre-operative stage the ocular signs predominate over the general manifestations of the disease (Leiter, 1950), or the B.M.R. is low (Sturgis, 1953) or lid oedema is associated with the exophthalmos (Robertson, 1945), or when in the post-operative stage there is a dramatic fall in the basal metabolic rate (Dobyns, 1945). Thyroidectomy has been considered to be a greater danger in

precipitating the occurrence of severe exophthalmos than any other form of treatment designed to reduce the functioning power of the thyroid gland (Ruedemann, 1949; Chandler, 1950), although sub-total thyroidectomy is safer than total thyroidectomy (Johnson, 1949). It is certainly an outstanding feature of the surgical treatment of Graves' disease that very often the only residual manifestations of the condition are ocular ones (Martin, 1948).

(2) Exophthalmos following thiouracil administration.

Experimentally, there is evidence that thiouracil administration may be followed by exophthalmos in rats (Sellers and Ferguson, 1949; Baird, Sellers and Ferguson, 1950; Sellers, Hill and Lee, 1953; Campbell and Tonks, 1955), although Campbell and Tonks have shown that the exophthalmos persists only during the period of administration of the goitrogen, and Rawson, Tannheimer and Peacock (1944) failed to produce exophthalmos by such treatment. A rapid and severe form of exophthalmos has been produced in marine teleost fish by thiouracil (Leloup and Olivereau, 1950). Cima (1951) considered that although experimental exophthalmos may follow thiouracil administration it is less marked than after thyroidectomy.

Clinically, there is no doubt that an increase in exophthalmos may follow thiouracil therapy (Givner, Bruger and Lowenstein, 1947; Netherton, 1949; Strong, 1949; Taylor, Large and North, 1950; Ferguson, 1951; Hanley and Philip, 1952; Richtsmeier, 1952; Fraser and Wilkinson, 1953; Fernández, Landazuri and Matas, 1954; Wayne, 1954) and there is certainly no evidence that thiouracil

causes a reduction in exophthalmos (Haines and Keating, 1946), although opinion varies on the extent of this exophthalmos and on how it compares with the exophthalmos which follows other anti-thyroid measure, particularly thyroidectomy. There is no doubt that severe exophthalmos may follow such treatment (Bastenie, 1950), but it may be that it is prone to do so only in cases showing a progressive type of exophthalmos before treatment (Beierwaltes, 1948).

Dobyns and Haines, (1946a, b) considered that although exophthalmos may progress after thiouracil therpy it does so to a lesser degree than following thyroidectomy, and Ruedemann (1949) thought that malignant exophthalmos may be avoided completely by treating Graves' disease with goitrogens. Several series of cases of Graves' disease have been treated in this way without the occurrence of malignant exophthalmos (Gabrilove, Kerr and Soffer, 1945; McCullagh, Ruedemann and Gardner, 1946; Beierwaltes, 1948; Wing and Asper, 1942; Donoso, 1953), so it may be that this is the treatment of choice in patients who are considered to be susceptible to the development of severe exophthalmos following the reduction of the hyperthyroidism (Chandler, 1950).

On the other hand it has been considered that thiouracil is just as prone to cause severe exophthalmos as thyroidectomy (Barr and Shorr, 1945; McCullagh and Sirridge, 1948; Fralick, 1947, 1949; Dayton, 1953). It has even been suggested that thiouracil is more liable to cause exophthalmos than thyroidectomy (Taylor,

Large and North, 1950). Campbell and Tonks (1955) came to the conclusion that thiouracil is no clinical safeguard against the occurrence of exophthalmos as a result of their experimental observations on the effect of thiouracil on exophthalmos and Andersson (1950) was very careful when using thiouracil in a case in which exophthalmos preceded the other manifestations of hyperthyroidism by several years.

It should be noted, in connection with the role of thiouracil in the production of exophthalmos, that a thiouracil-like action has been attributed to para-amino-salicylic acid (PAS) and it is of interest that treatment with PAS may be followed by hypothyroidism and even by the development of exophthalmos (Hamilton, 1953).

(3) Exophthalmos following thyroid gland irradiation.

A progressive form of exophthalmos may follow irradiation of the thyroid gland applied in the form of surface X-rays (Soley, 1942; Strong, 1949; Richtsmeier, 1952) or in the form of radio-active iodine (Blomfield and others, 1951; Wong, 1953; Haines, 1954). There is some evidence to suggest that this form of treatment for Graves' disease may be less prone to cause severe exophthalmos than thyroidectomy (Soley, 1942; Haik, 1944; Chandler, 1950; Sturgis, 1953), and in a series of cases treated in this way there was no increase in the exophthalmos or in the sense of retro-ocular resistance following therapy (Ferguson, 1951).

It may be that irradiation of the thyroid gland is less prone to be followed by exophthalmos because there is no rapid reduction in the amount of circulating thyroid hormone (Wayne, 1954), and this form of treatment may be especially suited to cases showing a susceptibility to severe exophthalmos particularly as it is possible to give small doses of radiation (Haines, 1954). On the other hand this view is in conflict with that of Engel (1953) who has stated that treatment of Graves' disease with radio-active iodine is not the ideal form of treatment because it does not permit enough elasticity of management and that after administration of the radio-active drug there is no further control of the response of the thyroid gland.

(4) Exophthalmos following sudden cessation of thyroid hormone therapy.

Exophthalmos of the progressive type may follow the sudden cessation of thyroid hormone administration after a prolonged period of treatment with the hormone (Behrman, 1945, 1946; Rubin and Billet, 1954). It may be that the sudden withdrawal of exogenous thyroid hormone in such cases is responsible for a hypersecretion of TSH from the pituitary gland as part of a release phenomenon.

(5) Exophthalmos following spontaneous thyroid gland hypofunction.

Certain cases of Graves' disease may exhibit a spontaneous

reduction of the thyrotoxic state, and this may coincide with the development of a progressive form of exophthalmos (Mann, 1946b, 1951). It may be that the decline in thyroxine production is associated with a compensatory increase in TSH secretion.

Exophthalmos-reduction following thyroid hormone administration.

Experimentally, there is evidence that thyroid hormone reduces the incidence of exophthalmos which has been induced in guinea-pigs by TSH administration (Smelser, 1947; Williams, 1953) and by TSH and cortisone administration (Aterman, 1952a). It is also known that the development of a thyrotoxic state may coincide with a reduction in the degree of experimental exophthalmos (Aterman, 1954a). The exophthalmos which occurs in the thyroidectomised rat on a thyroxine-free diet may be controlled by the administration of thyroid hormone (Leblond and Eartly, 1952), and the incidence of exophthalmos in rats following thiouracil administration is reduced by similar treatment (Sellers, Hill and Lee, 1953). The exophthalmos-producing effect of TSH in guinea-pigs is annulled by preliminary incubation of the TSH with thyroid hormone (Rawson, 1949; Dobyns and Rawson, 1951).

Clinically Marine (1938) considered that thyroxine offers specific protection against the development of exophthalmos and there are many reports that the exophthalmos which occurs in Graves' disease following a reduction in the function of the thyroid gland,

either by surgical or medical means, may be lessened in degree after the administration of thyroid hormone (Means, 1939; Salter and Soley, 1944; Brain, 1945; Dobyns, 1945; Juler, 1945; Woods, 1946; Lederer, 1950; Blomfield and others, 1951; Sloane, 1953; Igersheimer, 1954, 1955), even although this may be associated with a slight recurrence of the thyrotoxic state (Dobyns, 1945; Juler, 1945); an event not without danger because it may necessitate further anti-thyroid measures which in turn may lead to a renewal of the exophthalmic process (Engel, 1953). It may be that thyroid hormone therapy is most effective in cases of exophthalmos occurring in a hypothyroid phase.

Exophthalmos-reduction or exophthalmos-production following iodine administration.

The role of iodine in exophthalmos is most uncertain. There is some evidence that it may be effective in reducing the degree of exophthalmos in some cases of progressive exophthalmos (Means, 1945, 1948; Givner, Bruger and Lowenstein, 1947), although Zondek and Ticho (1951) failed to find this effect with di-iodotyrisine. Means (1945) has suggested that the value of iodine may lie in its ability to exert a controlling influence on metabolism, and, therefore, to enable larger doses of thyroid hormone to be administered than would otherwise be possible. There is also evidence that iodo-thiouracil is less prone to cause progressive exophthalmos than other anti-thyroid drugs because of its iodine content (Artunkal, 1953). A further indication of the exophthalmos-reducing property of iodine may be inferred from the suggestion of Thomas (1951) that a factor is the causation of progressive exophthalmos is a relative iodine lack in the body.

Plummer (1926) is an enthusiastic advocate of iodine therapy, and he stated that he has seen grave progressive proptosis begin to recede within a few hours of iodine administration. Plummer based his faith in iodine on his two-product theory of the thyroid gland. This postulates that in Graves' disease there are two products secreted by the thyroid gland; first, an excess of normal thyroid

hormone (thyroxine), and, secondly, an excess of an abnormal hormone which is believed to be an incompletely iodised form of thyroxine. It is this abnormal hormone which Plummer considered to be responsible for the ocular manifestations and nervous reactions of the disease. He believed that the abnormal hormone loses its toxicity following iodine administration because the hormone then becomes fully iodised, and with this change in the character of the hormone there is an improvement in the ocular manifestations. There is, however, no conclusive evidence for the hypothesis of Plummer, and it is difficult to explain the occurrence of progressive exophthalmos following thyroidectomy on such a basis. It has been suggested that any thyroid tissue which remains after the operation may continue to manufacture the abnormal product, but there seems no reason why the residual thyroid tissue should secrete this hormone without also secreting the normal hormone.

It is conceivable to regard the findings which indicate an exophthalmos-reducing effect of iodine as further evidence of the role of TSH in the production of exophthalmos, because it has been shown that iodine may annul the influence of TSH (Albert and others, 1946; Junqueira, 1947; Jefferies, 1949b) although this was only an in vitro effect.

On the other hand there is evidence that iodine, in certain cases of exophthalmic goitre, may cause an increase in the

degree of exophthalmos (Haines, 1928; Thompson and Thompson, 1931). It is still possible, however, to use an exophthalmos-producing effect of iodine as an indication of the role of TSH in the production of exophthalmos because it may be argued that iodine, by reducing the output of thyroid hormone, may cause an indirect increase in the secretion of TSH. It is interesting, therefore, to note that Soffer and others (1947) have demonstrated a transient rise in TSH in the serum in cases of Graves' disease treatment with iodine.

The role of iodine in the exophthalmic process is undoubtedly conflicting and it would appear to be unwise in the present state of knowledge to draw any far-reaching conclusions from this aspect of the work on the wider issue of the relation of TSH to exophthalmos.

It is apparent that there is a great mass of direct and indirect evidence to implicate TSH as the responsible factor in the production of exophthalmos, but there are certain difficulties in the full acceptance of this hypothesis and these will be detailed now.

Difficulties in hypothesis that TSH causes exophthalmos.

(1) It has been shown that experimental exophthalmos may follow the administration of crude anterior pituitary extracts containing small quantities of TSH, and yet there is evidence that a purified form of TSH may fail to produce exophthalmos (Lambie, 1939; Dobyns, 1946a; Dayton, 1952; Smelser and Ozanics, 1955).

(2) It has been shown clinically that TSH may be responsible for the production of exophthalmos, and yet there are cases in which large amounts of TSH have been administered for prolonged periods without the development of exophthalmos (Thompson, 1946; Simkin and Starr, 1953; Simkin, Petit and Starr, 1954). It is important to note, however, that the thyroid gland was intact in these cases so that the ability of the thyroid gland to respond to TSH stimulation may have limited the effectiveness of TSH as an exophthalmos-producing hormone. Furthermore, it has been noted experimentally that there is often no correlation between the amount of TSH administered and the subsequent degree of exophthalmos

(Jefferies, 1949a; Smelser and Ozanics, 1954). TSH has never been isolated from the orbital tissues in experimental exophthalmos (Simkin, Petit and Starr, 1954).

(3) It has been shown that a high level of TSH may be found in the blood of certain cases of progressive exophthalmos, and yet there are many cases showing a severe form of exophthalmos in which there is no evidence of any abnormal titre of TSH in the serum (Collard and others, 1940; Purves and Griesbach, 1949; d'Angelo and others, 1951b; Falconer and Alexander, 1951; Simkin, Petit and Starr, 1954), or even of any disturbance in the activity of the thyroid gland (Medine, 1951). There is also sometimes an absence of a positive correlation between the amount of circulating TSH and the degree of exophthalmos (Falconer and Alexander, 1951).

Further evidence of the possible occurrence of exophthalmos in the absence of a high titre of TSH would appear to be derived from a study of a case of myxoedema reported by Degowin (1952) in which exophthalmos and pretibial myxoedema followed the development of a pituitary tumour without any thyrotoxic manifestations, and, also from a study of certain cases of primary (thyroidal) myxoedema showing localised skin myxoedema (Gabrilove, Ludwig and Soffer, 1952). This is not necessarily a valid conclusion, however, because in primary myxoedema the thyroid gland is in a refractory state so that

it is not capable of responding to TSH stimulation. The absence of thyrotoxicosis in such cases may not be evidence, therefore, of the absence of circulating TSH.

There are, of course, other cases of hypothyroidism in which there is a deficiency of pituitary secretion in addition to the deficiency of thyroid hormone (Marine, 1935), and the absence of exophthalmos in such cases is no argument against the role of TSH in exophthalmos production (Greene, 1955). On the other hand, Dobyns and Haines (1946a, b) have claimed that the administration of thyroid hormone to cases of myxoedema with pituitary insufficiency may be followed by a reduction in the prominence of the eyes and from this it is argued that the effect of thyroid hormone cannot be on TSH thereby casting a doubt on the role of TSH as an exophthalmos-producer. It may not be correct, however, to assume that there is a complete cessation of TSH secretion in cases of this type.

(4) It has been shown that a high level of TSH in the blood may be associated with exophthalmos, and yet a marked titre of TSH may be found in the serum in certain cases of hypothyroidism (Hertz and Oastler, 1936; Collard and others, 1940; Galli-Mainini, 1942; McCullagh, Ruedemann and Gardner, 1946; de Robertis, 1948; Schrire, 1948; d'Angelo and others, 1949; Purves and Griesbach, 1949), and of acromegaly (Galli-Mainini, 1942; McCullagh, Ruedemann and Gardner, 1946; d'Angelo and others, 1949, 1951b), without the

occurrence of exophthalmos (Haines, 1939; Savin, 1943). Similarly, exophthalmos associated with a high level of TSH may become greatly reduced without any apparent change in the TSH titre (d'Angelo and others, 1951b).

It should be noted that Copper (1948) has described the occurrence of exophthalmos in acromegaly, although it would appear to be distinct from thyrotrophic exophthalmos because it is associated with a diminished sense of retro-ocular resistance. In this connection it is interesting to remember that acromegaly is a disorder of the acidophile cells of the anterior pituitary, whereas TSH is a product of the basophile cells.

Non-toxic goitre is also never associated with the development of exophthalmos (Soley, 1942). Rawson, Graham and Riddell (1943) have shown that this type of thyroid tissue is unable to inactivate TSH, whereas normal thyroid gland tissue can inactivate a certain amount of the hormone. This may be evidence that non-toxic goitre is associated with some increase in the level of TSH in the blood, and yet exophthalmos does not occur in the condition.

(5) It has been shown that thyroidectomy in Graves' disease may be followed by a rise in the titre of TSH in the serum, and yet, although exophthalmos may develop or become accentuated post-operatively, the occurrence of severe exophthalmos following thyroidectomy is a relatively rare event (Cattell, 1934; Ryan, 1949),

and in some large series of cases may even be absent (Dollerup, Hansen and Mølgaard, 1953). In fact, Savin (1943) declared that there is some recession in the degree of exophthalmos in 70% of cases after thyroidectomy, and Fischer (1948) found an increase in exophthalmos in only 5% of cases post-operatively. On the other hand, Hunt (1947), Shannon and Hunt (1947) and Pagliarani and Cavicchi (1950) thought that 50% of such cases show a temporary increase in exophthalmos during the immediate post-operative period, and Lamberg (1954) put the figure as high as 72%, but, of course, these figures do not refer to the occurrence of severe exophthalmos. The rarity of progressive exophthalmos following thyroidectomy certainly presents a distinct difficulty in the acceptance of the hypothesis that TSH is the exophthalmos-producing hormone (Duke-Elder and Goldsmith, 1951; McCullagh, 1953; Oastler, 1953).

Zondek and Ticho (1945) put forward the unusual suggestion that exophthalmos following thyroidectomy is unrelated to pituitary secretion. They postulated that the normal thyroid hormone has a dehydrating influence, and that its sudden removal allows a water retaining factor to become dominant. This concept is completely at variance with the hypothesis that TSH is an exophthalmos-producing factor.

In the experimental field Jefferies (1949a) considered that thyroidectomy is not followed by exophthalmos, a view supported

by Aird (1940) and Pochin (1944) but Jefferies amplified this by the statement that thyroidectomy does not intensify the exophthalmos produced by TSH alone, so that he concluded (Jefferies, 1952, 1953) that any apparent increase in exophthalmos following thyroidectomy is due purely to an increase in body weight; a conclusion which is a contradiction of most other accepted experimental observations, details of which have been given in an earlier part of the thesis.

(6) It has been shown that thyroid hormone may exert a restraining influence on TSH, and yet, although it may exert a beneficial effect on certain cases of exopthalmos, it is often singularly ineffective (Means, 1945; Beierwaltes, 1948; Cole, 1951; Falconer and Alexander, 1951; McCullagh, 1953; Simkin, Petit and Starr, 1954). A reduction of TSH may be noted in the blood following thyroid administration without any decrease in the degree of exophthalmos (Falconer and Alexander, 1951). There is also evidence that, although some improvement may be found in exophthalmos as a result of thyroid therapy, no correlation exists between the amount of thyroid hormone administered and the degree of reduction of exophthalmos obtained (Hedges and Rose, 1953). Jonnson (1947), however, doubted the ability of thyroid hormone to exert any inhibiting action on the pituitary gland.

It may be that thyroid hormone is able to exert an effect on exophthalmos quite apart from an influence on TSH and such a concept would appear to be necessary to explain the reduction in exophthalmos which may follow thyroid hormone administration without any apparent

reduction in the high level of TSH in the serum. Thyroid hormone has a diuretic and dehydrating influence (Gaunt, Cordsen and Lilling, 1944; Curtis, Cawley and Johnwick, 1949; Heinbecker, 1949) and this effect may be operative on the oedematous orbital tissues in exophthalmos (Chandler and Hartfall, 1952). Thyroid hormone also has a depressing influence on the number of circulating lymphocytes (Heinbecker, 1949), and it causes a decrease in the amount of metachromatic staining material which is believed to be of a muco-proteinous nature and which occurs in localised myxoedema (Gabrilove, Ludwig and Soffer, 1952) although it has no effect on the normal mast cells of the dog (Devitt, Pirozynski and Samuels, 1953). Conversely, a deficiency of thyroid hormone results in an accumulation of mycopolysaccharides in the skin tissues (Werner, Hamilton and Frantz, 1951).

Furthermore, it has been suggested by Aterman and Greenberg (1954) that any beneficial effect of thyroid hormone on exophthalmos is due to the hormone preventing the build-up of excessive quantities of adrenocortical steroids owing to the greater utilisation of these steroids following the increase in the basal metabolic rate.

(7) It has been shown that iodine may act as an exophthalmos-producing factor or as an exophthalmos-reducing factor and their evidence has been brought forward to show that iodine

favours the secretion of TSH or lessens the effect of TSH, respectively, and yet there is also evidence that iodine fails to alter the level of TSH in the serum (Smelser, 1938a; Paulson, 1939; Simkin, Starr and Hancock, 1953).

(8) It has been shown that there is a claim that parahydroxypropriophenone (PHP) may be effective in reducing the secretion of TSH so that it causes a reduction in exophthalmos, and yet there are several reports in which PHP has proved to be of no value (Schaffenburg and others, 1951; Weekers and Dedoyard, 1951; Brady and Hedges, 1952; Hedges and Rose, 1953; Wong, 1953; Danis, 1954), or at best of little value (Pagliarani, 1952). On the other hand this may not necessarily be a point against the influence of TSH on exophthalmos because doubt has been cast on the ability of PHP to act as an inhibitor of TSH; PHP fails to affect the collection of iodine by the thyroid gland of the rat or chick (Money and others, 1951b), and it also fails to produce any histological changes within the pituitary gland (Schaffenburg and others, 1951).

(9) It has been shown that there is evidence that TSH causes exophthalmos, and yet it is surprising that exophthalmos is seldom associated with evidence of increased activity of the thyroid gland in view of the known action of TSH as a stimulator of the

thyroid gland (Prunty, 1949). Of course, in many cases the thyroid gland is absent, following surgical removal, or in a refractory state, following medical treatment, but there are other cases in which there has been no previous surgical or medical treatment. It may be that, as suggested by Friedgood (1934), there is an establishment of an antibody reaction to the thyroid stimulating effect of TSH without the extablishment of a similar reaction to the exophthalmos-producing factor. It is doubtful, however, if this interpretation may be applied to the clinical sphere (Prunty, 1949).

It is apparent, therefore, that, despite the many experimental and clinical findings which point to TSH as the hormone responsible for the production of exophthalmos, it is not possible at this stage to fully substantiate such a hypothesis, so that, as Albert (1952) has stated, the evidence which supports the view that TSH produces exophthalmos is equivocal and circumstantial. It is natural that attention should have been directed to other hormones in an attempt to cast more light on the basic nature of the hormonal upset. On the other hand the importance of TSH must not be overlooked in a search for other hormones because there is little doubt that TSH plays an important role in exophthalmos-production

(Oastler, 1953) or at least that it acts as an accessory in the crime (Greene, 1955), acting perhaps in conjunction with a gonadal factor (Marine and Rosen, 1936). It has been suggested, however, that the association of an increased TSH with exophthalmos in certain cases may merely be because they are both manifestations of the same unknown primary lesion (Purves and Griesbach, 1949).

Relation of some unknown Pituitary Hormone to Exophthalmos.

(Exophthalmos-producing substance, EPS.)

There is a great deal of evidence to suggest that the pituitary gland plays a decisive role in the production of exophthalmos even if the relation of TSH to exophthalmos is discounted (Dinsmore, 1952). Certain cases of progressive exophthalmos are associated with an enlargement of the sella turcica and an abnormal glucose tolerance test (Zondek and Ticho, 1945) or with acromegaly (Worster-Drought, 1927, 1934; Brain, 1943; Copper, 1948; Vail, 1949). An interesting case of myxoedema has been reported in which exophthalmos developed in the later stages of the condition following the onset of a pituitary tumour (Degowin, 1952). Bardram (1944) found an increase in the output of gonadotrophic hormone in the urine in three cases of progressive exophthalmos presumably evidence of increased pituitary activity. Iglesias (1948) reported a bitemporal constriction of the visual fields in one-third of a series of cases of hyperthyroidism, evidence of hypophyseal disturbance, although such an unusual finding must be regarded with a certain amount of caution. Piper (1952) noted a rapid increase in height in a five year old who developed thyrotoxicosis and exophthalmos, presumably all effects of an excessive pituitary secretion.

Furthermore, there is evidence that irradiation of the pituitary body may be followed by some reduction in the degree of exophthalmos (Mandeville, 1934; Ginsburg, 1939; Mann, 1946a, b;

Ravdin, Rose and Maxwell, 1949; Beierwaltes, 1951; Van Manen, 1951; Zondek and Ticho, 1951; Hermann, 1952; Juler, 1952; Gedda and Lindgren, 1954a, b; Igersheimer, 1954, 1955; Brain, 1955; Muñoz and Barca, 1955), although it is emphasised by Beierwaltes (1953) that the response to irradiation may be delayed for many months. This effect on exophthalmos may be the result of a reduction in the secretion of the pituitary hormone responsible for exophthalmos, and it is interesting that Dinsmore (1952) found a direct association between the reduction of exophthalmos and a drop in the serum count in cases treated in this manner. It has been claimed that irradiation is effective in re-establishing a synergy between the hypophysis and the subthalmic region (Berkman, 1954).

On the other hand, doubt has been cast on the ability of pituitary irradiation to influence exophthalmos (Hedges and Rose, 1953), and in certain series of cases treated in this way the effect has been a negative one (McGregor, 1940; Cole, 1951; Jones, 1951; Keyes and Parisi, 1953). Irradiation of the pituitary may not be followed by any histological changes within the gland (Kelly and others, 1951), and although it may produce a slight fall in the sperm count, it does not influence menstruation (McCullagh, Ruedemann and Gardner, 1946). It has even been suggested that any beneficial effect of pituitary irradiation is due to a scattering of the rays into theorbit where they are able to exert a reducing influence on the swollen orbital tissues

(Stallard, 1955). It should be noted, however, that despite their negative findings with irradiation, McCullagh, Ruedemann and Gardner (1946) appeared to confirm the role of the pituitary in exophthalmos-production because they found a marked reduction in exophthalmos following electro-cauterisation of the pituitary.

It has been suggested that the pituitary secretes an exophthalmos-producing factor or substance (EPS) which is distinct from the thyroid-stimulating factor (TSH) (Dobyns, 1946a; Klotz, 1948c; Purves and Griesbach, 1949; Jefferies, 1949a, 1952, 1953; Simkin and Starr, 1953; Smelser and Ozanics, 1955), and this is supported by the hypothesis of Schrire (1948) that the different components of Graves' disease, the creatinuria, the increased basal metabolic rate, the exophthalmos, etc., may be the responsibility of different hormones.

There are several observations which support the concept of a separation of the EPS and TSH effects. Crude preparations of the pituitary gland containing TSH produce exophthalmos and thyroid hyperplasia in guinea-pigs, and yet purified TSH does not cause any significant degree of exophthalmos although it retains its full thyroid-stimulating property (Dobyns, 1946a). Oestrone has been shown to cause a limitation of the effect of TSH on the thyroid gland without influencing the effect of TSH on exophthalmos (Gassner, Barrett, and Gustavson, 1947). Iodination of a pituitary extract at PH 5 - 6 may cause an inactivation of the thyroid-stimulating

and exophthalmos-producing effects of TSH, but when this iodination is carried out at PH 4.2 there is a loss of practically all the thyroid-stimulating effect without any reduction of the exophthalmos-producing effect (Jefferies, 1949b). Antibodies develop in the serum to the thyroid-stimulating property of TSH (Collip and Anderson, 1934; Friedgood, 1934; Scowen and Spence, 1936; Loeser, 1937), but not to the exophthalmos-producing fraction (Friedgood, 1934; Pochin, 1944), so that the establishment of the antigen-antibody reaction is not associated with any regression of exophthalmos (Friedgood, 1934; Pochin, 1944). It may be that the exophthalmos-producing factor is non-protein in nature so that it does not excite the formation of antibodies (Friedgood, 1934), but in any case this study of antibody reaction may be construed as evidence that some factor other than TSH is responsible for exophthalmos (Friedgood, 1941).

On the other hand, there is little doubt that TSH and EPS are closely allied to one another (Smelser and Ozanics, 1954), and Rawson, (1949) has demonstrated that both the TSH and EPS effects are annulled on incubation in vitro with thyroid tissue. There is evidence, however, that the two factors may co-exist in the serum in inverse proportions to one another (Dobyns and Stedman, 1953), and this finding provides an explanation of the apparently anomalous cases in which there is a low titre of TSH in the serum in severe exophthalmos and a high titre in the serum in mild exophthalmos. An interesting expermiment has been carried out by Dobyns and Wilson (1954) in which serum from

cases of progressive exophthalmos, containing known quantities of EPS, was injected into the common Atlantic minnow with the production of an exophthalmos which was roughly in proportion to the degree of exophthalmos in the donor.

Relation of hypothalamus to exophthalmos.

In a consideration of the role of the pituitary in exophthalmos it must be remembered that any change which occurs in the pituitary gland may be initiated by a stimulus from the diencephalon, and this is borne out by the fact that shock or fright (Mann, 1947), or even purely psychogenic sources of emotion (Simpson, 1945), may predispose to the development of progressive exophthalmos. A most interesting case has been recorded by Rosman (1950) of localised skin myxoedema following thyroidectomy in which, some time after the condition had been greatly improved by local hyaluronidase injections, there was a dramatically sudden return of the skin lesion immediately after a severe emotional shock. Brull (1953) described a case of Graves' disease without any exophthalmos in which exophthalmos developed after a bereavement.

Marine and Rosen (1933) sought to implicate the hypothalamus in the production of experimental exophthalmos. It was found that administration of methyl cyanide to rabbits results in the production of exophthalmos (Marine, Spence and Cipra, 1932), and Marine and Rosen (1933) considered that this exophthalmos is closely related to that which they produced by the administration of TSH to the thyroidectomised animal. They postulated that methyl cyanide causes inhibition of tissue oxidation, and that this affects the hypothalamic autonomic nerve centres, which in turn stimulate the anterior pituitary so that there is an increased secretion of TSH.

They suggested that the upset of tissue oxidation may also have a direct stimulating effect on the anterior pituitary. The increased amount of TSH produces two effects. First, it causes thyroid hyperplasia, and secondly, it causes stimulation of the hypothalamus. The hypothalamic excitation results in contraction of the smooth muscles in the orbit and eyelids with the production of exophthalmos.

Marine and Rosen (1934) postulated that the exophthalmos which follows thyroidectomy in experimental animals is produced by the same mechanism. The thyroidectomy causes a depression of the oxidative processes within the tissues, which in turn sets up a similar chain of events to those which follow methyl cyanide administration. They stressed the necessity for a state of thyroid insufficiency before it is possible for the exophthalmos to become established. They regarded the thyroid hyperplasia which follows methyl cyanide administration as signifying a state of exhaustion of the thyroid gland with a consequent decline in its secretion.

On the other hand Salter (1940) considered that the depression of tissue oxidation due to cyanide acts in the same way as various stimuli like cold, fear, lactation, etc., by causing an activation of the thyroid gland. On this interpretation the hyperplasia of the thyroid gland noted by Marine would indicate an excessive secretion of thyroid hormone. Uotila (1939) regarded the thyroid hypertrophy which follows exposure to cold as being due

to a marked increase in the secretion of TSH. He considered that this effect on the pituitary is mediated by the hypothalamus, and that it is dependent on the integrity of the connecting nervous pathways between these two regions. He showed that under ordinary enviromental conditions the influence of the hypothalamus on the pituitary is a humoral one, but that in abnormal circumstances there is an additional nervous influence.

It is, therefore, possible that following methyl cyanide administration there is an increase in the production of TSH. This is borne out by the observations of Marine, Rosen and Spark (1935) who found similar histological changes within the anterior pituitary gland after methyl cyanide as after thyroidectomy. These changes are related to an increased secretion of TSH.

The exophthalmos produced by methyl cyanide differs, however, radically from the so-called thyrotrophic exophthalmos. Marine, Rosen and Cipra (1933) found that exophthalmos does not occur if the cervical sympathetic pathways have been cut prior to the administration of methyl cyanide. This contrasts sharply with the findings of Smelser (1936, 1937) that exophthalmos could be produced, by administration of TSH to thyroidectomised guinea-pigs, without any dependence on the integrity of the sympathetic nerve pathways .

Furthermore , the exophthalmos produced by methyl cyanide does not appear to be dependent on definite histological

changes within the orbit. In fact, Marine (1938a) considered that any orbital changes, for example, oedema or congestion, are purely secondary to the exophthalmos. Another contrasting feature is that iodine when given concomitantly with methyl cyanide protects against the development of exophthalmos.

It would appear that the exophthalmos produced by Marine and his associates has certain characteristics of thyrotoxic exophthalmos with its dependence on an increase in sympathetic tone. Marine, Spence and Cipra (1932) found that the development of exophthalmos was accompanied by a marked nervousness of the rabbit, and that there was obvious hyperaemia of the suprarenal medulla. Smelser (1938a) considered that this type of exophthalmos is unrelated to the pituitary hormones.

There is no doubt that a vast amount of evidence has accumulated which implicates the anterior pituitary gland in the production of endocrine exophthalmos, although, as yet, it cannot be regarded as conclusive (Benedict, 1950). It is, however, peculiar that exophthalmos is seldom a feature of primary pituitary disease or of destructive lesions in the neighbourhood of the pituitary gland, and it is natural that attention should have shifted to other endocrine centres, notably the adrenal cortex and the gonads. These will be considered now.

Relation of adrenocorticotrophic hormone (ACTH) and of adrenocortical hormone (cortisone) to exophthalmos.

There is undoubtedly a close relationship between the thyroid and adrenal glands, and it is natural that the adrenal cortex and its associated pituitary hormone should have been investigated as possible factors in the genesis of endocrine exophthalmos.

Thyroid-adrenal relationship.

The evidence regarding the nature of the thyroid-adrenal relationship is conflicting and each suggested type of relationship will be examined separately.

1. There is evidence that an increase in the function of the thyroid gland is followed by a decrease in the function of the adrenal gland.

Experimentally, the administration of thyroxine to rats produces a hyperthyroid state which is followed, after a short initial phase of increased adrenocortical function, by a marked reduction in adrenocortical function (Wallach and Reineke, 1949). In dogs the experimental production of Graves' disease may be associated with adrenal atrophy (Heinbecker, 1952).

Clinically, thyrotoxicosis may be associated with a deficiency of adrenocortical function (Marine, 1930a; Blomfield and others, 1951), and the increased number of circulating lymphocytes which is found in hyperthyroidism may be evidence of a similar deficiency (Simms, Pfeiffenberger and Heinbecker, 1951). The occurrence of pigmentation of the eyelids in certain cases of thyrotoxicosis may have a similar explanation in view of the known association between pigment deposits in the skin and hypoadrenalism in Addison's disease (Doggart, 1949). Begbie (1868) mentioned in a footnote to his translation of a paper of Virchow's on "struma exophthalmica", that he had seen a case of pigmentation of the skin in Graves' disease. It has been postulated that there is an increased need for adrenocortical steroids in thyrotoxicosis so that a state of thyro-adrenal equilibrium is achieved only when the thyroid and adrenal hormones are present in optimum concentration (Aterman and Greenberg, 1954).

2. There is evidence that an increase in the function of the thyroid gland is followed by an increase in the function of the adrenal gland.

Hoskins (1910) produced hypertrophy of the adrenal cortex on administering thyroid extract to guinea-pigs. Gaunt, Cordsen and Liling (1944) and Wallach and Reineke (1949) induced the

same effect in rats using thyroxine and they showed that the hypertrophy was associated with an increased output of adrenocortical hormones, although the latter authors found that this effect was only a temporary one and was followed by a hypofunction of the adrenal cortex. Deane and Greep (1947) showed that the increased function of the adrenal cortex following experimental hyperthyroidism in rats, was limited to the zona fasciculata. It has been noted during the production of exophthalmos in guinea-pigs by the administration of TSH that there is an associated hypertrophy and hyperplasia of the adrenal cortex (Marine, Baumann, and Rosen, 1934; Scowen and Spence, 1934; Aird, 1940).

3. There is evidence that a decrease in the function of the thyroid gland is followed by a decrease in the function of the adrenal gland.

Experimentally, it has been shown that thiouracil adminstration in rats induces a hypothyroid state which is associated with an involution of the adrenal cortex (Baumann and Marine, 1945) an effect which is particularly marked in the zona fasciculata and zona glomerulosa (Deane and Greep, 1947).

4. There is evidence that an increase in the function of the adrenal gland is followed by a decrease in the function of the thyroid gland.

Experimentally, it has been shown by Aterman (1954) that cortisone is able to depress the thyrotoxic state normally induced by TSH.

Clinically, it has been shown that ACTH or cortisone may induce a hypothyroid state (Wolfson and others, 1950, 1951), as illustrated by the reduction in the uptake of iodine by the thyroid gland (Reiss and others, 1950; Rawson, 1951), by the fall in the serum protein-bound iodine (Frederickson, Forsham and Thorn, 1952), and by the rise in serum cholesterol (Adlerberg, Schaefer and Crachman, 1950). When the dose of cortisone is massive there maybe a marked suppression of thyroid function (Frederickson, 1951). A similar effect has been found after the liberation of endogenous ACTH as a result of exposure to low oxygen pressure (Verzár, Sailer and Vidovic, 1952). The administration of ACTH or cortisone in Graves' disease may be followed by some reduction in the hyperfunction of the thyroid gland (Chandler and Hartfall, 1952; Brain and others, 1955), an effect which had been noted earlier with a more crude extract of the adrenal cortex (Shapiro and Marine, 1921; Marine, 1930b).

5. There is evidence that an increase in the function of the adrenal gland is followed by an increase in the function of the thyroid gland.

It has been shown by Reiss, Forsham and Thorn (1949) that an increase in the amount of available adrenocortical steroid,

whether as a result of increased endogenous production following ephedrine stimulation or as a result of exogenous administration, is followed by an increased uptake of iodine by the thyroid gland due presumably to thyrotrophic stimulation. Similarly it has been noted in cats that the administration of cortisone may be followed by histological signs of increased thyroid gland activity.

There is evidence that epinephrine may act as a stimulus to adrenocortical secretion (Long, 1947), and in this respect it is similar to the effect obtained with ephedrine (Reiss, Forsham and Thorn, 1949). It is believed that the stimulus to adrenocortical secretion is provided by an increased liberation of ACTH following a stimulation of the anterior pituitary gland (Solomon and Shock, 1950) or following stimulation of the cerebral cortex (Simms, Pfeiffenberger and Heinbecker, 1951).

6. There is evidence that a decrease in the function of the adrenal gland is followed by an increase in the function of the thyroid gland.

Marine and Baumann (1921) found that removal of the adrenal cortex in rabbits is followed by a sustained increase in the basal metabolic rate, and, clinically it is known that Addison's disease may lead to the production of Graves' disease (Heinbecker, 1952), although such an association is regarded as a rare event (Frederickson, 1951).

It is apparent that in the main these observations show an inverse relationship between the thyroid and adrenal glands, whereby an increased activity of the one is associated with a decreased activity of the other. The mechanism of this association has been considered by Heinbecker (1952) to be an interference with the neural mechanism regulating the hypothalamico-hypophyseal system, so that, for example, a hyperthyroid state leads to a diminution of ACTH secretion with consequent impairment of adrenocortical function. This is in keeping with an earlier observation (Heinbecker, 1950) of an increase in the basophilic cells and a decrease in the eosinophilic cells of the pituitary in Graves' disease, evidence of an increased TSH and decreased ACTH secretion respectively, so that the thyroid function is raised whilst the adrenal function is lowered. Rawson (1951) thought the over-responsiveness of the thyroid gland to alarming stimuli in adrenal deficiency may be due to an increased sensitivity of the thyroid gland to TSH.

On the other hand, certain of the observations which have been detailed above conflict with the concept of an inverse thyroid-adrenal relationship, although a closer examination of some of these apparent anomalies may provide an explanation in keeping with the main conclusion.

In the first place, the finding that a decrease in the function of the thyroid gland was followed by a <u>decrease</u> in the function of the adrenal gland may have been due to the fact that

the thiouracil, which produced the hypothyroid state, led to an increased secretion of TSH and consequently to a decreased secretion of ACTH with the production of a hypoadrenal condition.

In the second place, the finding that an increase in the function of the thyroid gland is followed by an increase in the function of the adrenal gland requires careful scrutiny because it has been shown (Wallach and Reineke, 1949) that such an effect is only temporary and leads after a short time to a decrease in the function of the adrenal gland.

In the third place, the finding that an increase in the function of the adrenal gland is followed by an increase in the function of the thyroid gland also requires further examination because Reiss and others (1950) have shown that such an increase is short-lived and is replaced within a few days by a decrease in the function of the thyroid gland. Furthermore, they showed that, whilst small amounts of adrenal hormone may produce an increased secretion of TSH, large amounts of the hormone have an inhibitory effect on TSH. Simkin, Starr and Hancock (1954) have shown also that, although cortisone administration in rats causes a slight increase in TSH in the serum, the effect is only temporary and is followed by a decrease in TSH in the serum. Another explanation of the apparent anomaly may be that the increase in the thyroid gland function

is the result of the increase in the amount of available cortisone leading to a diminished need for ACTH production with consequently an increased secretion of TSH.

These anomalies certainly serve to emphasise the difficulties which are inherent in any study of inter-related hormonal functions.

An examination of the part played by the adrenal gland and its associated pituitary hormone in the field of endocrine exophthalmos reveals a confusing and contradictory pattern of event. The various claims which have been put forward are discussed under the following heading:-

A. Evidence that ACTH and cortisone affect production of exophthalmos.

1. An exophthalmos-producing effect.

2. No exophthalmos-producing effect.

B. Evidence that ACTH and cortisone influence developing exophthalmos.

1. An exophthalmos-reducing effect.

2. An exophthalmos-increasing effect.

3. No exophthalmos-reducing or exophthalmos-increasing effect.

A. Evidence that ACTH and cortisone affect production of exophthalmos.

1. An exophthalmos-producing effect.

Experimentally, there is only scanty evidence that ACTH and cortisone are responsible by themselves for the production of exophthalmos. Williams (1953) found that cortisone alone causes exophthalmos in guinea-pigs, and Campbell and Tonks (1955) obtained a similar effect in rats. A minimal degree of exophthalmos in

association with a slight hypertrophy of the orbital fat and an increase in the size of the Harderian gland was found by Smelser and Ozanics (1955) following the administration of ACTH or cortisone to guinea-pigs.

2. No exophthalmos-producing effect.

Experimentally, Aird (1940) and Jefferies (1949c, 1952, 1953) found no evidence to suggest that ACTH administration is associated with the production of exophthalmos, and Dayton (1952) confirmed this finding. Smelser and Ozanics (1951, 1954) also failed to produce exophthalmos with cortisone or ACTH and they concluded that ACTH is not the exophthalmos-producing factor, and that it does not exert any influence of this factor. It must be noted, however, that, as shown above, Smelser and Ozanics (1955) have contradicted this negative finding at least to a certain extent in a more recent paper. Aterman (1954a) failed to produce exophthalmos in the intact or thyroidectomised animal by cortisone administration; the cortisone was given by systemic and by intra-orbital injection.

Clinically, there does not appear to be any evidence that the administration of ACTH or cortisone is followed by the development of exophthalmos (Berson and Yalow, 1952), except in the presence of some other endocrine dysfunction which favours the production of exophthalmos. This will be considered later.

B. Evidence that ACTH and cortisone influence developing exophthalmos.

1. An exophthalmos-reducing effect.

Experimentally, there is no conclusive evidence that ACTH or cortisone cause a reduction in the degree of exophthalmos, but it is interesting to note that Ludwig, Boas and Soffer (1952), although they failed to find any effect of the hormone on the exophthalmos produced by TSH administration, did find a diminution in the abnormally high hexosamine and water content of such exophthalmic tissues. It may be, therefore, that ACTH and cortisone exert an affect on the orbital tissues but not an extent detectable by ordinary exophthalmometric measurements. A reduction in the volume of the orbital contents of the normal rat after cortisone administration has been found by Boas and Scow (1954).

Clinically, a decrease in the degree of exophthalmos following ACTH administration has been reported by Hill and others (1950) in four cases of Graves' disease, and by Lederer and Hambresin (1950) and Collier (1954) in isolated cases. A similar effect has been shown with cortisone by Cole (1951), Bennett (1954) and Villiaumey (1954), and with the combined administration of ACTH and cortisone by Chandler and Hartfall (1952) in three out of five cases, by Rubin and Billet (1954) in an isolated case, and by Brain and others (1955) in a few cases particularly when the exophthalmos

was of recent origin or had suddenly and rapidly progressed. It has been noted that when there is a marked reduction in exophthalmos following administration of these hormones, the therapy must be continued for prolonged periods if an exacerbation is to be avoided (Koepf, 1950: Kinsell, Partridge and Foreman, 1953; Collier, 1954).

There is evidence that ACTH and cortisone may exert an important reducing effect on chemosis and on lid oedema in certain cases even when there is no obvious effect on the degree of exophthalmos (Thorn and others, 1950; Woods, 1951; Harsløf and Sørensen, 1954; Brain and others, 1955).

2. An exophthalmos-increasing effect.

Experimentally, there is evidence that ACTH and cortisone augment the response of other hormones in the production of exophthalmos. Aterman (1951, 1952a) and Pagliarani and Cavicchi (1953) have shown that the combined administration of cortisone and TSH to guinea-pigs increases the amount of exophthalmos produced by TSH alone, or even produces exophthalmos in certain animals when the dose of TSH is insufficient by itself to cause exophthalmos. A similar effect with ACTH has been shown by Smelser and Ozanics (1954) and Pisano (1955), and, in a later paper, Smelser and Ozanics (1955) noted that the TSH fraction need be present only in a minimal amount. Campbell and Tonks (1955) found that the exophthalmos produced by cortisone in rats is more marked when thiouracil is given with the cortisone.

Clinically, evidence has been put forward to suggest that ACTH and cortisone may cause an increase in the degree of exophthalmos already present (Zondek and Ticho, 1951), and a case has been described (Dayton, 1952) in which an orbital decompression had to be performed shortly after the administration of ACTH. It has been suggested by Braley (1955) that ACTH may produce exophthalmos particularly in susceptible individuals, and Aterman (1952b) thought that the occurrence of exophthalmos following infection or trauma may point to the additional implication of the adrenocortical steroids in the mechanism responsible for the exophthalmos. A similar conclusion, based on the results of their experimental work in which exophthalmos followed cortisone administration in rats, has been put forward by Campbell and Tonks (1955) who felt that clinical exophthalmos may be exacerbated by stress due to an effect of the adrenocortical steroids. Charleux, Lacrosaz and Dombre (1953) described a case of Graves' disease in which exophthalmos became aggravated five days after systemic treatment with ACTH.

3. No exophthalmos-reducing or exophthalmos-increasing effect.

Experimentally, Ludwig, Boas and Soffer (1952) found that ACTH and cortisone do not inhibit the formation of exophthalmos produced by the administration of TSH, and Dayton (1952) also found that the exophthalmos of intact and thyroidectomised guinea-pigs produced by TSH administration is not influenced by the subsequent administration of ACTH.

Clinically, there is a considerable weight of evidence to show that progressive exophthalmos is uninfluenced by ACTH administration (Means and Stanburg, 1950; Salassa, 1950; Olson, 1951; Scheie and others, 1951; Terplan and others, 1951; Engel, 1952; Moffatt, 1952; Simkin,Petit and Starr, 1954) or by cortisone administration (Salassa, 1950; Thomas, 1951; Jefferies, 1952, 1953; Inch and Rolland, 1953; Keys and Parisi, 1953; Brini, 1954; Simkin, Petit and Starr, 1954). Furthermore, certain cases from the series reported under the heading of an exophthalmos-reducing effect must be included in this negative category because not all these cases demonstrated a reduction in exophthalmos. Dollfus (1954) injected hydrocortisone into the orbital tissues in a case of oedematous exophthalmos without any effect.

On the other hand, it must be emphasised that many of the cases which fail to show a reduction of exophthalmos following ACTH and cortisone administration are not entirely unresponsive to the hormone because they may show a reduction in the degree of lid oedema and of chemosis (Woods, 1951a), together with a lessening of pain (Plessier, 1954).

In order to assess the significance of these conflicting claims an attempt will be made to examine the basic hypotheses which lie behind them.

A. Examination of hypothesis that ACTH and cortisone have an exophthalmos-producing effect.

(1) ACTH and cortisone may increase the effectiveness of TSH.

In a case of thyrotoxocosis Werner (1950) found a slight increase in the basal metabolic rate following ACTH administration, and it may be that this represents an augmentation of the effectiveness of TSH. Similar effects have been reported following cortisone administration, for example, histological changes in the thyroid gland suggestive of TSH stimulation (Higgins, Woods and Kendall, 1951; Halmi, 1952), a rise in the level of the protein-bound iodine in the serum (Halmi and Barker, 1952), and a slight but temporary rise in the level of TSH in the serum (Simkin, Starr and Hancock, 1954).

There is evidence that this effect of ACTH and cortisone is mediated through the pituitary, and not merely a direct influence on the thyroid gland, because an increase in the basal consumption of oxygen, following ACTH and cortisone administration, has been found in two cases of spontaneous myxoedema despite the refractory state of the thyroid gland (Beierwaltes and others, 1950). On the other hand it would appear that the cortisone-induced augmentation of the TSH response is evident only when the thyroid hormone is inhibited simultaneously (d'Angelo and others, 1953), for example by thiouracil administration.

It is interesting to note, therefore, that the stimulating effect of cortisone on the thyroid gland is particularly marked when given in conjunction with TSH (Halmi, 1952), and it may be that cortisone not only plays a part in increasing the production of TSH (Smelser and Ozanics, 1955), but also plays a permissive role in the field of action of TSH (Smelser and Ozanics, 1954).

(2) ACTH and cortisone may increase the volume of the orbital tissues.

In the field of experimental exophthalmos it has been postulated by Aterman (1952a) that cortisone may produce exophthalmos by an effect on the connective tissues of the orbit, and, although the nature of this effect is not specified, it has been presumed that it is a generalised one on all the connective tissues of the body (Aterman and Greenberg, 1953). Aterman (1952a) considered that the effect of the adrenocortical steroids is paramount in the production of exophthalmos, and he postulated that the more marked exophthalmos of the thyroidectomised animal as compared with the intact animal is due to the greater availability of these steroids after thyroidectomy; on the grounds that thyroidectomy decreases the normal utilisation of the steroids. In a later paper Aterman (1954a) suggested that cortisone may increase the water content of the orbit by augmenting the amount of the water-binding

mucopolysaccharides in the orbital tissues or by changing their degree of polymerisation. An increase in the sodium content of the extra-ocular muscles has been found by Campbell and Tonks (1955), although without causing any change in their weight or in their water content.

It must be remembered, however, that the occurrence of exophthalmos in the experimental animal is by itself no proof of the existence of a change in volume of the orbital tissues unless such a change is demonstrated chemically or histologically, or unless proof is given that there has been no change in the relative eyeball-orbit growth rates. It is well known that hormones may alter differentially the growth rates of certain structures of the body. For example, thyroidectomy in rats causes a retardation of body growth without affecting the growth of the eyeball or brain (Scow and Simpson, 1945) and hypophysectomy in rats causes a similar effect (Walker and others, 1952). Cortisone administration to chick embryos causes a retardation of body growth but does not alter the rate of eyeball growth (Evans, 1953).

Boas and Scow (1954) applied this concept of differential rates of body growth to a study of the exophthalmos which occurs in rats following cortisone administration, and they found that the exophthalmos follows an inhibition of head and body growth so that the orbit becomes smaller than normal although there is no change in eyeball growth. The exophthalmos is due simply to the inability of

an eye of normal size to be contained within the abnormally small orbit, and, in fact, Boas and Scow showed that there is even a reduction in the volume of the orbital contents in such animals. These findings have been verified by Essex (1955) and Williams (1955).

Clinically, Sayer and others (1949) found an inhibition of a water diuresis in one case following ACTH administration, and Palassa (1950), who noted an increase in the degree of periorbital oedema and chemosis in one of three cases treated with ACTH and cortisone, suggested that this may be related to the fullness of the face and pitting oedema which may follow administration of these hormones.

In addition to the glucocorticoids of the adrenal cortex there are the minerocorticoids which are known to have an influence on fluid accumulation within the body, and it has been postulated, therefore, that an adrenocortical hormone may play some part in the production of exophthalmos, particularly in causing orbital oedema (Benedict, 1938). Desoxycorticosterone (DOCA) has been investigated as a possible exophthalmos-producing agent because of its effect on the accumulation of fluid (Jefferies, 1949c; Smelser and Ozanics, 1951) and because of its slight lymphocytopoietic effect (Higgins, Woods and Kendall, 1951), but there is no evidence that DOCA is associated in any way with the production of experimental exophthalmos (Jefferies, 1949c; Smelser and Ozanics, 1951).

A further suggestion has been put forward that ACTH and cortisone may produce exophthalmos by a mobilisation of fat from the body depots to the orbit, an idea elaborated by Jefferies (1949c) because of certain known facts. Fry (1937) had found that fatty infiltration of the liver occurred on administration of an anterior pituitary extract to intact rats, but not when adrenalectomised rats were used, and Baker and others (1948) had shown that it was the ACTH fraction which produced the fatty infiltration. The fat which accumulated in the liver came from the body fat depot. (Barrett, Best and Ridout, 1938). Furthermore Jefferies (1949c) had shown that the administration of a pituitary extract containing TSH to guinea-pigs resulted in exophthalmos and in fatty infiltration of the liver. He did not find any positive correlation between these two effects of the extract despite their close relationship, but they were equally affected when the extract was selectively inactivated by exposure to iodine (Jefferies, 1949b). It was reasonable to postulate in view of these considerations that ACTH might influence the production of exophthalmos by inducing fatty changes within the orbit, but the result of the experimental investigation proved to be negative (Jefferies, 1949c). The implication of ACTH in the mobilisation of depot fat has also been postulated by Levin and Farber (1950), although they thought that some other pituitary hormone acts as a trigger substance initiating the reaction.

B. Examination of hypothesis that ACTH and cortisone have an exophthalmos-reducing effect.

(1) ACTH and cortisone may decrease the effectiveness of TSH.

ACTH and cortisone have been shown to cause a decrease in the collection of radio-active iodine by the thyroid gland (Money and others, 1950, 1951; Bogoroch and Timiras, 1951), a decrease in the serum protein-bound iodine in patients with collagen disease (Hardy, Riegel and Erisman, 1950), an inhibition of the increase in protein-bound iodine normally found after TSH administration(Woodburg, Ghosh and Sayers, 1951), a fall in the basal metabolic rate in hyperthyroidism (Engel, 1950) although such a fall may be only temporary (Moseley and Merrill, 1950), and a decrease in the thyrotoxicosis induced in guinea-pigs by the administration of TSH (Aterman, 1954a). These findings suggest that the effectiveness of TSH is diminished by ACTH and cortisone, and it is tempting to postulate that this is the mechanism which is responsible for the reduction of exophthalmos following treatment of endocrine exophthalmos with these hormones (Brain, 1952; Chandler and Hartfall, 1952).

Evidence that ACTH and cortisone are able to decrease the secretion of TSH from the pituitary has been put forward by Hill

and others (1950), Thorn and others (1950), and Thorn (1951) because they found that the depression of iodine accumulation in the thyroid gland and the fall in the level of protein-bound iodine in the serum, following ACTH and cortisone administration, are counteracted by the additional administration of TSH. This view is supported by Heinbecker (1952) who found a degranulation of the basophile cells of the pituitary in dogs receiving cortisone in association with a diminution in thyroid activity, and by Simkin, Starr and Hancock (1952) who demonstrated a partial suppression of TSH in the serum after cortisone therapy.

On the other hand, there is some evidence to suggest that the decreased effectiveness of TSH following ACTH and cortisone administration may operate at an extra-pituitary level because ACTH and cortisone may reduce the effects of exogenous TSH in the hypophysectomised animal (Verzár and Vidovic, 1952; Epstein and others, 1953), although this finding does not exclude an effect on the hypophysis of the intact animal. There is an increased rate of renal clearance of iodine following cortisone administration (Albert, Tenney and Ford, 1952; Benson and Yalow, 1952; Kuhl and Ziff, 1952), and it may be, therefore, that cortisone causes a decrease in the accumulation of iodine in the thyroid gland by exerting an effect on the glomerular filtration rate (Halmi and others, 1953). This

finding, however, does not exclude an effect of cortisone on TSH because the increased excretion of iodine in the urine may represent a failure in the iodine concentrating mechanism of the thyroid gland as a result of a suppression of TSH secretion (Bogoroch and Timiras, 1951).

Perry (1951) claimed that ACTH may operate directly on the thyroid gland. Aterman (1954a) also explained on an extra-pituitary basis his finding of a reduction in the TSH-induced thyrotoxicosis in guinea-pigs following cortisone administration, and he postulated that the cortisone and thyroid hormones are directly antagonistic to one another. This view, however, is contradicted by Bersen and Yalow (1952) who considered it unlikely that cortisone produces thyroid inhibition by a direct effect on the gland because such an effect would favour a secondary increase in TSH secretion with the possible production of exophthalmos, an effect which did not occur in their investigation.

(2) ACTH and cortisone may decrease the volume of the orbital tissues.

There seems little doubt that, despite the contradictory evidence regarding the influence of ACTH and cortisone in the fields of clinical and experimental exophthalmos, these hormones ought to be able to exert a reducing effect on exophthalmos by virtue of their known action of decreasing the bulk of new-forming tissues such as found in the exophthalmic orbit (Browne, 1950; Olson, 1951). In

this connection it is of interest to note that Smelser and Ozanics (1951, 1955) expressed a similar view despite their finding experimentally of the production of exophthalmos with these hormones.

It has been suggested by Thorn and Forsham (1950) that ACTH and cortisone reduce chemosis by a direct effect on the orbit, although there is no evidence that injectionsof cortisone into the orbit relieve exophthalmos (Inch and Rolland, 1953). There is evidence, however, that local administration of cortisone produces a temporary improvement in areas of localised skin myxoedema, a condition of the skin which has many similar features to endocrine exophthalmos (Inch and Rolland, 1953).

There are several ways in which ACTH and cortisone may cause a reduction in the volume of the tissues of the exophthalmic orbit:-

First, ACTH and cortisone may act by reducing the amount of oedema within the orbit.

Experimentally, it has been shown that ACTH and cortisone cause a reduction in the oedema which is usually found in the orbital tissues in exophthalmos due to TSH administration (Ludwig, Boas and Soffer, 1952), and clinically such a mechanism has been suggested by Collier (1954), Igersheimer (1954, 1955) and Brain and others (1955). Indeed, it would appear to be essential to postulate that the removal of oedematous fluid plays an important part in the reduction of exophthalmos by ACTH and cortisone in order to account for the

extremely rapid improvement which may occur in certain cases treated in this way (Ruben and Billet, 1954), and in order to explain why the most dramatic effect is found usually in cases of recent onset (Brain and others, 1955).

Secondly, ACTH and cortisone may act by reducing the volume of ground-substance within the orbit.

Experimentally, it has been shown that ACTH and cortisone cause a reduction in the hexosamine content of the orbital tissues which is normally increased in exophthalmos due to TSH administration (Ludwig, Boas and Soffer, 1952), and clinically the same authors have demonstrated a reduction in the hexosamine level in the serum in certain of the collagen diseases (Boas, Ludwig and Soffer, 1952). It has been postulated by Werner Hamilton and Frantz (1951) that a deficiency of adrenal steroids may be directly responsible for the accumulation of mucopolysaccharides in the tissues. It is interesting, therefore, that a reduction in the size of the localised areas of skin myxoedema in association with a decrease in the amount of gelatinous myxoedematous infiltrate follows ACTH therapy (Werner, Hamilton and Frantz, 1951) and cortisone therapy (Inch and Rolland, 1953), although the effect persists only during the period of administration of the hormones.

There is evidence that the mast cells of the tissues are the site of production of hyaluronic acid, an important component

of the ground substance of connective tissue, and it is of significance that a reduction in the number of mast cells within the tissues in association with a decrease in the amount of hyaluronic acid may be found after cortisone administration in rats (Cavallero and Braccini, 1951) and after ACTH and cortisone administration in humans, rabbits, mice and guinea-pigs (Asboe-Hansen, 1952). Stuart (1951) demonstrated a similar effect of cortisone on the mast cells of the connective tissues. This would appear to be another indication of the reducing effect which ACTH and cortisone may have on the ground substance of connective tissues, although Devitt, Pirozynski and Samuels (1953) have shown an absence of any effect of cortisone on the normal mast cells content of the dog. On the other hand Bloom (1953) showed a dramatic regression of a mast-celled tumour in the dog treated with cortisone, so that cortisone certainly appears to affect the mast cells when they are present in abnormal amounts.

Thirdly, ACTH and cortisone may act by reducing the amount of neo-fibrosis within the orbit.

It has been shown experimentally that cortisone may cause a striking depression of the activity of the connective tissues in the process of wound healing (Plotz and others, 1950), and a similar effect has been shown with ACTH (Ragan and others, 1949). This diminished response of the fibroblastic tissue has also been demonstrated clinically by observing the rate of healing of biopsy

wounds in patients receiving ACTH (Baxter, 1951; Sauer and others, 1951). It would appear, therefore, that ACTH and cortisone may be of value during the evolution of exophthalmos in reducing the amount of scar tissue within the orbit, and thus diminishing the degree of exophthalmos and the extent of the residual ophthalmoplegia. It must be emphasised, however, that these hormones are able to exert an effect only on new-forming fibrous tissue so that they must be administered in the early stages of the condition.

Fourthly, ACTH and cortisone may act by reducing the extent of the lymphocytic infiltration within the orbit.

There is evidence that the accumulation of lymphocytes within the orbit in endocrine exophthalmos is the result of an adrenal hypofunction and it is interesting, therefore, that cortisone therapy may be associated with a reduction in the number of circulating lymphocytes (Long, 1947; Simms, Pfeiffenberger and Heinbecker, 1951), and in the number of lymphocytes within the tissues (Dobriner and others, 1950; Werner, Hamilton and Frantz, 1951). It may be that the reducing effect of cortisone on lymphocytic infiltration contributes to a reduction in the degree of exophthalmos in certain cases.

Conclusion regarding relation of adrenocorticotrophic and adrenocortical hormones to exophthalmos.

It is clear that at present no dogmatic conclusion may be advanced on the role of the adrenocortical gland and its associated pituitary hormone in the process of endocrine exophthalmos.

The effect of these hormones on TSH secretion is conflicting; some evidence shows that they favour an increased TSH secretion whereas other evidence shows that they favour a decreased TSH secretion. Furthermore, to add to the confusion there are claims that cortisone does not influence TSH secretion; as shown by an absence of any significant change in the serum iodine level (Werner, 1950), an absence of any change in the iodine content of the thyroid gland (Botkin and Jensen, 1951; Migeon and others, 1952), and an absence of any histological change within the thyroid and pituitary glands (Winter, Silber and Stoerk, 1950), following cortisone administration.

In any case, even if the true effect of the adrenal hormones on TSH secretion is established, there is no clear-cut evidence that this will affect the concept of endocrine exophthalmos unless it is known to what extent TSH represents the exophthalmos-producing factor.

The effect of ACTH and cortisone on the pathological changes which characterise the exophthalmic orbital tissue would appear to be more clearly established, and it is reasonable to advocate the administration of these hormones particularly in the early stages of the exophthalmos before the onset of irreversible fibrotic changes within the orbital structures. It is perhaps unfortunate that earlier experimental work gave evidence of an exophthalmos-producing effect of ACTH and cortisone, because it is now believed that this effect is due to the abnormal differential rates of growth between the eyeball and the orbit, a state of affairs confined to animals. This finding serves to emphasise the importance of exercising caution before relating experimental observations to clinical experience, particularly in view of the obvious structural differences between the orbit of man and the orbit of animals. In man the orbit is closed except anteriorly, whereas in animals the lateral orbital wall is grossly deficient. In this way a rise of intra-orbital pressure is more readily effective in man (Dobyns, 1950). Furthermore, there is no counterpart in the human to Harder's gland which plays so prominent a role in the production of exophthalmos in the guinea-pig, the animal most favoured for the experimental study of exophthalmos. There is, however, evidence that exophthalmos may occur in the guinea-pig even after removal of Harder's gland (Smelser, 1942).

It is also important to realise that, quite apart from the obvious differences between animal and human conditions, there are also fundamental differences between the various species of animals in their reactions to certain hormones. For example, Bangham (1951) studied the influence of cortisone on wound healing and demonstrated that, although there is a delay in wound healing in the rabbit, there is no obvious effect of the hormone on wound healing in the guinea-pig or in the rat. This species difference is also brought out in an investigation on the influence of cortisone on corneal vascularisation in the guinea-pig and in the rabbit (Wybar and Campbell, 1952), and these findings are reported in a separate appendix at the end of the thesis.

This species difference is also illustrated in the production of exophthalmos by the administration of TSH. Most of the experimental work on exophthalmos has been carried out in guinea-pigs and I have confirmed the production of a progressive type of exophthalmos in intact and thyroidectomised guinea-pigs following TSH administration. The same hormone, however, was administered to intact and thyroidectomised rabbits and monkeys without the production of a satisfactory degree of exophthalmos. (It was intended to study the effect of cortisone on exophthalmos in the rabbit and monkey and to compare the results with those obtained in the guinea-pig. This was not carried out, however, in view of the difficulty in obtaining an adequate exophthalmos.)

To a certain extent, therefore, it would appear to be essential to form basic conclusions on the nature of exophthalmos from clinical observation, although, it must be remembered that in clinical experience the results of an empirical form of treatment are difficult to assess (Duke-Elder and Goldsmith, 1951), particularly as endocrine exophthalmos is a condition which may be characterised by spontaneous remission (Said, 1952; Greene, 1955).

Relation of gonadal hormones to exophthalmos.

There is evidence that the gonads are implicated in the production of exophthalmos, particularly in view of the fact that progressive exophthalmos is a much more frequent occurrence in the male than in the female despite the greater incidence of Graves' disease in the female than in the male (Brain, 1945, 1946).

Female gonads.

Thyroid-ovarian relationship.

It is well known that there is a pituitary-ovarian axis, just as there is a pituitary-thyroid axis, and in this way the ovarian and thyroid glands are related to one another through the influence of the pituitary gland, although it is also possible that the thyroid gland and the ovary may exert a direct effect on one another without the intervention of the pituitary (Salter, 1948). The relationship between the ovary and thyroid gland would appear to be an inverse one, and this is borne out by the fact that thyrotoxicosis is more likely to develop during a hypogonadal phase (Lederer, 1948a; Keynes, 1952), and also by the fact that the degree of thyrotoxicosis may be diminished by treatment with ovarian hormones (de Gennes, 1951).

Influence of oestrogen on exophthalmos

(1) An exophthalmos-reducing effect.

Experimentally, there is evidence that oestrogen may decrease the degree of exophthalmos produced in guinea-pigs by thyroidectomy or by TSH administration (Smelser and Ozanics, 1951), and these authors have suggested that the greatly diminished incidence of progressive clinical exophthalmos in the female than inthe male may be attributed to the presence of endogenous oestrogen in the female. Furthermore, exophthalmos in Graves' disease has been noted to diminish during pregnancy (Givner, Bruger and Lowenstein, 1947), and to increase following the termination of the pregnancy (Paschkis and Cantarow, 1947). Exophthalmos may become more severe during menstruation (Savin, 1943; Muller, 1949). It is natural, therefore, that the administration of oestrogen has been found to be effective in reducing the degree of exophthalmos in certain cases of endocrine exophthalmos (Savin, 1945; Paschkis and Cantarow, 1947; Klotz, 1948b; Lederer, 1948; Paufique and Guinet, 1948; Vilanova and Cañadell, 1949; Lederer and Hambresin, 1951; Okie, Denee and Daley, 1951; Okie, Daley and White, 1952), particularly in cases in which the exophthalmos followed the menopause or ovariectomy (Lederer, 1948b). It is interesting that in a series of 5

female cases successfully treated in this way, one had been ovariectomised, two were menopausal and one suffered from psychical amenorrhoea (Paufique and Guinet, 1949; Paufique, Guinet and Papillon, 1950).

(2) No exophthalmos-reducing effect.

On the other hand oestrogen therapy has been shown to be ineffective in many cases of endocrine exophthalmos (Moffatt, 1943; Brain, 1945, 1946; Hedges and Rose, 1953; Carra, 1954) and there are many other cases in which it is difficult to prove any association between the administration of oestrogen and a slight reduction in the degree of exophthalmos, particularly as other forms of therapy were also being applied and as progressive exophthalmos is known to suffer spontaneous remission.

In order to assess the significance of these conflicting claims an attempt will be made to examine the basic hypotheses which lie behind them.

A. Examination of hypothesis that oestrogen has an exophthalmos-reducing effect.

(1) Oestrogen may decrease the effectiveness of TSH.

Aron and Benoit (1932) showed that oestrogen may cause an inhibition of TSH secretion in the guinea-pig. This action was postulated by Marine (1938a) who suggested that the greater resistance of the female than of the male rabbit to the development of exophthalmos is due to the protecting influence of oestrogen on the anterior pituitary gland. This effect was verified histologically by Nelson and Hickman (1937) and by Leblond, Albert and Selye (1942) who demonstrated that oestrogen administration in rats prevents the characteristic changes which are found in the pituitary basophile cells following thyroidectomy, and which are due to an excessive secretion of TSH. Similarly, Franck (1937) found a reduction in the number of basophile cells on oestrogen administration. The depressing influence of oestrogen on the anterior pituitary is a selective one, however, and it has been

shown to cause a stimulation of the acidophile cells (Cramer and Horning, 1938; Abarbanel, 1944; Baker and Everett, 1947). On the other hand it is possible that oestrogen may exert its effect at an extra-pituitary level because it has been shown by Gassner, Barrett and Gustavson (1947) that oestrogen controls the effect of the excessive secretion of TSH which occurs in rats on a low iodine diet without affecting the pituitary hypertrophy which follows the dietary deficiency.

The antagonism which exists between oestrogen and TSH has been demonstrated in an interesting experiment by Cramer and Horning (1938). They showed that injections of TSH can prevent the carcinogenic effects which normally follow prolonged oestrogen administration in certain mice.

Kippen and Loeb (1936) found that gonadectomy in guinea-pigs causes an increased production of TSH. Rowland and Sharpey-Schafer (1940) showed that at the menopause there is a failure of oestrogen production with a consequent excessive secretion of pituitary gonadotrophic hormone which can be controlled by oestrogen administration. Rundle (1941) postulated that associated with the hypersecretion of gonadotrophic hormone there may be an increased secretion of TSH, and a similar increase of gonadotrophic hormone and TSH may occur during menstruation.

It is reasonable, therefore, to postulate that oestrogen therapy may be beneficial in the treatment of Graves' disease by reducing the secretion of TSH (de Gennes and others, 1951), and that this may be the effective mechanism in the cases in which there is a decrease in the degree of exophthalmos after such treatment (Okie, Daley and White, 1952).

(2) Oestrogen may decrease the volume of the orbital tissues.

Smelser and Ozanics (1951) have shown that massive doses of oestrogen may cause a decrease in the degree of exophthalmos produced in guinea-pigs by thyroidectomy or by TSH administration, and that this decrease is associated with a reduction in the amount of stainable oedematous infiltrate within the orbital fat. The fact that this effect may occur in the thyroidectomised animal even when no TSH is administered has been considered by Smelser and Ozanics to be proof of the influence which oestrogen is able to exert directly on the orbital tissues, quite apart from any influence which it may exert on TSH secretion. It must be remembered, however, that this conclusion may not be wholly valid because thyroidectomy alone may be responsible for an increased secretion of TSH, and oestrogen may affect this endogenous TSH.

B. Examination of hypothesis that oestrogen has no exophthalmos-reducing effect.

(1) Oestrogen may increase the effectiveness of TSH.

It has been shown that oestrogen administration in rabbits may cause a stimulation of the anterior hypophysis with the production of a thyrotoxic state as a result of an excessive secretion of TSH (Zondek, 1945). Heinbecker (1949) also believed the oestrogen facilitates the secretion of TSH from the hypophysis, and that this may account for the higher incidence of hyperthyroidism in the female than in the male. The stimulating effect of oestrogen on the hypophysis was noted by Baker and Everett (1947), although this effect was selective on the acidophile cells. Baker and Everett considered that the action of oestrogen is independent of the thyroid gland because it occurs even in the thyroidectomised animal.

(2) Oestrogen may increase the volume of the orbital tissues.

It is interesting to note that Smelser and Ozanics (1951), despite their finding of a reduction in the bulk of the orbital tissues in experimental exophthalmos following oestrogen administration, subscribed to the view that in general oestrogen should act by favouring the accumulation of oedematous material, and Simpson (1945)

put forward the view that oestrogen is unsuitable in the treatment of exophthalmos because it has the property of causing a fluid retention.

Aykroyd and Zuckerman (1938) demonstrated that the active sexual phase in female rhesus monkeys is associated with swelling of the sexual skin, as a result of the accumulation of considerable amounts of intercellular and intracellular fluid, and of the swelling of connective tissue elements. This effect follows oestrogenic stimulation, and the female hormone has been isolated from the fluid in the swollen area (Fisher, Krohn and Zuckerman, 1936). Similarly, Obal (1950) showed that oestrogen causes an increase in the amount of intercellular mucoid material with complete inhibition of hyaluronidase activity.

Conclusion regarding relation of oestrogen to exophthalmos.

It is difficult to reconcile the opposing views which have been put forward on the influence of oestrogen on TSH secretion, but it must be remembered that different oestrogenic substances have been shown to exert a variable effect on the iodine uptake of the thyroid gland; some oestrogens cause an increased uptake whereas others cause a decreased uptake (Money and others, 1951a). Furthermore, a variable effect may be evident even with the same oestrogenic substance when it is administered in low and in high concentrations (Money and others, 1952), although at times small doses may prove to be entirely ineffective (Paschkis, Cantarow and Peacock, 1948). On balance, however, it is most likely that oestrogen may diminish the effectiveness of TSH, and it may well be of value in the treatment of exophthalmos.

Similarly, it is difficult to reconcile the reducing effect which oestrogen is supposed to exert on the orbital tissues with the increasing effect of the hormone on the other tissues of the body. The reported influence on the orbital tissues is certainly atypical.

Male gonads.

Influence of androgen on exophthalmos.

Marine, Rosen and Cipra (1953) found that exophthalmos occurs more readily in male than in female thyroidectomised rabbits following administration of methyl cyanide, and it has been shown that this exophthalmos may be prevented by preliminary gonadectomy (Marine and Rosen, 1936), and that it may be increased by administration of androgen (Marine, 1938b). On the other hand there is no further experimental evidence to support this concept, and it has been shown that the exophthalmos which occurs in thyroidectomised guinea-pigs following TSH administration is unaffected by a lack of androgen (Dobyns, 1946a; Smelser and Ozanics, 1951), or by an excess of androgen (Smelser and Ozanics, 1951).

There is only scanty evidence to suggest that androgen affects TSH secretion, and, although Money and others (1950) have shown that androgen may cause an increase in the secretion of TSH, the effect is a variable one because it may produce a diminished secretion of TSH merely by being administered in a different concentration(Money and others, 1951a). Furthermore, it has been shown that androgen fails to prevent the histological changes which occur in the basophile cells of the pituitary following thyroidectomy in the rat (Leblond, Albert and Selye, 1942).

In the clinical sphere it has been postulated that there is an additional gonadotrophic factor, as well as a thyrotrophic factor, in the production of exophthalmos. This hypothesis would provide an explanation for the absence of exophthalmos in the hypothyroid states of cretinism and myxoedema, because in these conditions there is an associated hypogonadalism. It also gains weight from the observation of Brain (1945) that the ratio of males to females who develop progressive exophthalmos following thyroidectomy is 3 or 4 to 1. When account is taken of the fact that thyrotoxicosis is very much more common in the female than in the male, approximately in the ratio of 9 to 1, this sex difference in the occurrence of progressive exophthalmos is very striking.

In contrast to the concept that a gonadotrophic hormone influences the production of exophthalmos, it has been postulated that androgen may exert a beneficial effect on the course of progressive exophthalmos (Simpson, 1945; Mann, 1946a, b; Basto, 1950) because it is supposed to partially inhibit the secretion of TSH. On the other hand androgen is often ineffective in the treatment of such cases (Donoso, 1953).

It is difficult to draw any conclusions at the present time on the basic role of androgen in the exophthalmic process.

A few reports have appeared from time to time which seek to implicate certain other glands or certain forms of vitamin deficiency in the exophthalmic process. These are mostly of a fragmentary and inconclusive nature but they will be considered briefly now.

Relation of thymus to exophthalmos.

The hormonal activity of the thymus is imperfectly understood, but there is no direct evidence that it is related to the production of exophthalmos. Bryan, McDonald and Clagett (1948) examined the thymus in cases of exophthalmic goitre and of myasthenia gravis. They found an increase in glandular tissue in many of the cases of exophthalmic goitre, but there was rarely any lymphoid hyperplasia. In myasthenia gravis, an increase in glandular tissue was rare, but lymphoid hyperplasia was more common. The thymus, therefore, presents a different picture in the two conditions.

Dudgeon and Urquhart (1926) demonstrated enlargement of the thymus in 3 out of 8 cases of exophthalmic goitre showing atrophic changes and the formation of lymphorrhages in the ocular and skeletal muscles. Brain (1943) commented on the fact that hyperthyroidism and myasthenia gravis may very occasionally co-exist. It may be that thymic over-activity is a link between the two conditions.

Rawson, Sterne and Aub (1942) showed that, in vitro, the thymus is able to neutralise a certain amount of TSH. It is not known what significance, if any, may be attached to this finding.

Relation of parathyroid to exophthalmos.

Heinbecker (1950) described the occurrence of a parathyroid adenoma in two cases in which there was an associated depression of thyroid gland function, due, it was suggested, to an inhibiting effect of the adenoma on the hypophyseal basophile cells. The removal of the adenoma was followed by a phase of hyperthyroidism with an associated exophthalmos as a result perhaps of a temporary overaction of the basophile cells. It is difficult, however, to draw any conclusion from these two cases regarding an influence of the parathyroid gland on exophthalmos, and it is possible that the effect described was the result purely of the change in thyroid gland function following the local influence of the parathyroid growth.

Relation of vitamin B_{12} to exophthalmos.

Emerson (1949) has shown that vitamin B_{12} protects rats against the toxic effects of large doses of thyroid hormone, so that the hyperthyroid animal presumably has an increased need for vitamin B_{12}. A similar protecting influence has been found with liver residue, the so-called anti-thyrotoxic factor of the liver (Ershoff, 1950). There is no evidence, however, that these isolated findings are related to exophthalmos.

Relation of vitamin C to exophthalmos.

There is an abundance of ascorbic acid (vitamin C) in the adrenal cortex, and it is known that this concentration undergoes a cyclic rise and fall in relation to adrenocortical activity There is, therefore, a relationship between ascorbic acid and the adrenocortical hormones.

It is interesting to note that Marine, Rosen and Cipra (1933) found that ascorbic acid causes a marked inhibition of the experimental exophthalmos which normally follows methyl cyanide administration. Marine, Baumann and Rosen (1934) considered that this is due to the fact that ascorbic acid directly or indirectly counteracts TSH. On the other hand Dobyns (1946a) found that ascorbic acid does not influence the exophthalmos which follows TSH administration in thyroidectomised and in non-thyroidectomised guinea-pigs, and he concluded that ascorbic acid does not have any effect on TSH. Aterman (1954a) has shown that ascorbic acid protects guinea-pigs to a certain extent against the production of thyrotoxicosis following TSH administration. Aterman considered that this only indicates that thyrotoxicosis is aggravated by an ascorbic acid deficiency and it cannot be concluded that ascorbic acid is an anti-thyrotoxic substance.

Relation of vitamin E to exophthalmos.

Grósz (1950) has suggested that vitamin E may be of value in cases of exophthalmic ophthalmoplegia because of the beneficial effect of the vitamin in certain systemic dystrophies of the striated musculature. There is no evidence, however, that vitamin E exerts any influence on exophthalmos or on exophthalmic ophthalmoplegia (Givner, Bruger and Lowenstein, 1947; Cima, 1950).

Relation of dental cement to exophthalmos.

Kupfer (1954) has declared that the absence of dental hypercementosis in certain cases of hyperthyoidism suggests that these cases are prone to develop malignant exophthalmos. This conclusion was arrived at by the finding that hypercementosis occurred in 14% of normal persons, in 60% of hyperthyroid patients without malignant exophthalmos, and in only 7% of hyperthyroid patients with malignant exophthalmos. It is impossible, however, on the data presented in Kupfer's paper to elaborate of this concept, particularly as no details are given of the state of the hyperthyroidism. It is unlikely that the patients with malignant exophthalmos were all in a hyperthyroid phase because 70% had been subjected to thyroidectomy, and it would be interesting to know whether any of them had evidence of hypercementosis during the pre-operative hyperthyroid phase.

Other clinical considerations of thyrotrophic exophthalmos.

In the absence of any uniformly satisfactory procedure for the treatment of progressive exophthalmos, it is important to try and prevent the occurrence of the condition as far as possible. This can best be done by exercising great care in the selection of cases of Graves' disease suitable for surgical or medical treatment (Plessier, 1954). Salter and Soley (1944) considered that thyroidectomy should be avoided in all cases of thyroidectomy should be avoided in all cases of thyrotoxicosis associated with only a small rise in metabolism. Ruedemann (1949) considered that rest and thiouracil therapy are safer procedures in such cases than removal of the thyroid gland.

Means (1945) recommended that thyroidectomy should be avoided in all cases of Graves' disease in which there are signs of a thyrotrophic type of exophthalmos. It is not always easy, however, to detect the early manifestations of thyrotrophic exophthalmos particularly when they are superimposed on a thyrotoxic condition. It is in this sphere that the orbitonometer (Copper, 1948) may prove of great value, because it is possible to detect with this instrument an early rise of intra-orbital resistance. Certainly thyroidectomy should be avoided in any case in which the presenting feature is an oedematous form of exophthalmos (Shannon and Hunt, 1949; Paufique, 1954), and there is no doubt that

exophthalmos is particularly prone to occur when there is an early dominance of the eye signs over the general manifestations of the diease (Givner, 1950).

If, however, progressive exophthalmos develops it is essential to maintain the integrity of the eye during the active phase of the condition, particularly as progressive exophthalmos is usually a self-limiting entity even in the absence of any specific treatment (Mann, 1947; Falconer and Alexander, 1951), with a tendency for the eyes to show some spontaneous recession within 6 - 12 months of the onset of the condition. Conjunctival infection or corneal ulceration must be guarded against by appropriate local treatment. If the cornea is not adequately protected by the lids, a tarsorrhaphy should be performed, but as has been pointed out by Pfeiffer (1950) it is necessary to perform the tarsorrhaphy before the intra-orbital tension becomes excessive. King (1952) has suggested that the tarsorrhaphy is more effective if preceded by a generous lateral canthotomy. The pressure of inflated bags placed over the eyes may also be of value in certain cases (Horrax, 1952).

These measures may fail in the more severe cases, and it may be necessary to protect the integrity of the eye and the optic nerve by performing an orbital decompression operation (Naffziger, 1933, 1952, 1954, 1955; Poppen, 1950; Offret, 1954; Jackson, 1955), although Hollingsworth (1952) considered that a

simple direct incision into the orbit may prove equally effective in certain cases. On the other hand the results of orbital decompression are sometimes disappointing (Mason, 1947; Law, 1952).

Undoubtedly, a rational and successful method of treatment of endocrine exophthalmos must await a deeper understanding of the basic hormonal processes.

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Appendix.

The Influence of Cortisone on Corneal Vascularization in the Guinea-pig and in the Rabbit.

This is a joint investigation which was carried out at the Tennent Institute of Ophthalmology and Institute of Physiology, Glasgow, with Dr. F.W.Campbell.

It is included in this thesis because, although unrelated to exophthalmos, it serves to illustrate the different effect which cortisone may exert on different animals; a feature of importance in an assessment of the experimental influences of the adrenal cortex on exophthalmos.

It is clear from recent experimental and clinical reports that cortisone has a measurable effect on the rate and extent of invasion of the cornea by new vessels. Vessels enter the cornea in response to a wide variety of stimuli, but the basic nature of this mechanism is ill-understood.

We have studied the action of cortisone on wound healing and on new vessel formation in the cornea of the guinea-pig. In addition a small-scale experiment was carried out on the rabbit. These results are reported as five separate series of experiments.

EXPERIMENTAL.

Technique of Injury.

A cautery was made from a loop of 32 S.W.G. platinum wire. A predetermined constant current was fed to the cautery through a relay which activated the cautery for exactly one second. Each cornea was anaesthetized by instilling 2 per cent. pontocaine hydrochloride into the conjunctival sac. This produced adequate anaesthesia and the animals remained quiet during and after the injury.

A standard heat injury was inflicted by holding the cautery in contact with each cornea for one second at a point 2 mm. from the limbus in guinea-pigs, and 3 mm. from the limbus in rabbits. This produced a lesion approximately

1 mm. in diameter, involving the anterior two-thirds of the corneal thickness.

Assessment of Epithelial Healing.

The degree of epithelial healing was assessed by instilling two drops of 2 per cent. sodium fluorescein solution into the conjunctival sac and allowing it to act for one minute, after which the excess was removed with Ringer solution. The eye was examined immediately thereafter with ultra-violet light. The intensity of fluorescence from the injured area was compared against a standard scale. A lesion which fluoresced maximally was given the value of 5 units and lesser intensities were given appropriately smaller values (Campbell and Boyd, 1950). Observations were made every 12 hours.

Assessment of Vascularization.

The corneae were examined with a Zeiss binocular loupe (magnification X 2.5) under illumination from a hand-slit lamp. In Experiment II an assessment was made of the length of the new vessels growing into the cornea. Maximal vascularization was regarded as full encroachment of new vessels on to the lesion and lesser lengths of vessels were expressed as percentages of maximum.

In Series III, IV and V, two additional factors were considered; firstly, the breadth of the area of cornea showing vascularization, and secondly, the density of the vessels within the vascularized area. Each result was again expressed as a percentage of maximal vascularization. These additional factors were combined with the factor of length and the whole was given a numerical representation on a percentage basis.

Histological Method.

The entire enucleated eye was fixed in 10 per cent. neutral formalin, sectioned by the celloidin method and stained with haemalum and eosin.

Series I.

Ten young male and ten young virgin female guinea-pigs were used. The average weight of the animals at the start of the experiment was 360 grams. The twenty animals were balanced for weight and sex, and divided into two similar groups. All animals were kept in two large cages, the sexes being separated.

Each animal in the control group was given intraperitoneally 0.5 ml. of Aqueous Vehicle No.1 (Merck & Co.) daily. All animals in the cortisone group were given intraperitoneally 12.5 mgm. of cortisone acetate daily (Merck Suspension 25 mg./ml.). Administration of the drugs was

was started three days before the corneae were injured.

The aim of this series was to assess the action of cortisone on the progress of healing of deep corneal heat injuries. This was measured by the fluorescein technique. The lesions were examined histologically at the termination of the experiment on the ninth day of healing.

Series II.

This was a group of twenty guinea-pigs similar to those in Series I, although all the animals were albino. The corneae were injured and the animals given cortisone and aqueous vehicle as in Series I. The aim of this experiment was to assess the influence of cortisone on corneal vascularization resulting from heat injuries.

Series III.

This series was an extension of Series II, and the same technique was followed throughout, although only ten guinea-pigs were involved.

Series IV.

Twenty guinea-pigs were dealt with as in Series I with this difference, that cortisone was administered

subconjunctivally (1.25 mg. every third day, commencing three days before infliction of corneal injury.) The site of injection was adjacent to the corneal lesion. The control animals received an equivalent volume (0.05 ml.) of aqueous vehicle. In this experiment an assessment was made of the influence of local cortisone on the formation of new vessels within the cornea.

Series V.

Six albino adult rabbits of comparable weight were used in this series. Preliminary work had shown that a single thermal injury of the type inflicted in the previous experiments was insufficient to induce corneal vascularization in every rabbit. The injured area was, therefore, re-traumatized on two further occasions, 24 and 72 hours after the original injury, and this technique was followed by new vessel invasion in all the animals. Cortisone was administered subconjunctivally (2.5 mgm. every second day, commencing three days before infliction of corneal injury). The control animals received an equivalent volume (0.1 ml.) of aqueous vehicle.

RESULTS

In each series the animals were weighed daily, and in no case did the administration of cortisone significantly

retard the normal growth curve.

Series I.

Fig. 1 shows the mean degree of fluorescence obtained from the eyes of the ten control and ten cortisone-treated guinea-pigs. Cortisone caused a delay in epithelialization between the second and sixth day of healing.

Fig. 2 illustrates the histological appearance of the corneal wound on the ninth day of healing. Section A was taken from a control animal and Section B from a cortisone-treated animal. It is apparent that the degree of cellular reaction is less well marked in the corneal stroma in the guinea-pig which received cortisone. In this animal, moreover, the new formation of fibrous tissue is less abundant. While most of the other sections examined showed this quantitative difference, the histological results were not entirely uniform, and in a few instances the lesions in the cavies injected with cortisone resembled those in the controls.

Comment. The results of the fluorescent gradient suggest that cortisone delays the epithelialization of deep corneal lesions. Epithelial regeneration is, however, dependent upon the presence of a suitable collagenous substratum (Campbell, Ferguson and Garry, 1950). Cortisone can affect the regenerating stromal tissues, and its influence

FIG.1.

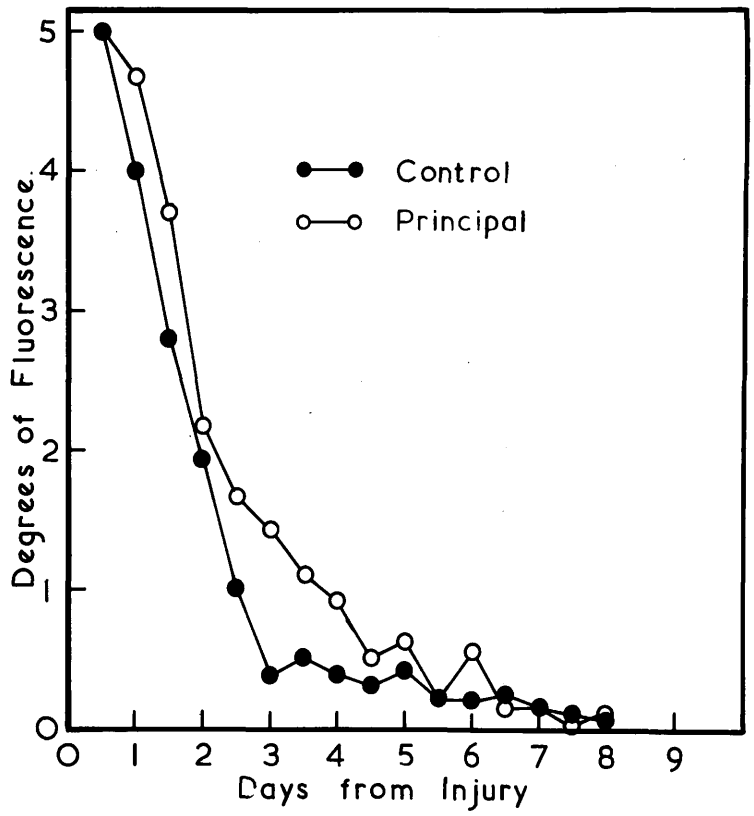
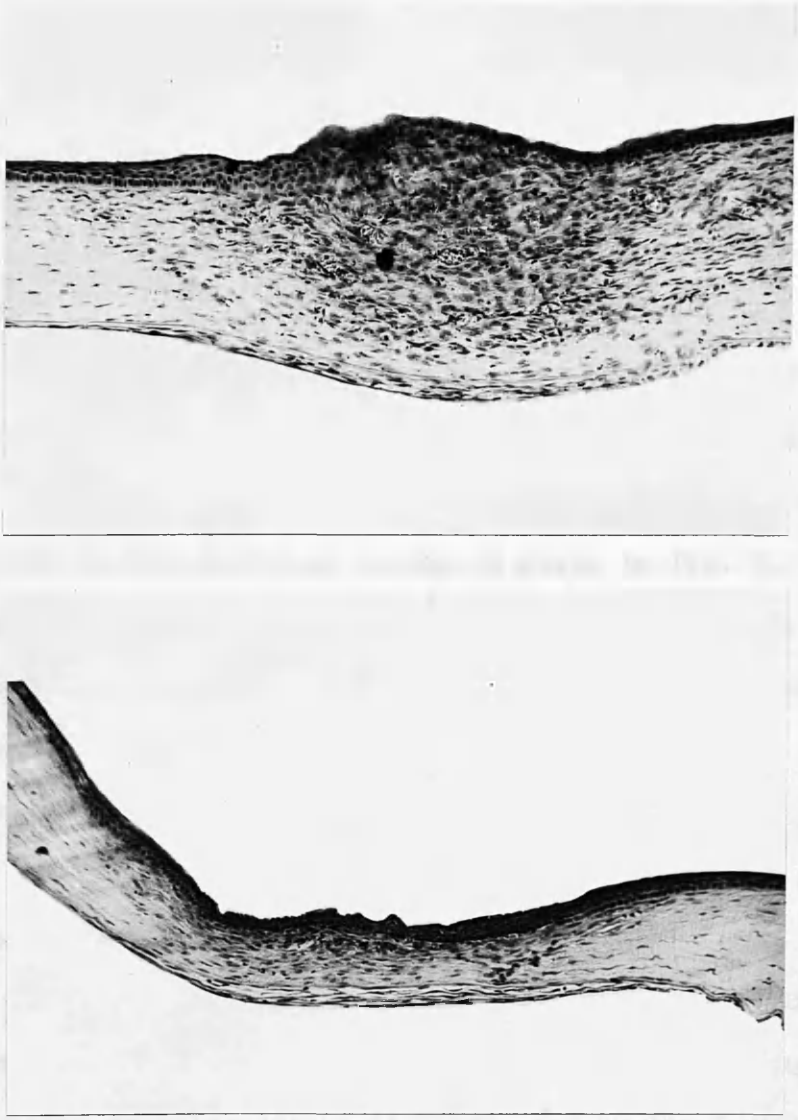


Diagram to show mean effect of cortisone on progress of epithelial healing following corneal heat injury in the guinea-pig.

FIG.2.



Histological appearances of corneal wounds on the ninth day of healing, following corneal heat injuries in the guinea-pig.

A - Control animal.

B - Cortisone treated animal.

on epithelialization may therefore be secondary to a primary action on the regeneration of underlying fibrous tissues.

Series II.

Three eyes in the control series developed an infective keratitis, and these eyes have been excluded from the results.

The mean degree of corneal vascularization in the control and in the cortisone groups is shown in fig. 3. It is apparent that in both groups vascularization occurred in two phases. This phasing was not due solely to the adoption of a mean figure, but was representative of the course of events in the individual cornea. Indeed, 32 eyes out of a total of 37 clearly showed this double phase of vascularization.

There was an initial phase of vascularization which reached a peak at the end of the second day of healing. Thereafter vascularization declined, and by the fourth day was only moderate in extent. It was noted that shortly after the infliction of the injury there was a localized area of corneal œdema surrounding the lesion and extending to the neighbouring limbus. This œdema became less obvious after the first few days and then disappeared. There was no marked difference in the amount of œdema in the control and cortisone groups.

After the initial phase, vascularization increased once more and by the sixth day reached a maximum which was higher than the initial peak recorded on the second day. This extension of vascularization was due partly to the re-opening of the vessels which had become attenuated at the end of the initial phase, and partly to an ingrowth of new vessels. A gradual decline in the degree of vascularization then occurred, and at the termination of the experiment on the eighteenth day there was only a slight residual vascularization in a few eyes.

It can be seen that although the general form of the vascularization in the two groups was similar, there were certain minor differences. The cortisone treated group showed slightly less vascularization than the control group up to the seventh day of healing, but thereafter the degree of vascularization was somewhat greater in the cortisone group.

Series III.

This was a confirmatory experiment to Series II. Fig. 4 shows that, as in Series II, there was a prolongation of vascularization in the cortisone-treated group, and that there was a similar, though less marked, tendency for the vessels to show two phases in their passage towards the lesion. The animals in this series

FIG.3.

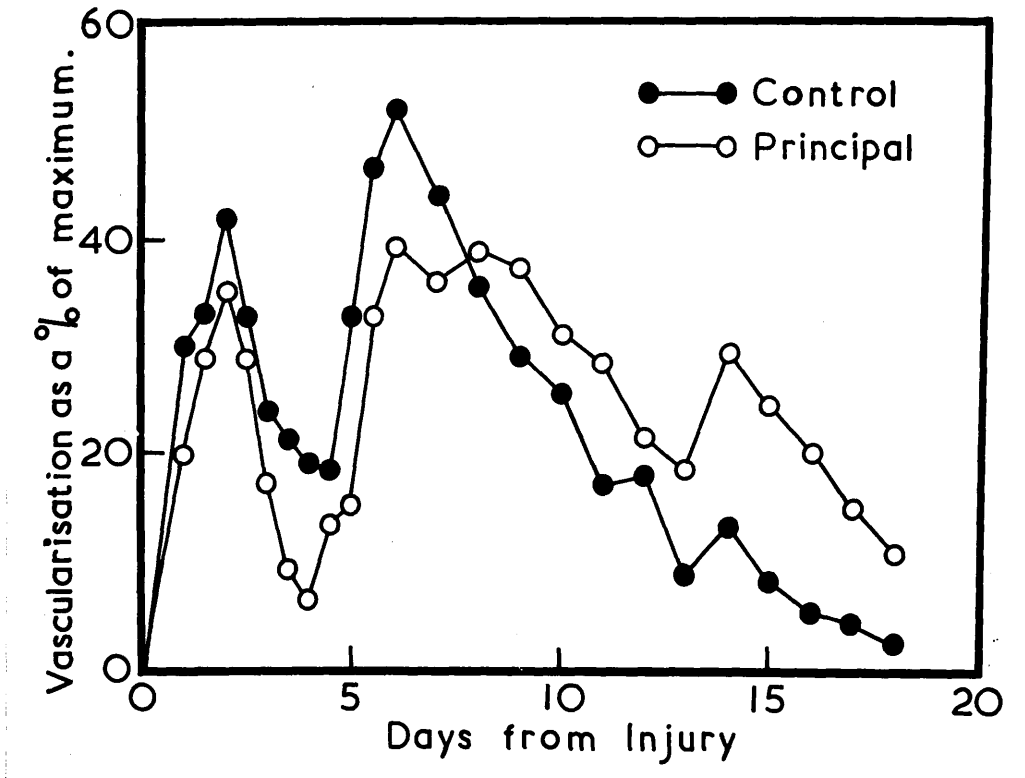


Diagram to show mean effect of intraperitoneal cortisone on progress of corneal heat injury in the guinea-pig.

(Series IL)

were not albinos, and, therefore the fine changes in the vessels were less obvious than in Series II.

Comment. These experiments show that there is a greater persistence of vessels in the corneae of guinea-pigs receiving cortisone systemically.

Series IV.

Fig. 5 shows that cortisone applied subconjunctivally did not inhibit the rate of formation of new vessels within the cornea, and that again there was a greater persistence of the new vessels in the cavies receiving cortisone.

It was noted in this series that corneal œdema was more marked in the initial phase of healing, and that this œdema persisted for a longer time than in Series II and III. There was, however, no detectable difference in the amount of œdema between the control and cortisone-treated eyes. Furthermore, the break between the first and second phases of vascularization was less obvious in this experiment.

Comment. It would appear that cortisone does not inhibit the formation of new vessels in the cornea of the guinea-pig irrespective of the route of administration.

Series V.

In contradistinction to the results previously found in guinea-pigs, fig. 6 shows that cortisone given subconjunctivally

FIG.5.

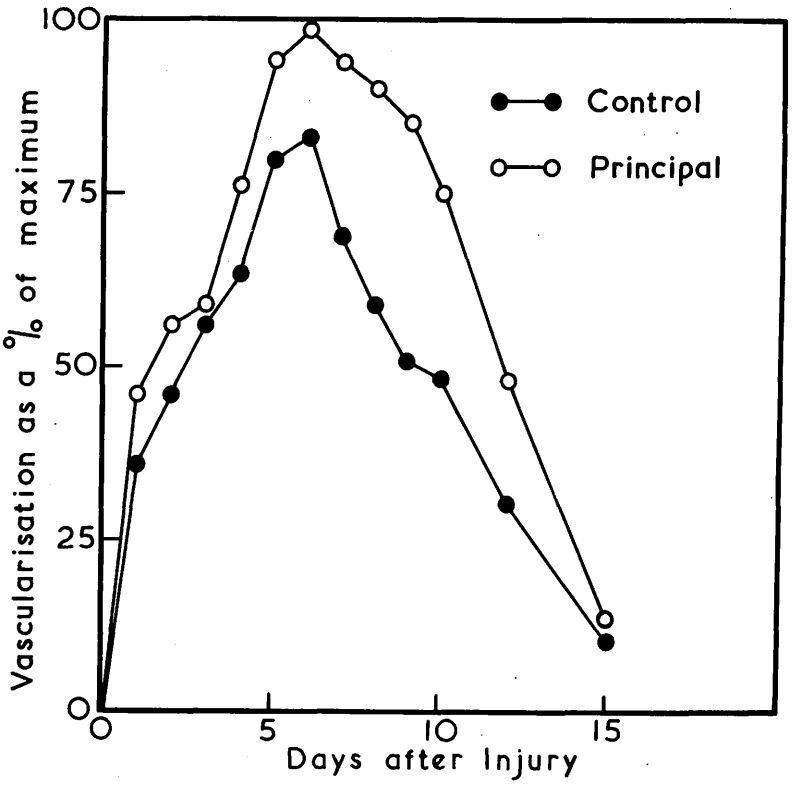


Diagram to show mean effect of subconjunctival cortisone on progress of corneal vascularization following corneal heat injury in the guinea-pig. (Series IV.)

FIG.6.

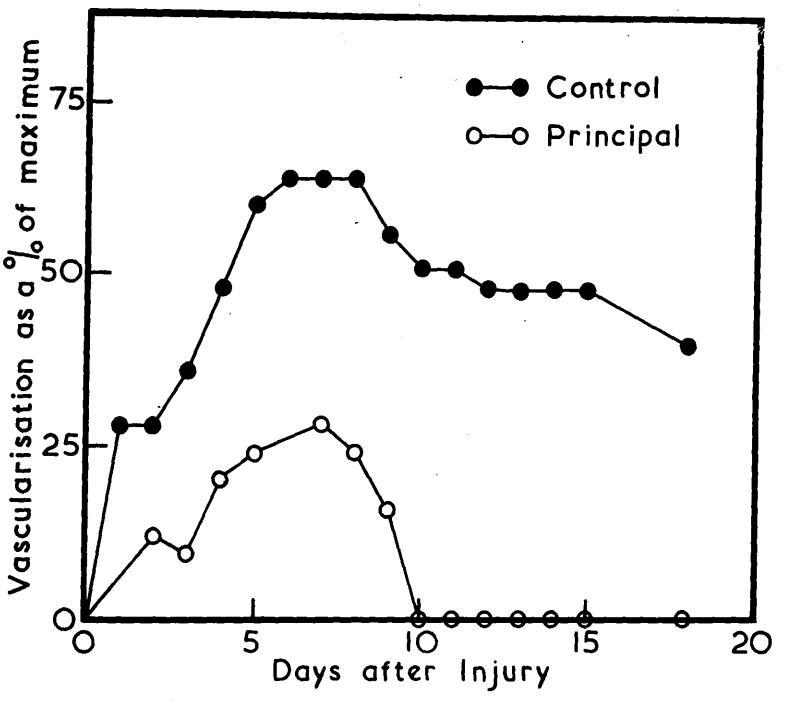


Diagram to show mean effect of subconjunctival cortisone on progress of corneal vascularization following corneal heat injury in the rabbit. (Series V.)

to the rabbit caused a diminished vascular response, although not a complete inhibition of new vessel formation, in the cornea. It was noted that the corneal vessels in the eyes receiving cortisone were finer in calibre than those in the control eyes. Furthermore, oedema around the lesion was somewhat less marked in degree and extent in the cortisone-treated group.

Comment. This result confirms the results of Jones and Meyer (1950), Ashton, Cook and Langham (1951), Lister and Greaves (1951), and Irvine and Irvine (1951), who found an inhibiting influence of cortisone on new vessel formation in the cornea of the rabbit.

DISCUSSION

There is evidence to suggest that the presence of œdema in the cornea is an important factor in the establishment of corneal vascularization. Cogan (1949) considered that œdema, by opening up the interlemellar spaces of the corneal stroms, facilitates the ingrowth of new vessels from the limbal plexus. Conversely, the subsidence of œdema may produce some degree of occlusion of the vessels. We have noted a close relationship between the degree of corneal œdema and the extent of vessel invasion.

In our experiments the entry of new vessels into

the cornea was preceded invariably by œdema of the corneal stroma. Furthermore, in the experiments using guinea-pigs in which cortisone or aqueous vehicle was administered intraperitoneally, the progress of vascularization was not strictly continuous. The temporary diminution in the extent of vessel invasion which was seen about the third day after injury, coincided with a subsidence of the corneal œdema around the lesion. In the experiment using guinea-pigs in which the drugs were administered subconjunctivally, there was no obvious diminution of vascularization around the third day. This experiment, however, was characterized by a greater and more persistent degree of corneal œdema, which was probably the result of the increased local trauma and irritation of the repeated conjunctival manipulations. The increased duration of œdema presumably diminished the tendency for vessel regression around the third day.

In the guinea-pig, cortisone does not lessen either the degree of corneal œdema or the extent of new vessel ingrowth. On the other hand, in the rabbit, cortisone exerts a well-marked depressant effect on new vessel formation. This is associated with a slight decrease in the amount of corneal œdema and there may well be

a relationship between this and the decreased vascularization.

It is, however, unlikely that œdema is the sole factor determining vascularization throughout the whole period of vessel invasion. In all our experiments vascularization of the cornea continued and increased in the later stages, despite the fact that by that time corneal œdema was diminishing and in some instances practically absent. There would appear to be some 'stimulus' from the injured area which attracts vessels into the cornea. The nature of this 'stimulus' is not known. It has been suggested that it is some chemical substance, perhaps allied to histamine, but there has never been any precise evidence for this hypothesis. Irvine and Irvine (1951) considered that some other factor, such as tissue necrosis, must play a part in the stimulation of new vessel formation, in addition to the influence of œdema of the corneal stroma. The healing of the traumatized area of the cornea is associated with an increase in the number of ærobic cells, and therefore, there may be a relative anoxia in that zone. This may have some bearing on vascularization.

It may be that cortisone in the guinea-pig, by causing a delay in the regenerating process within the healing area, maintains the 'stimulus' for vascularization

for a more prolonged time, and, therefore, indirectly causes an increase in vascularization. On the other hand, in the rabbit, cortisone exerts a depressant effect on vascularization throughout the entire period of healing, and this may indicate a more direct action of the drug on the vascular response. In any case these results disclose a fundamental difference between the guinea-pig and the rabbit in the action of cortisone on the new vessel formation.

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Acknowledgements

I am greatly indebted to Dr. N. Ambache, Dr. N. Ashton, Sir Stewart Duke-Elder, Professor R. C. Garry, Dr. C. J. Gavey, Mr. A. J. B. Goldsmith, Professor Sir John McNee, and Professor W. J. B. Riddell, for giving me access to their patients and for granting me facilities for carrying out the observations recorded in this thesis.