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Thesis on

THE PITUITARY BODY IN ITS RELATION TO THE SKELETON:

A Review of the Literature, with a Preliminary Report on Personal Experiments, and Notes on Experimental Surgery.

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INTRODUCTION.

This research is not presented as a completed scientific investigation. It may be worth while, however, to give an account of the objects in view and the methods employed, together with a preliminary communication of the results obtained up to the present time.

The object of this research is primarily to further the elucidation of the problems which concern diseases of bones. It is recognized that a thorough knowledge of the physiological conditions which influence bone growth, bone maintenance and bone repair is essential before pathological states are fully comprehensible and their rational treatment possible. The subject of normal bone growth and maintenance has therefore been taken up first; and the investigation resolves itself into an inquiry into the factors which exercise an important influence on this.

Osseous tissue is of course subject to conditions which affect the organism and all its component tissues generally, e.g., suitable nutrition, the proper exercise of its functions, etc.

Considered as a separate organ, the development and maintenance of bone is dependent on the powers which life and heredity have conferred upon its cells. Into this obscure and metaphysical realm

I do not propose to enter.

Considered as an individual part developing in the organism as a whole, it is subjected to those influences which regulate the time, the rate and the amount of growth of each part, and which eventually produce the perfectly proportioned adult form. For these influences we look to the <u>organs of internal secretion</u>. The adult form having been attained, the growth of tissue does not cease. Its continuous loss and replacement are essential features of its life - it has to be maintained. Under these conditions we should expect those factors which influenced its developmental growth to influence its proper maintenance as a part of the body.

The injuries inflicted by pathological processes or traumatisms make an increased demand on this power of regeneration, and under these conditions also we should expect our original tissue regulators to play an important rôle.

Derangements of the internal secretions may take the forms of (a) excess, (b) deficiency, (c) possibly perversion. Excess and deficiency may be investigated on physiological lines, while the possibility of perversion must be borne in mind in the interpretation of pathological conditions of these glands. The investigation may be outlined as follows:-

I. During developmental growth.

The effects of a) excess b) deficiency of an internal secretion

II. During adult maintenance.

The effects of a) excess b) deficiency of an internal secretion

III. Under conditions of disease or traumatism.

The effects of a) excess b) deficiency of an internal secretion

The organ of internal secretion which I have selected in the first place for investigation is the pituitary body. The following are my reasons:-

As will appear in Section I, the influence of the pituitary body on osseous tissue is a peculiarly important one. Very little research has been carried out in this particular direction.

Before proceeding to apply the scheme of investigation outlined above to the pituitary body certain points require consideration. It is necessary to review any previous investigations bearing on the subject. This must include the effects of pituitary disturbances on the other endocrine organs, and the influence of any such disturbance of another organ on bone. The importance of this general review is obvious when we consider the interdependence of the members of the endocrine group, the complex derangements which may thus follow a lesion of any one of them, and the consequent difficulty in interpreting the results of such a lesion. This subject is dealt with in Section I.

The available methods of investigation then fall to be considered. In Section II the more general points are set forth; and in Section III the operative methods used are given in detail. The general results of operations and pituitary feeding are dealt with in Section IV. Section V contains summaries of individual experiments; and Section VI gives my own results in relation to bone growth.

SECTION I.

A. THE INFLUENCE OF ENDOCRINE ORGANS ON BONE.

Pituitary.

In respect of growth changes I shall consider only the anterior lobe, for, as will appear in this section and in Section IV, the posterior lobe has no direct influence on skeletal growth.

Evidence on this subject is derived from experimental states of deficiency and excess in pituitary secretion, and from clinical observations of the same conditions in man.

Experimental Deficiency. This has been produced by various operative lesions. Of early observations one may mention the work of Caselli (1900)[1], who noted a general failure of development in puppies whose pituitary had been partially removed; and Fischera (1905)[2], who made a similar observation in chickens. These observations were quite incidental: even the authors lay little stress on them. Aschner (1909)[3] reported definitely an arrest of development in hypophysectomized puppies. Of the skeleton he says that the epiphyseal cartilages persist far beyond the normal time for closure; the bones are diminutive, retain their proper infantile characters, and are well formed. Microscopic examination of the epiphyseal region shows no striking alteration from the usual infantile condition. Ascoli and Legnani[4] noted similar results as regards epiphyseal changes, but they found osteoporosis and spontaneous fractures. The epiphyses were wide and projecting, while the diaphysis was weak and thin. The skull and longbones were mainly affected. Crowe, Cushing and Homans[5] noted general retardation in growth, including skeletal infantilism. Cushing[6] describes definite retardation of skeletal growth, the animals failing to reach the expected stature. X-ray examination showed the persistent epiphyseal cartilages, but no special changes in these are commented on: "a certain amount of epiphyseal thickening and a tendency to delayed ossification." Biedl[7] Houssay[8] and Blair Bell[9] also noted arrest of skeletal development in puppies. P. E. Smith[10] working with tadpoles, found hypophysectomized animals grew slowly but eventually reached adult development. Allan[11] obtained similar results.

We have then ample evidence that artificial pituitary deficiency causes a failure in skeletal development. More recent observations (Cushing[6], Biedl[7], and Blair Bell[9]) prove that the anterior lobe is responsible.

<u>Experimental Excess</u>. The production of this state has been attempted by feeding; subcutaneous, intravenous and intraperitoneal injection of various pituitary preparations; and by implantation of pituitary tissues. Many of the earlier investigations are

open to criticism. Often animals of widely divergent species were used as source and recipient of the extract; and while no doubt the pituitary function is fundamentally similar in all animals, nevertheless this objection forms a ground for suspicion of the results. Whole gland substance or extracts were also frequently employed. Prolonged administration of the posterior lobe is now well known to be definitely toxic in its effects, so that any increase in growth which the administration of anterior lobe might have produced was counterbalanced by an opposite effect of the posterior lobe. This is well shown by the fact that sometimes actual retardation of growth was obtained under these circumstances. Cushing[6)] pointed out this fallacy in criticising his own results. I therefore only quote such observations as appear to be free from these objections. Schafer[12)] fed young rats on dried anterior lobe of the ox, and obtained acceleration of growth. Exner[13)] performed homoplastic transplantations of whole glands in young rats, and obtained a temporary acceleration of growth, which he attributed to slow absorption of the active principle before the grafted tissue underwent degeneration. Goetsch[14)] administered dry powdered extract of anterior lobe of ox to litters of young rats, and obtained a remarkable increase in general growth, including that of the skeleton. Marinus[15)] obtained similar results.

P. E. Smith[10], feeding tadpoles on extract of the anterior lobe of the ox, observed an acceleration of growth which attained to a condition of gigantism. Uhlenhuth[16] confirmed this. Allan [11], also working with tadpoles, grafted anterior lobe substance under the skin, and confirmed these observations. He further notes that the growth of the hindlegs is specially increased. Recently Uhlenhuth[17] has induced true gigantism in salamanders, as distinct from mere acceleration of growth.

These observations prove that the production of an effective artificial excess of anterior lobe secretion induces an acceleration of general, including skeletal, growth. In tadpoles and salamanders gigantism has been produced, with a disproportionate elongation of the longbones — a feature of that condition.

In discussing the clinical evidence of pituitary disorders no attempt is made to give a detailed account of the diseases mentioned. On the contrary, I have endeavoured to gather the facts from the literature and to present a clear delineation of the results of pituitary disorders in man in their uncomplicated forms.

Clinical Hypopituitarism. It is convenient here to sketch briefly the complete clinical picture, but special attention is directed in this section to skeletal changes, while some of the other features will be treated later in their appropriate places. As the condition affects the skeleton, it is best considered when it arises (a) before and (b) after complete epiphyseal ossification.

Before epiphyseal closure a state of infantilism is produced, its degree depending on whether the condition is congenital, or whether the pathological state affects the gland in early or in later childhood. It is characterised by somatic infantilism. If of early onset, the body retains its truly infantile proportions; if of later onset, growth is stunted, and an individual approximating to a miniature adult is the result. Sexual infantilism is always a striking feature. Hypotrichosis is constant. Less constant features are varying degrees of psychosis, all of them tending to underdevelopment. There may be great adiposity, which assumes a feminine distribution in the male, and is accompanied by a high sugar tolerance. On the other hand, there may be emaciation, accompanied by glycosuria and often polyuria. There is a tendency to somnolence. A sub-normal temperature is the rule.

After epiphyseal closure a ~~very~~ similar train of symptoms is induced. The adult stature having been attained, dwarfism does not occur. Sexual and mental changes are of a retrogressive character.

In both cases of course, local tumour symptoms will be in evidence if a neoplasm is the cause of the pituitary deficiency; and local alterations in the contour of the sella turcica may be disclosed by X-ray examination, e.g., the deformation caused by the tumour, or the unduly small sella of the congenital case.

Skeletal Changes. In infantilism the bones are small, but quite well formed, retaining in greater or less degree their infantile characters. In the latter cases the male skeleton tends to assume female traits, e.g., light, thin bones, tapering limbs and hands, wide pelvis and genuvalgum. The epiphyseal cartilages and cranial syndesmoses remain unossified apparently indefinitely. The fully formed adult skeleton may undergo structural changes. In the male the broad pelvis and genuvalgum of feminine type may be developed; and, as far as can be judged from the literature, actual diminution in the width of the bones of the extremities may occur, producing the tapering feminine type (Cushing)[6]. Alteration in length does not occur.

The literature of the subject is now enormous, and only a few illustrative cases can be quoted. Babinsky (1900)[18] first clearly described such a case of infantilism with pituitary tumour. Fröhlich (1901)[19] defined the condition as a clinical entity. Levi[20] made a radiographic study of the skeleton, describing unossified epiphyses and open cranial sutures. Franckl--Hochwart (1909)[21] published a collected account of cases and discussed their diagnosis. Cushing[6] gives an admirable description of the condition, and details twenty-one cases of his own. Since then very many publications have been added, but little if any new light has been thrown on the subject. Of considerable interest are two cases of gunshot trauma of the pituitary. Madelung (1904)[22] described the case of a girl of nine years in which a rifle bullet lodged in the sella turcica. Growth was arrested, and the syndrome dystrophia adiposo-genitalis supervened. At this early date hypo-pituitarism was not recognized as the responsible factor. A similar case is reported by Marañon and Rosique[23], where the infundibular stalk was divided by a bullet (interference with blood supply of pituitary). Growth was arrested, and dystrophia adiposo-genitalis developed. I have cited these two cases as they are so closely comparable with the artificial tumour experiments of Blair Bell[9], and experimental division of the infundibulum. We have then clear evidence that in man, as in the laboratory animal, retardation of skeletal growth obtains in pre-adolescent cases of hypopituitarism, with indefinite delay in epiphyseal and syndesmotic ossification. The bones are well formed, and tend to assume permanently the size and characters which they possessed when hypopituitarism affected them. In the adult actual retrogressive diminution in the width of the bones and alterations in their architecture may occur.

Clinical Hyperpituitarism. As in the preceding section, the condition will be considered as a whole, and particular attention given to any evidence of skeletal change. Futher, the state of clinical hyperpituitarism in its uncomplicated form will be dealt with as far as possible, though this condition is rarely seen in practice. In the first place, it is often a fluctuating disease (comparable in this respect to exophthalmic goitre), and hence its permanent results rather than the active disease are usually in evidence. In the second place, hyperfunction, either from a functioning adenoma or simple hyperplasia, is almost invariably followed by a permanent deficiency consequent on the pathological process; so that again only the permanent changes produced by the excessive secretion remain, while the clinical picture is further complicated by the symptoms of pituitary deficiency. Tamburini[24)] and Cushing[6)] have pointed out this double phase. (Again it is to be noted that this is comparable to hyperthyroidism followed by myxoedema.) In the third place, the pituitary hyperplasia would appear in many cases to be secondary to genital deficiency, with its accompanying syndrome (see p. 19.). I should also state that under the heading "Clinical Hyperpituitarism" one must include the possibility of pituitary perversion. Again it will be convenient to consider the condition as it affects an individual (a) before and (b) after epiphyseal ossification.

<u>Before epiphyseal Closure</u>. This is not a mere matter of age, for under certain conditions the epiphyses remain open apparently indefinitely, and hence the possibilities of gigantic growth are constantly present. Under other conditions the epiphyses may ossify unduly early, as in pubertas praecox.

<u>Gigantism</u> usually manifests itself shortly after puberty (15 to 20 years). It may begin earlier, but this is very rare. Similarly it is uncommon for it to begin after the twenty-fifth year. But continued increase in stature up to the age of thirty or thirty-five years is by no means infrequent in such cases. The long bones are chiefly affected, particularly those of the lower extremities, but the skeleton of the hands and feet is also disproportionately large. The distal segments of the limbs are more enlarged than the proximal; the epiphyseal cartilages long remain unossified; the head and trunk are relatively small, though they may far surpass normal dimensions. Sufferers from gigantism are usually feeble. The muscular system is poorly developed, and such static deformities as kyphosis, scoliosis, genu valgum and flat-foot are the rule. Their resistance to disease is low, and they commonly succumb early to some incidental infection. They are mentally weak or actually deficient. A <u>constant</u> feature of true pathological gigantism is hypoplasia of the genital organs. Glycosuria is common in the

early stages and may persist.

Either definite hyperplasia or a functioning adenomatous condition of the pituitary body has been demonstrated post mortem in the vast majority of cases examined while the disease was still active. * Local pressure signs, and symptoms of general increase of intracranial tension are usual but by no means constant. Enlargement of the pituitary fossa can usually be shown with the X-rays.

This picture of pure gigantism is rarely seen, for giants either die early or, if they survive, acromegalic features often develop, consequent on a partial or total closure of the epiphyses and continued hyperpituitarism.

After Epiphyseal Closure. The condition of ACROMEGALY results. Again this is not dependent on the age of the individual. Consequent on pubertas praecox the epiphyses may ossify at a very early age. True acromegaly has been recorded as early as eleven and fourteen years of age (Cushing [6]): and certain unmistakable signs, not skeletal however, in newly born infants (Allaria[25], and Garibaldi[26]). The disease usually manifests itself between the twentieth and fortieth years of life, and begins in the majority of cases between the twentieth and thirtieth. It is characterized by an increase of fibrous tissue throughout the body: notably the eyelids and lips are thickened, the ears and nose may be enormous, the tongue is large and the subcutaneous tissues thickened by fibrosis; the viscera are often similarly affected. Hyperostosis is seen especially in the face bones, the hands and the feet, but general increase in bone substance occurs throughout the skeleton. In the face the lower jaw is most affected, while the upper jaw and malar bones also show marked increase in size. The teeth of both jaws become separated; the superciliary ridges are thickened and prominent; the frontal and maxillary antra increased in size. In the hands the ungual phalanges are particularly enlarged, showing a terminal "tufting" of bony outgrowth; while in the other phalanges and in the distal limb segments there are often marked exostoses at the sites of muscular attachments. These changes have been shown to be due to an increased periosteal deposition of normal bone substance, and the distribution is suggestive, as Keith[27)] has pointed out, of a hypersensitive condition of the osteoblasts: for the hyperostosis is most marked where repeated and slight traumatic stimulation takes effect, viz., the jaws - especially their alveolar parts - the terminal phalanges and sites of muscular attachment. The skin is thick and rough from hypertrophy of the papillae and cutis vera. Hypertrichosis is constant. The genital organs are curiously affected. In the male there is definite evidence (Cushing[6)]) that in the earliest stages of the malady there may be increased sexual activity. This condition is soon followed by sexual incompetence, which occurs though the bone changes are still actively in progress. Permanent atrophy of the genitals does not develop, however, until the final stage of pituitary deficiency is reached; for during remissions in the disease sexual functions may be resumed. In the female, masculine secondary sex characters are developed, e.g., distribution of the hair, deep voice, coarser skin, etc. The menses soon cease, but again resumption of sexual function may accompany remissions in the progress of the disease until permanent pituitary deficiency produces a permanent genital atrophy (Blair Bell[9]). Glycosuria and occasionally polyuria are common early in the disease, and represent its active stage. They are followed later by a high sugar tolerance, which indicates the onset of pituitary deficiency. The mental functions, apart from local intracranial disturbances, are not impaired until glandular insufficiency manifests itself. Local tumour symptoms are comparatively common, though they may be neither early nor severe. On the other hand, they are occasionally the leading features of the case. Distortion of the sella turcica is, as a rule, demonstrable by X-ray examination.

In acromegaly we are dealing with a pathological hyperfunction of the pituitary, and by far the commonest if not the only cause of this is a simple adenomatous enlargement of the anterior lobe. It is difficult to determine the cell elements involved, for the subjects of the disease do not die while it is in the active stage, nor have many surgical interventions been carried out at this period. When the gland comes to the pathologist, pituitary deficiency has existed for some considerable time, and degenerative changes are prominent. Any available evidence points to an adenoma of the eosinophilic element as the causal lesion of the malady (Benda[28)] and Fischer[29)]). However this may be, the lesion has been shown very constantly to be of a neoplastic nature. It is of importance here to note that the failure to bring clinical hyperpituitarism into harmonious comparison with experimental hyperpituitarism - as can be done in the opposite condition - is probably referable to this neoplastic element. One would certainly expect the secretory product of such a neoplasm to differ from the normal secretion in quality as well as in quantity.

Sex Glands.

The sex glands exercise a primary influence on the attainment of physical maturity. Their ripening initiates those changes which soon lead to the full development of the permanent adult form. At this time the skeleton is profoundly affected by them.

Before this period they must exert a certain influence productive of the skeletal sex distinctions, which are apparent even during foetal life: but apart from this there is no evidence that they affect the growth of bone before the onset of puberty.

From the onset of puberty until complete maturity is reached their effect on bone development is striking.

After maturity is reached there is no evidence that they exert any direct influence on the bones. It is, then, only the disturbances of the internal secretory functions of the gonads during the adolescent period which are of interest to us here.

<u>Deficiency</u>. Castration in the pre-adolescent period leads to a marked departure from normal bone development. It is about this time that the most active bone growth is taking place at the epiphyseal junctions of the long bones - in man, particularly those of the lower extremities. Under normal conditions the effect of the newly matured sex glands is to cause the cessation of this growth and the ossification of the epiphyseal cartilages. Castration by removing this influence permits an undue growth to occur in these situations. Sellheim (1899)[30] showed this in cockerels. In man, eunuchs and the Skopzen sect, who are early subjected to castration, show similar undue growth in length of the extremities - particularly in the lower - and a delay in ossification of the epiphyses (Tandler and Gross, 1907[31]): Launnois and Roy, 1903[32]). There seems to be little evidence as to any effect of the sex glands on periosteal growth of bone, although no doubt they do exert an influence

on it during the adolescent period.

Deficiency of the internal secretion of the gonads also affects the skeleton in an indirect manner by inducing a secondary hyperplasia of the pituitary body. This effect of castration on the pituitary was first shown by Fischera (1905)[33], and has been demonstrated since by many observers.

In the human subject the same interrelation between sex glands and pituitary has been noted (Launois and Roy[32] : Tandler and Gross[34] (Skopzen)). This point will be referred to later when the possible interpretation of gigantism is dealt with.

Excess. I am unable to find in the literature any record of the production of an artificial pubertas praecox by hypergenitalism, although successful transplantations of both testicular and ovarian tissue have been accomplished in adult animals. Early limitation of skeletal growth has been observed to follow injections of testicular extracts (Dor, Maisonave and Meurids, 1905[35]: Parhon[36]). Fischera[33] also found that injection of testicular extract into castrated animals caused the secondary pituitary hyperplasia to retrogress - an observation of therapeutic interest.

Pubertas praecox is the condition brought about by excess of the internal secretion of the generative glands in the pre-adolescent period. It may be due to abnormally early maturation of these structures or to a functioning neoplasm of testicle or ovary. The child, usually between three and seven years old, grows abnormally rapidly for a limited period of time: then growth permanently ceases. This rapid growth is not associated with enfeeblement; on the contrary the child is well developed, with good musculature, and precocious mentality (but sometimes imbecility). The early cessation of growth is associated with ossification of the epiphyseal cartilages. This has been radiologically demonstrated (Neurath, 1909 [37]). In addition to skeletal changes all the usual features of the attainment of puberty are found. In girls the breasts enlarge, the pubic and axillary hair makes its appearance, the generative organs mature and menstruation begins. In boys the external genitals enlarge, the growth of hair on face, axillae and pubes is seen, the voice becomes deep, and sexual instincts are developed.

This evidence suggests that excess of the internal secretion of the generative glands leads to an acceleration of the function of the epiphyseal cartilage and at the same time to an unduly early cessation of that function.

I have already mentioned that the condition may be associated with primary functioning tumours of ovary or testicle (Sacci, 1895 [38] - Knopfelmacher (1903 [39]) : Verebely[40]). There may be apparently simple premature hyperplasia of the gland, which would seem to be secondary to disturbances of other endocrine glands. Such a case in association with hyperpituitarism has been already cited (acromegaly at eleven years with pubertas praecox), and others in connexion with suprarenal and pineal tumours will be mentioned later.

It is an unsolved problem whether the interstitial cells of the testicle and ovary are entirely responsible for those changes, or whether the germinal epithelium also plays a part here. The weight of evidence appears to be in favour of the former view.

Thymus.

The life history of the thymus gland leads one to expect that it should influence some growth process in particular. Its relatively large size at birth, its continued enlargement until 10 - 15 years of age, and its subsequent involution lead one to such a conclusion.

The literature on the influence of the thymus on general and skeletal growth is very abundant, but little can be drawn from it as proven or even probable. I would especially refer to an excellent paper by Park and McClure (1919) [41)], which contains an exhaustive critical review of the literature, and a detailed description of their own experimental work on thymus extirpation. In their criticism of previous investigations, which appears to me just and unbiased, these authors show that little importance can be attached to most of the observations contained in the literature. In the first place, observations concerning extirpation experiments are of the most conflicting nature. The negative findings are largely invalidated by the employment of operative methods which could not achieve total extirpation with reasonable certainty, and by failure to conduct careful post mortem and histological examinations on the experimental animals. Suspicion falls on the positive results on account of their variety and wide divergence in the hands of different observers. Moreover, most of them can be interpreted as results of infections, confinement, unsuitable diet, etc., affecting animals which had been subjected to the devitalising effects of a major operation, in contrast to the controls. Most of the changes described in the skeleton have been attributed also to experimental deficiency of other ductless glands (pituitary, pineal), which lends support to the view that any major operation in conjunction with unsuitable laboratory conditions may cause them. The authors have induced similar changes by simple confinement of young animals.

I shall therefore refer to a few of the more important communications only.

Thymus Deficiency. Basch [42)], Sommer and and Floekern [43)], Ranzi and Tandler [44)], Soli [45)], Klose and Vogt [46)], and Matti [47)] record positive findings of great variety. They removed the thymus from mammals, principally using dogs.

Collectively, as regards skeletal development, their results are:- Retardation of bone growth and a tendency to dwarfism; considerable retardation of endochondral ossification. The epiphyseal cartilages are wide and irregular. The shafts of the long bones are weak and exhibit curvature deformities; and are shorter and thicker than normal. Cancellous bone is weak and deficient in calcium. There is general osteoporosis. Microscopically the process of ossification is much disturbed. In the epiphyseal cartilage the cells are irregularly arranged, and calcification of the matrix at the erosion line is deficient. Osteoblasts are diminished both in number and activity. Such skeletal changes are accompanied by various and often extreme signs of general sickness, such as muscular weakness, skin diseases, cachexia, and even mental deficiency.

Among those who obtained entirely negative results, as regards the skeleton, after thymectomy in mammals may be noted Paton and Goodall [48)], Fischl[49)], Hart and Nordmann [50)], Pappenheimer [51)], Renton [52)], Park and McClure [41)].

Recently, work on thymus extirpation in tadpoles has been done by Adler [53)], and Allan [54)]: their results are entirely negative.

Excess: Hyperthymism. Attempts to produce this condition in mammals have been made by feeding or transplantation of thymus tissue, or by injection of various thymic extracts. Either these attempts have been without obvious effect, or retardation of growth has been produced, presumably due to a toxic influence of the particular preparation used. Contributions to this subject have been made by Gebele[55] Ranzi and Tandler [44], Hart and Nordmann [56].

Sommer and Floekern [43] ascribe to thymus implantation an increased growth in length of the long bones: this has not been confirmed.

Recent work on tadpoles gives mainly negative results as regards growth. Gudernatsch[57] and Kahn[58] obtained increased growth but delayed metamorphosis. Stettner[59], Swingle [60], and Uhlenhuth [61] were unable to confirm their results. The last named author shows that the quantity of food given, whether containing thymus ingredients or not, is the main factor, and possibly explains the positive results of thymus feeding obtained by others.

Thus nothing can be definitely stated with regard to the influence of the thymus either on general or skeletal growth. However, as regards extirpation experiments in mammals, I think one may accept Park and McClure's[41] statements with confidence, as their experiments were done under ideal conditions and their conclusions are critically drawn. These are as follows:-

"The thymus gland is not essential to life in the dog. Extirpation of the thymus produces no detectable alteration in the hair, teeth, contour of the body, muscular development, strength, activity or intelligence of the experimental animal.

Extirpation of the thymus probably does not influence growth or development. The possibility that it may cause retardation in development and delayed closure of the epiphyses, however, cannot be excluded absolutely.

Extirpation of the thymus probably produces an alteration in the organs of internal secretion. It is possible that it produces well marked changes in the organs of internal secretion in the period immediately following thymectomy, which was not covered in our experiments."

Experimental hyperthymism furnishes us with practically no positive evidence.

Clinical. In the clinical literature I have been unable to find evidence of skeletal changes associated with thymic disease.

Krabbe [62] describes a case of "thymic dwarfism". There was shortness of the legs and bowing of the tibiae, with general underdevelopment of stature, genital infantilism, hypotrichosis, and pigmented patches on the scalp. There were no local signs of thymic disease. The author states that dwarfism and rickets are a constant sequel to thymectomy in various animals; and makes the diagnosis of "thymic dwarfism" by a process of "exclusion" of other known causes of the condition. The diagnosis seems hardly justified either by experimental evidence or by the symptoms presented.

Thymic medication has been employed chiefly in exophthalmic goitre and rickets. The results reported have been either entirely negative or inconstant, and cannot be considered to throw any light on the subject.

It should be noted here as a matter of general interest that recent investigations point to a protective and antitoxic function of the thymus. Hammar[63)] gives an excellent literary review and discussion of the subject. Such an hypothesis alone, however, hardly gives a satisfactory explanation of the life-history of the organ.

Parathyroids.

The parathyroid glands are important to the present investigation in their influence on calcium fixation in bone.

Deficiency. Total parathyroidectomy is fatal. Death is due to acute toxaemia, induced by a rapid cachexia and symptoms of nervous irritation (tetany). It has been supposed that normally the parathyroids antagonise or neutralise some responsible metabolic poison.

Partial, or total extirpation combined with implantation of parathyroid tissue, permits a longer or indefinite survival, with varying degrees of toxic symptoms according to the extent of the deficiency produced. Notable among these are wasting, loss of appetite, and increased nervous irritability.
Iselin [64)] records retardation of skeletal growth in

such experiments; but in the presence of severe general cachexia and malnutrition one cannot consider this as necessarily a specific action on bone growth. The effect of parathyroid deficiency on the growing skeleton is to prevent calcification of the newly formed osseous tissue. Cartilaginous matrix substance is seen to persist in the forming cancellous bone; and in the new osteoblastic tissue originating at the metaphysis there is failure of calcification together with persistence of the cartilaginous processes which abut into this region and, normally, become calcified and absorbed (Iselin [64]).

<u>Excess</u>. Administration of parathyroid tissue to kittens was found by Morel[65] to cause an increased calcium deposit in the skeleton, independent of the calcium content of the diet. This observation remains unconfirmed. Apart from this, the majority of administration and implantation experiments have been done in connexion with the acute nervous symptoms of parathyroid deprivation and not with growth of bone.

<u>Parathyroids and Rickets</u>. Erdheim [66] found in white rats which had developed spontaneous rickets that the parathyroids were considerably hypertrophied, the microscopical appearances being those of hyperplasia.

His observations are at first sight contradictory to the experimental findings of parathyroid deficiency in which "spasmophilic" symptoms and failure of calcification are prominent features. Erdheim's view that the parathyroid hyperplasia is responsive to a toxin which produces rickets, and which the parathyroids are attempting to antagonise seems plausible. If we accept the view that, in experimental deficiency, a metabolic toxin is responsible for the "spasmophilia" and failure of calcification in bone, and that the normal parathyroids keep this toxin in check, it appears reasonable to suppose that rickets is due to an abnormal increase in production of the toxin, with which even the hypertrophic parathyroids are unable to cope.

Ostemalacia. In many cases of osteomalacia a similar hypertrophy of the parathyroids has been observed (Erdheim[67]), Strada[68]), Bauer[69])). In this disease a decalcification of the bones occurs; there is general wasting, and nervous irritability (increased knee-jerks, etc.). Further, the condition is restricted almost entirely to the female sex, its onset in the vast majority of cases being associated with pregnancy, particularly with the later stages of that state. In pregnancy there is increased metabolic strain, and it would therefore seem likely that we are dealing with the same (?) metabolic toxin as affects the organism in artificial parathyroid deficiency and in rickets.

The fact that adenomatous tumours of the parathyroids have been reported in connexion with osteomalacia (Bauer[69], Erdheim[67]) does not contradict this view, since it is well known that excessive stimulation of such an organ may lead to an adenomatous formation; and, further, the other parathyroids in the reported cases were greatly hypertrophied.

Fracture of Bone. In experimental parathyroid deficiency failure in calcification of callus in fractures of bone, with consequent non-union, has been noted (Canal[70], Morel[71], Erdheim [72]). Morel also succeeded in showing that in these circumstances osseous union was accelerated by administration of parathyroid substance.

Calcium Metabolism. The evidence here is very conflicting. It would appear, however, that calcium fixation in the tissues is interfered with, as in parathyroidectomised rats the soft tissues contain a relative excess of Ca, while the bones exhibit a corresponding deficiency (Leopold and v. Russ[73]). Calcium retention is diminished both in experimental tetany parathyropriva (MacCallum and Voegtlin[74], and others), and in children and adults affected with tetany (Neurath[75], and others).

Although the views here expressed as to the probable action of the parathyroids in relation to bone are admittedly hypothetical, the evidence given would lead one to believe that their action is an indirect one.

As to the hypothetical metabolic toxin which has been referred to as the probable cause of the symptoms of parathyroid deprivation and of certain diseases, several theories have been advanced. Stoeltzner[76)] thought the symptoms were attributable to a metabolic derangement which led to an excess of free calcium in the blood and soft tissues. MacCallum and Voegtlin[77)] thought that a deficiency of calcium in these tissues accounted for the condition. Noël Paton[78)] considers guanidin the causal metabolic toxin: by its injection he has induced experimental tetany.

Thyroid.

It is well known that the thyroid gland by means of its internal secretion exerts a powerful influence on the cellular activity of the body generally. During the phenomenon of growth the tissues concerned in it are especially affected, the growing skeleton being no exception. In adult life, when the body no longer increases in size, its activities are chiefly directed towards energy production and self-maintenance. These functions are expressed in metabolism, which is profoundly affected by the thyroid gland, through the medium of the active tissues taking part in the process. Such tissues as the bones which, being fully formed, require a minimum of vital activity for their maintenance, are much less obviously affected.

The connexion of the thyroid gland with growth disturbances is so well known that little reference to the literature is required.

Deficiency. Athyroidism and hypothyroidism may be conveniently considered during the growing period and in adult life; in the experimental animal, and as evidenced by pathological states in man.

Experimental Deficiency in growing animals. The exact effect produced on the skeleton by thyroidectomy depends on the age of the animal at the time of operation. There is a tendency for the skeleton to remain permanently in the condition it presented when the deficiency was produced. A greater or lesser degree of skeletal infantilism results (Biedl[79]). The endochondral bone formation, being the more active in the growth process, is more markedly affected. Thus the greatest abnormality is seen in the "long" bones of the limbs. Epiphyseal union is long delayed: there is a reduction in the normal cell proliferation of the epiphyseal cartilages (Hofmeister[80]). As regards the condition of the epiphyses, it is important to note that arrest of development of the sex glands is a constant sequel to thyroidectomy in mammals. The thyroid deficiency may not be, therefore, directly or entirely responsible for the epiphyseal changes (vide p. 19.).

In adult life no obvious changes occur in the skeleton after thyroidectomy; but when the demand for active regeneration of bone is made by the production of fractures the effects of thyroid deficiency become apparent. The process of union is much delayed. It nevertheless proceeds slowly to completion. Thyroid feeding under these conditions accelerates union (Bayon[81], Steinlein [82]).

In man the most striking skeletal changes are seen in cases of congenital athyroidism. The bones remain almost as they were at birth, when the placental supply of thyroid secretion was lost. It is noteworthy that at this early stage both periosteal and endochondral ossification are arrested (Schilder [83], Zuckermann [84]). The more equal growth activity of periosteum and cartilage at this period explains this. The later onset of cretinism during childhood causes a remarkable retardation of skeletal growth affecting chiefly endochondral ossification, so that a stunted, relatively short-limbed figure results. Periosteal ossification is but little affected (v. Bruns [85]). As mentioned in dealing with the experimental condition, genital hypoplasia is constant in the clinical condition, and ? Pit. Hypo. demands consideration where the epiphyseal ossification is concerned.

The successful treatment of these conditions by thyroid-substitution therapy is too well known to require comment.

Excess: Hyperthyroidism. Bircher[86] fed young rats on thyroid substance. There was limitation in general growth, with early maturity. In the skeleton ossification proceeded rapidly and the epiphyseal cartilages were early closed.. Similar effects have been produced by feeding thyroid preparations to tadpoles, i.e., acceleration in the degree of development (metamorphosis) though not in increase of size (Gudernatsch[87]), and others).

Clinically hyperthyroidism is rarely seen during the growing period. When it does occur there is an acceleration of growth in height and an early epiphyseal ossification (Biedl[88])). Holmgren[89]) has shown by X-ray studies that in such cases epiphyseal synostosis proceeds rapidly, but in proper relation to the state of development of the skeleton and body generally.

In neither experimental nor clinical hyperthyroidism in the adult is there any skeletal change.

From this evidence one gathers that the thyroid gland regulates the <u>rate</u> of the normal active processes which occur in the skeleton, and that further than this the thyroid does not directly influence the bones.

Suprarenals.

There is little evidence that the suprarenal glands exert any direct influence on the bones.

<u>Experimental Deficiency</u>. De Mira[90]) noted

in unilateral adrenal extirpation cachexia and retardation of growth; the bones of the limbs were unusually slender. The observation is unconfirmed. Moreover, in presence of general cachexia it cannot be interpreted as a specific adrenal effect on bone. Gibelli[91)] produced bone fractures in animals which had been subjected to partial and total epinephrectomy, and in control animals. In the two groups no differences could be detected in the healing process.

Novak[92)] found in white rats after bilateral epinephrectomy a genital hypoplasia in the young, and genital retrogression in adults. The indirect bearing of this on skeletal development is obvious.

Experimental Excess. Carnot and Slava [93)] detached a small ring of bone from the tibiae of animals. To one series a daily dose of .006 grm. of adrenalin was administered. A series was kept as a control. Bone repair was further advanced on the eighteenth day in adrenalin treated animals. These authors conclude that adrenalin has a definite action on osseous tissue. Their observation remains unconfirmed.

R. G. Hoskins and A. D. Hoskins[94)] fed white rats on dried suprarenal substance. There was seen in from two to nine weeks an acceleration in development of the generative organs of both sexes. The possibility of an indirect influence on the skeleton through the medium of the sex glands is obvious.

Clinical Deficiency. Stoeltzner[95] believed that certain irregularities in epiphyseal ossification observed by him were due to suprarenal deficiency. He states that the condition was cured by administration of adrenalin.

It is stated that osteomalacia has been cured or its symptoms ameliorated by treatment with adrenalin (Guthrie[96], Bernard [97]).

Clinical Excess (or Perversion). The association of cortical suprarenal tumours with the condition of pubertas praecox is now well recognized. Cases of this nature have been reported by Wooley[98], Bullock and Sequeira[99], Linser[100], French[101], Adams[102], and many others. Glynn[103] and Vincent[104] have published collected series of cases and discussed their significance. In these cases precocious sexual development is the most striking feature, but there is often also acceleration of general and skeletal growth. As already pointed out in dealing with experimental evidence, the suprarenal effect is here an indirect one, exerted through the intermediation of the sex glands.

So far as the suprarenal glands affect the skeleton directly, evidence from the literature is very scanty and by no means convincing.

Pineal.

The pineal gland is an organ of internal secretion whose functions are at present very imperfectly known. It is well developed at birth, and continues in an active condition until about the seventh year of life in man, when it shows retrogressive changes. Retrogression is not complete, however, actively secreting cells being present throughout life (McCord[105]). The gland presents a similar relation to the developmental period in other mammals (e.g., in the sheep - Jordan[106] - it is in full activity during the first year, and its retrogression co-incides closely with the development of sexual maturity).

Experimental Deficiency. Exner and Boese[107] extirpated the gland in young rabbits; and observed, in comparison with controls, no abnoramlity in rate of growth or sexual development. Foà[108] removed the pineal from chickens. In cockerels he got acceleration of growth, and very definite acceleration in development of primary and secondary sexual characters. In pullets he observed temporary retardation of growth, but no other special effects. Dandy[109], working with dogs, got no physiological derangement following extirpation of the pineal. Horrax[110], excised the gland in guineapigs and rats. He observed no disturbance of growth, but in male animals the development of the generative organs was accelerated. In females this was not seen, but they showed a tendency to breed earlier than did controls.

Experimental Excess. McCord[111] fed to chickens and guineapigs small quantities of the pineal gland of the calf (in which the gland is in full functional activity). There resulted a marked acceleration of growth and a precocious development of the generative organs in both sexes, the effects being more pronounced in males. Gigantism, however, was not produced, and all obvious influence disappeared when maturity was attained.

Injections of extracts of the pineal body are without marked immediate physiological effects (Dixon and Halliburton[112], Jordan and Eyster[113]).

Clinical Evidence. There are recorded a considerable number of cases of tumours in association with the pineal body which showed precocious somatic, sexual and mental development, generally accompanied by adiposity. These disturbances have been observed to follow pineal lesions only before the age of seven years in man. They constitute a recognized type of pubertas praecox, the precocity being noted in boys only. The tumour most frequently found is a teratoma. The affection has been invariably looked upon as producing a state of hypopinealism; and it is concluded from such cases that the pineal normally plays a part in restraining sexual development until the appointed time for maturation changes, when its involution removes this restraint.

It will be seen that nothing can be said as to a definite action of the pineal on the skeleton. Feeding and destructive lesions are both credited with accelerating sexual and somatic development. It would appear that the rapid skeletal development is referable primarily to the generative glands, as the departure from the normal is most accentuated in this direction. The pineal gland, from its life history, and from experimental and clinical evidence seems to be chiefly connected with sexual development, especially in the male.

SECTION I.

B. THE EFFECTS OF PITUITARY DERANGEMENTS ON OTHER ENDOCRINE ORGANS.

Here one has to consider how pituitary derangements affect those endocrine organs which the evidence of the literature indicates may exert a direct influence on osseous tissue. Failure to take account of this factor would render quite unsound any interpretation put upon experimental or clinical findings. The glands which appear to have a direct and important influence on bone, in addition to the pituitary body, are the generative glands and the thyroid. The thymus seems in this connexion to be a negligible quantity; nevertheless we may note here that a persistent or hypertrophic thymus characterises both clinical and experimental pituitary deficiency (Cushing [114]). The parathyroids do not appear to be directly related to bone changes, though their significance is still uncertain. I can find no evidence of any changes in these organs consequent on pituitary disturbances. The suprarenal bodies and pineal gland probably influence bone solely by means of their action on the generative glands, and therefore do not demand consideration here.

Generative Glands.

In experimental hypopituitarism, according to the age of the animal either sexual infantilism or atrophy of the gonads is a constant sequel (Aschner[3], Cushing[6], Biedl[7], and many others).

In clinical hypopituitarism, as already stated, genital infantilism or retrogression is an invariable symptom.

In experimental hyperpituitarism acceleration in sexual development has been noted (Goetsch[14], Marinus[15]). In adult animals no special changes have been observed (Cushing[115]).

In clinical hyperpituitarism evidence is less easily led. Primary hyperpituitarism is rare before maturity. In such cases as have been recorded (See Acromegaly, p. 14) it was associated with pubertas praecox. Presumably therefore, the hyperpituitarism induced an acceleration in genital development. After maturity a pathological excess in pituitary secretion may stimulate sexual functions at first, but later inhibits them, although it does not induce atrophy of the gonads (See Acromegaly, p.14).

It is of importance here to repeat that castration is constantly followed by a functional hyperplasia of the pituitary, both in animals and in man.

Thyroid.

In experimental hypopituitarism the thyroid is always found to be atrophic or degenerated. Most observers describe the change as an excessive collection of colloid with flattening of the glandular epithelium

(Crowe, Cushing and Homans[5]), Houssay[116]), Blair Bell[117])).

In clinical hypopituitarism an exactly similar condition of the thyroid has been very frequently recorded.

In neither experimental nor in clinical hyperpituitarism can I find any record of thyroid changes. At the risk of undue repetition, I again refer to the fact that most acromegalics are in a state of hypopituitarism when they succumb, and hence the thyroid changes in them are the degenerative changes of pituitary deficiency.

SECTION I.

C. BEARING OF SUB-SECTIONS A AND B ON DEDUCTIONS MADE FROM EXPERIMENTS AND PATHOLOGICAL STATES.

I shall give merely a few examples of the significance of those inter-relations between endocrine glands which appear pertinent to the present research.

The explanations here offered are founded on information gleaned from the available literature which has been outlined above. Information on many important factors is scanty or wanting. Therefore the following hypotheses are not expressed as opinions, but as the most reasonable construction which can be put on the available facts at the present time.

In attempting to interpret the syndrome consequent upon experimental or clinical hypopituitarism we have to take into account the secondary deficiency which affects both the genital glands and the thyroid. For example, in the immature individual, while some of the bone changes are probably directly associated with pituitary deficiency, the delay in epiphyseal ossification is almost certainly referable to the secondary genital hypoplasia which is a constant sequel to hypopituitarism. The failure to develop the secondary sex characters is certainly due to this cause. Further it is difficult to decide whether such consequences of pituitary deficiency as retardation in general and

and skeletal development, lowered metabolic rate, and mental apathy are the direct sequelae of hypopituitarism or of secondary hyperthyroidism, or of both these factors.

In experimental hyperpituitarism (in mammals) an harmonious acceleration of developmental growth occurs, and no abnormality in growth - beyond its rate - is produced. Increase in body size is accelerated, but sexual development is proportionately advanced. This induces an earlier epiphyseal closure, and growth in size is therefore stopped. Hence the effect of hyperpituitarism on growth may be considered as self-limited to normal proportions.

Gigantism, in view of this experimental evidence, cannot be explained as a consequence of a primary hyperpituitarism (i.e., increase of a qualitatively normal secretion): for in this case, by analogy from the experimental state, growth would be accelerated but would cease early within normal limits. In gigantism genital hypoplasia is constant. If one assumes this to be the primary lesion, gigantism becomes explicable. The sequence of events would be primary genital hypoplasia, with delay in epiphyseal closure, secondary hypertrophy of the pituitary body, acceleration of growth (unchecked by epiphyseal ossification), growth beyond natural limits. Professor Tandler considered that the genital deficiency paved the way for, while the consequent hyperpituitarism actually caused the gigantic growth. In support of this hypothesis Tandler and Gross [34] have shown that the early castrated eunuchs and Skopzen show distinct features of gigantism, viz., their height averages above normal, their limbs are long, disproportionately to their trunks, their pituitary bodies are enlarged. To explain the more extreme degrees of gigantism it is necessary to assume that in these cases the pituitary is "unstable", or unduly sensitive to the effect of genital deficiency, so that an excessive hyperplasia or even an adenomatous formation results, and overgrowth is proportionately excessive.

As the cause of acromegaly, an hypothesis of increased production of a qualitatively normal pituitary secretion is also untenable on the grounds of the experimental and clinical evidence at present available. In the earliest stages of the disease it is possible that the secretion may be of normal quality. Thus in juvenile cases growth is accelerated harmoniously and pubertas praecox is induced. This exactly corresponds to experimental hyperpituitarism in young animals. Later, however, the distortions of the skeleton and the soft tissue changes which constitute fully developed acromegaly ensue; and simultaneously the sexual functions are inhibited. Such effects have never resulted in adult animals subjected to pituitary feeding (and this method of inducing hyperpituitarism cannot be altogether refuted in view of its marked effects in growing animals). One is therefore forced to conclude that in acromegaly the pituitary secretion becomes abnormal or perverted. A similar sequence of events is sometimes seen in the adult, when there is a hyperexcitation of sexual function at the onset, followed by the typical acromegalic symptoms mentioned above. As an explanation of this sequence, I would suggest that possibly the unknown factor which stimulates the cells of the pituitary, causes at first a simple hyperplasia, resulting in an increase of normal secretion; and that continued stimulation is followed by the pathological adenomatous formation (the characteristic lesion in acromegaly) which results in the production of a pathological and perverted secretion.

SECTION II.

EXPERIMENTAL METHODS.

A. GENERAL CONSIDERATIONS.

The functions of an endocrine organ are investigated by the physiologist by two main and distinct methods. 1) It is attempted to produce or simulate an exaggeration of function - to induce a state of hyperfunction - and from the results observed to infer what rôle the gland plays in the body under normal conditions. 2) A state of diminution or of complete absence of activity is produced. The consequences which ensue are interpreted in terms of its physiological function.

That the interpretations put upon the effects of such experiments in any particular system or tissue under investigation may represent the truth of the matter, it is necessary for the observer to take account of the effects of his procedure on the body as a whole. In order to avoid fallacies, his observations of the organism in its entirety can hardly be too extensive. Obvious examples of such possible fallacies are the effects which the anaesthetic and any operative procedures employed in "acute" experimental work may have. In experiments which involve the observation of the subjects for lengthy periods, the possibility of such errors is much increased. Anything which interferes with the general health, nutrition or proper activities of an experimental animal is sufficient to vitiate many experimental studies. More particular instances of possible fallacies in dealing with the endocrine organs have been alluded to already. Alterations in the function of one of these glands may have far-reaching consequences for the others: and failure to recognize this might cause a serious misinterpretation of the experimental results.

The most effective practical methods of investigating hyper- and hypo-function of the pituitary body are now to be considered.

B. EXPERIMENTAL ANIMALS.

The important question as to the most suitable experimental animals presents itself in the first place. Very many animals, ranging from the tadpole to the monkey, have been employed. It is obvious, other factors being equal, that investigations carried out on an animal whose physiological conditions approach those of man as nearly as possible, are more likely to prove of value than observation of more distant zoological relatives. When operative procedures are to be adopted the anatomical facilities offered by various species demand examination. Paulesco[118)], who published the first really satisfactory account of experimental operations on the pituitary body, made an investigation into the anatomical possibilities of approaching the organ by surgical means. His review covered the whole vertebrate series and was made as a preliminary to his experiments. He concluded that the frog, the fowl, the cat, and above all the dog offered the best possibilities. He confined his experimental studies to the latter animal; his reason being that the canine pituitary body is less deeply embedded in the sphenoid bone and in the dura mater than in other mammals, so that an intracranial mode of approach is possible. The dog is also satisfactory in that it closely resembles man physiologically. It is moreover an animal familiar to all, and any symptoms it may present are readily appreciated by anyone accustomed to clinical observation. It is a docile animal, and if one is careful to cherish its natural confidence all the necessary manipulations may be carried out without resort to forcible restraint, which would render the experiments inhumane, as well as much more difficult. Lastly, the dog may be kept under good laboratory conditions, with a reasonable certainty that it will remain normally healthy. For these reasons I decided to employ the dog in this research.

The cat is also suitable in many respects. Its use in experiments involving operations on the pituitary body has been precluded largely by technical difficulties. Some observers have attempted a buccopharyngeal approach in this animal, but the operative difficulties are great and complications are almost unavoidable. I have been able by a new method (fully described in Section III) to produce hypophyseal lesions in the cat. The technique is extremely simple, and the method is free from post-operative complications. The employment of the cat is more convenient than that of the dog for certain purposes. Especially in experiments on metabolism is this the case. The low cost of its purchase and maintenance is also a factor which cannot be overlooked. On these grounds I decided to employ the cat also for the present investigation.

As regards the general treatment, I make it a rule never to manipulate the animal in any way it can resent. Its natural confidence must remain undisturbed. Thus in the dog the preliminary shaving is done under morphia anaesthesia. X-ray photographs are usually taken under similar conditions. Sutures may often be removed without any anaesthetic, but if the animal is nervous morphia is used. In cats a general (inhalation) anaesthetic is necessary, as these animals do not tolerate morphia, and other available "injection" drugs (hyoscine, urethane, chloral, etc.) produce too prolonged an effect when given in sufficient doses. Bandages, which annoy animals greatly, are dispensed with.

A sharp look-out is to be kept for such infectious canine diseases as distemper, intestinal worms, and mange, and appropriate isolation and treatment adopted should they be discovered. In puppies under laboratory conditions rickets is also to be guarded against, or treated should it appear. In this disease cod-liver oil and exercise usually effect a cure. In severe cases and in distemper various "infant" foods have been found useful.

In cats distemper and round worms are the troubles most commonly met with.

The toilet of the eyes demands special care in both cats and dogs temporarily devitalized by operations. No animal with a suggestion of conjunctivitis should be operated on. In all cases I instil sterile vaseline oil immediately anaesthesia has been induced. Should there be any tendency for secretion to collect about the eyelids in the post-operative period thorough douching with 1/6000 hydrarg. perchlor. is resorted to at once.

It is in such treatment as eye-douching and the recording of the rectal temperature that the animal's confidence is essential to smooth and efficient working.

It is a sine qua non that the animal remain in perfect condition during any experiment which involves comparative growth studies.

Another important point concerning comparative growth studies is that pure-bred stock should be used. A litter of mongrels may diverge widely in size, etc., according to the hereditary traits which predominate. In my preliminary work I have used mongrels for reasons of economy, but for research on which I would hope to base scientific conclusions only pure-bred stock will be studied.

C. THE METHOD OF EXPERIMENTAL HYPERPITUITARISM.

This subject has been referred to under the heading, "Experimental Hyperpituitarism". It only remains to give here the reasons which have led me to employ feeding in preference to other methods. In the administration of any drug it is of vital importance to select the proper mode of introduction into the organism. When it is desired to maintain the effect for long periods - as in growth experiments - the effective grafting of the required tissue into the body is the ideal method. In the case of the pituitary body this procedure has completely failed up to the present time (Clairmont and Ehrlich[119]) ; Crowe, Cushing and Homans [5]) ; Exner [120]); Schafer [121])), except in the case of tadpoles (Allan[11])). Injection, subcutaneous, intravenous, or intraperitoneal has likewise met with little success. (This, however, has been due in most cases to one of the fallacies noted on p.7.). As Blair Bell[122]) points out, an analogy may be drawn between thyroid and pituitary extracts as regards alimentary absorption. That thyroid extract is absorbed effectively by the alimentary canal is well known. This may be ascribed to its morphological derivation from that structure (into which it originally poured its secretion). These conditions hold for the secretory portion of the pituitary body (derived from Rathke's pouch from the stomodaeum), so that effective alimentary absorption might be expected on these grounds. The dosage of the anterior (growth-affecting) lobe is not established, and can only be a matter for future experiment.

D. THE METHOD OF EXPERIMENTAL HYPOPITUITARISM.

Here one has to look to previous researches for guidance as to the most suitable mode of producing such a state of pituitary deficiency as will affect the skeleton.

It is unnecessary to give an historical account of the various procedures which have been carried out in the endeavour to produce states of hypopituitarism. An excellent review of this subject will be found in a paper by Crowe, Cushing and Homans[5]. Since its publication nothing of importance has been added to the literature as regards operative methods, with the notable exception of the communications by Uhlenhuth,[16] Allan[11] and others on pituitary extirpation in the tadpole. Their procedure does not demand description here.

Paulesco[123]) in 1908 published his brilliant monograph on the pituitary body, in which is described his method of bi-temporal, intracranial approach in the dog. With slight modifications by Cushing, Paulesco's procedure is the one used to-day in experiments upon the mammalian hypophysis.

Prior to this publication operations on the pituitary had been attempted in many species of animal and by diverse anatomical routes. In the frog a buccal and an intracranial method had been used. In the fowl a retropharyngeal approach was employed. In the rabbit an attempt to destroy the pituitary by a vertical, transcerebral approach was made. In the dog and cat many observers availed themselves of the bucco-pharyngeal route, and in these animals intracranial operations by frontal and spheno-palatine avenues had also been performed. The gland itself was variously treated - by total and partial removal, by gross contusion, by thermic and chemical cauterisation. A non-operative method by injection of a specific pituitary cyto-toxin had also been tried. Most of these experiments failed by reason of operative complications or insufficiently accurate post mortem examination. While they remained inconclusive, some of the accounts given obviously foreshadowed the more definite knowledge which later experimentation has yielded.

I shall not detail Paulesco's operation here, since it is his procedure which will be described in Section III as the operative method used in my own experiments on the dog. Such modifications of it as I have made affect only minor points.

Paulesco's treatment of the gland itself requires comment. He performed complete extirpation of the hypophysis, which was fatal. He largely removed or entirely destroyed the anterior lobe, which likewise was fatal. He removed the anterior lobe partially, and the posterior lobe completely. No obvious symptoms followed. He severed the organ from the base of the brain by section of the infundibulum, which he states is equivalent to total or almost total hypophysectomy. He separated the gland from its attachments to the sella turcica: and no apparent consequences were noted. In explaining the last two effects, he mentions that in dividing the infundibular stalk the main blood supply to the gland is cut off, while in separating it from the sella turcica only a few small vessels are severed. Paulesco makes no mention of skeletal changes following these various lesions.

Cushing and his co-workers have made the largest contribution to the knowledge of the pituitary body which we possess by virtue of experimental hypopituitarism. Cushing followed the methods of Paulesco, with slight modifications. His observations largely confirmed and amplified those of Paulesco.

He found that removal of large portions of the anterior lobe together with the posterior lobe was followed by the syndrome dystrophia adiposo-genitalis, and in young animals by retarded growth. Division of the blood supply to the anterior lobe was sometimes fatal, but recovery with symptoms of more or less anterior-lobe deficiency might also ensue. Removal of posterior lobe was without consequences beyond a raised carbohydrate tolerance.

Blair Bell[124)] confirmed the findings of these authors in the main. In his hands, however, division of the infundibular stalk was never fatal, but was followed by symptoms referable to degeneration of the anterior lobe, consequent on section of its vascular resources. The symptoms included dystrophia adiposo-genitalis and stunted growth.

Dandy and Goetsch[125)] showed that the anterior lobe receives its blood supply exclusively by arterioles which converge upon the neck of the gland and pass to the anterior lobe along the infundibular stalk. The posterior lobe receives a single arteriole which enters it at the base of the dorsum sellae. The vascular systems of the two lobes have but a very slight anastomotic connexion.

On these grounds I have decided to attempt to produce the desired state of hypopituitarism both by partial removal of the anterior lobe and by infundibular stalk section in the dog.

As stated above, I have been able to produce hypophyseal lesions in the cat by an apparently satisfactory metnod. I have availed myself of it also in the production of experimental hypopituitarism.

SECTION III.

EXPERIMENTAL OPERATIONS ON THE PITUITARY BODY.

I shall describe in detail the procedure I have employed. As regards the operation of Paulesco, this might appear superfluous, but the few workers who have performed it limit themselves to a brief description of its steps. They do not indicate many of the risks and difficulties which have to be met by the unitiated in this particular field. I shall accordingly lay special emphasis on the operative dangers which my short experience has impressed upon me.

A. PREPARATION OF THE ANIMAL.

Two days before the operation morphia is given to the dog. The hair is removed with clippers from the root of the nose to the shoulders and well out over the attachment of the ears. The clipped area is then shaved quite clean, and washed over with 1/20 carbolic lotion, which is not dried off. On the following day he is liberally fed. Carbolic is re-applied. On the day of operation milk food is given at least four hours before the commencement of the operation, after which the animal is shut away from food.

Cats require no special preparation before the transorbital electrolytic operation.

B. ANAESTHESIA.

Morphia. As I have indicated, this is largely used for dogs. The dosage I have found most suitable is 1/10 of a grain per kilo body weight. Some modification according to age is necessary, a young dog requiring relatively less morphia than an adult, regardless of weight. Occasionally morphia is disappointing in its action on the canine. It may render the animal weak and inco-ordinate and at the same time extremely nervous and excitable. Fortunately this effect is rare. The advantage of the initial dose for preparation purposes is obvious in guiding one in the subsequent use of the drug in individual cases. A solution of the hydrochloride 1cc. = 1 gr. is employed. The injection is administered with the finest hypodermic needles obtainable. To the insertion of a fine, sharp needle the dog makes no objection. The influence of a suitable dose of morphia passes off in 4-5 hours.

For cats an inhalation anaesthetic (chloroform or ether) is preferable to injected drugs, even for such procedures as the taking of X-ray photographs.

Morphia, as is well known, renders these animals extremely excitable, even when given in such quantity as to induce a general paresis. Hyoscine, urethane and chloral are (in my experience) uncertain of action and undesirably prolonged in their effect.

Inhalation Anaesthesia. I have used chloroform and ether. For the dog the latter is distinctly preferable. It is much less dangerous than chloroform in the induction period, the blood pressure is depressed to a less extent during the operation, and the post-operative recovery after ether administration is strikingly more rapid than after chloroform anaesthesia. In previous (abdominal) experiments on dogs insufflation of ether was employed on account of its reliability and easy control. The convenience of the intratracheal method in cranial work is obvious, especially in the canine, where tne close proximity of the anaesthetist and his mask to the field of operation would be a serious hindrance. (Blair Bell [9]) availed himself of this method of anaesthesia in his pituitary operations.) The method ensures a smooth and safe anaesthesia. The control of the depth of anaesthesia is easy and absolute. Risks of obstruction to the air way are entirely obviated. The apparatus employed was designed for clinical work, in which it has given satisfactory service for several years both in the hands of specialists and in my own. It consists essentially of three parts, viz., 1) for

Fig. 1. Apparatus for tracheal intubation.

Note the special construction of the laryngoscope. The catheter lies in place, and is held in position by the guiding spring.

Fig. 2. Anaesthetic vapour apparatus.

a, Ether chamber.
b, Chloroform chamber.
cc, Chloroform and ether needle valves.
d, glass cylinder, within which the anaesthetic droppers are visible.
e, Vapourising chamber.
f, Air inlet.
g, Air outlet.
hh, Pressure reducing valves.
i, Aneroid pressure gauge.
j, Electric heat-regulating switch.

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between
p 59 &
60.
Fig 1
Fig 2
as
separate
items.

A5

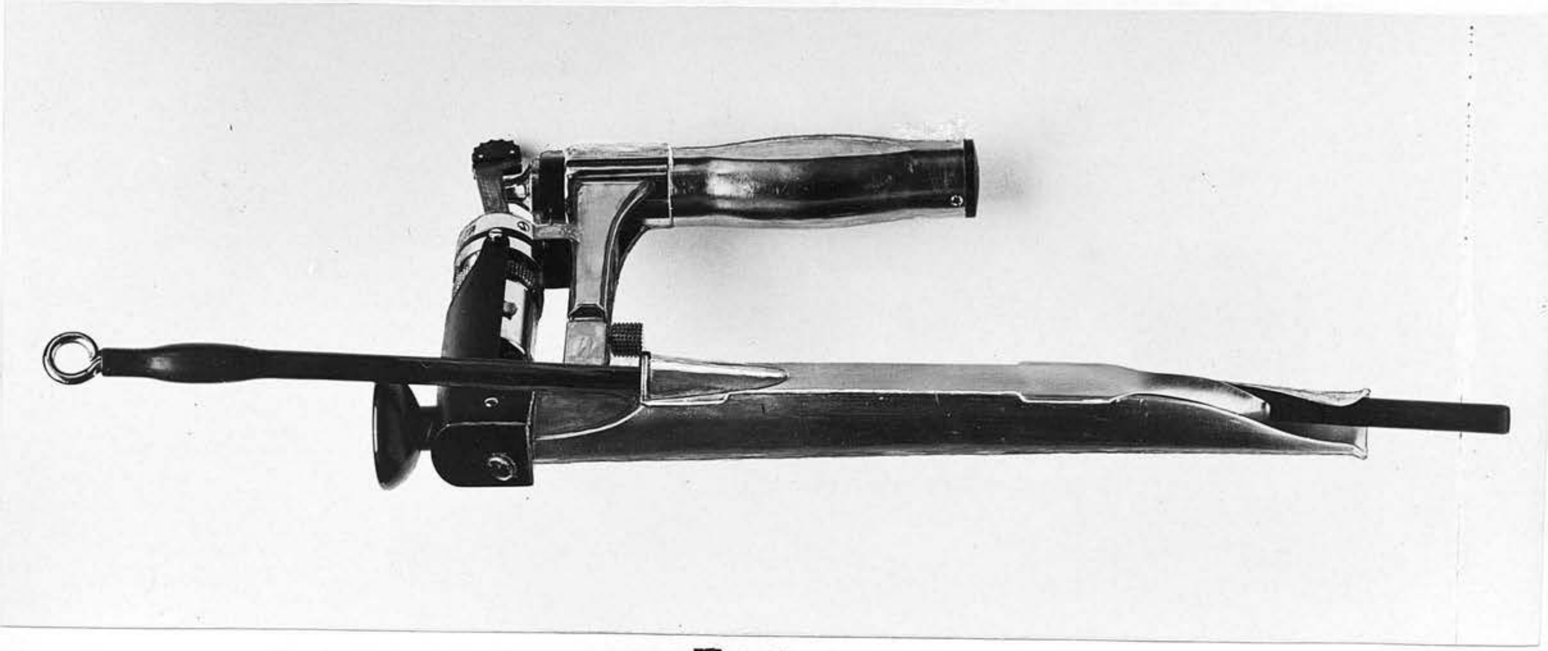

FIG. 1.

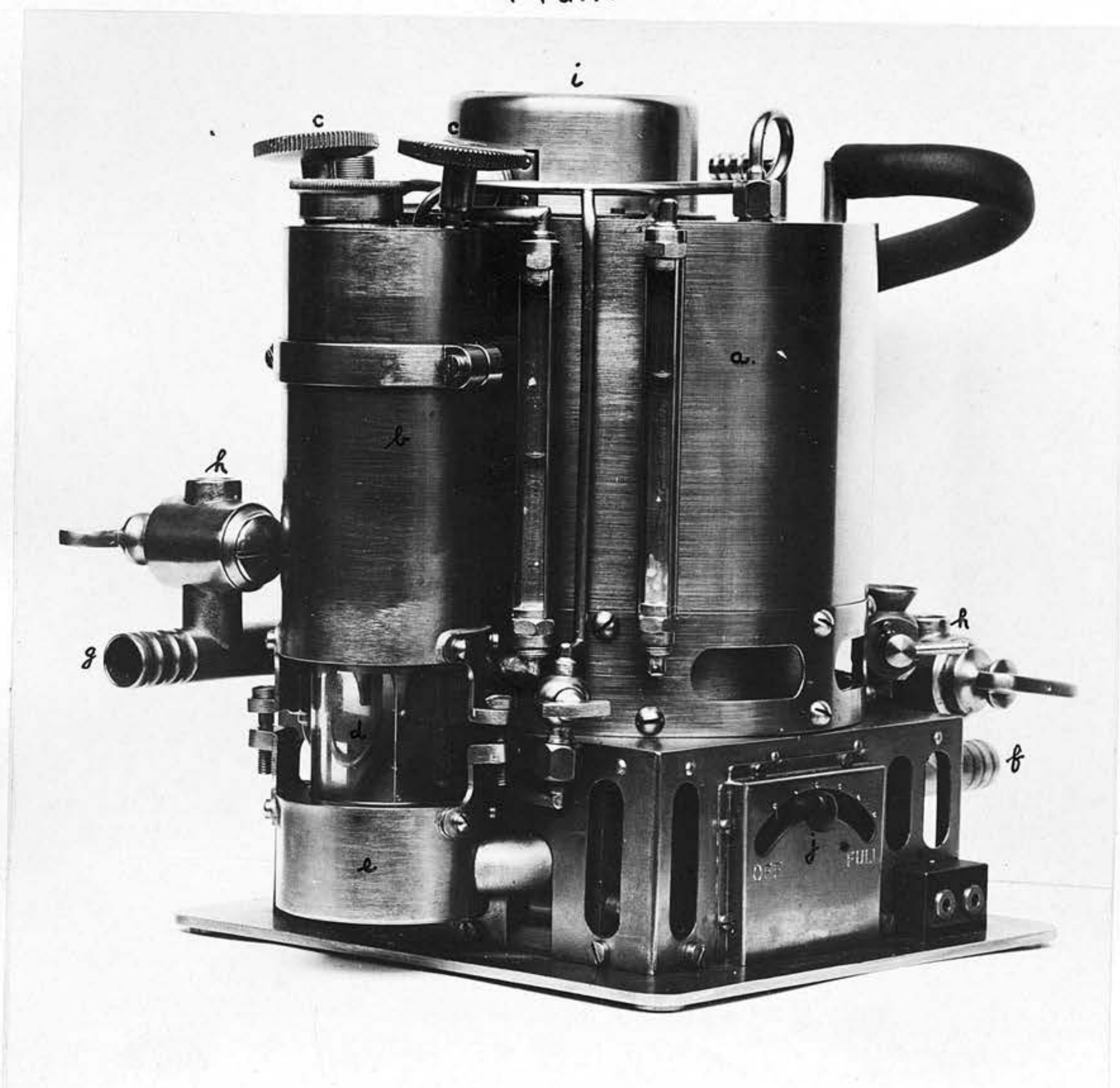

FIG. 2.

intubating the trachea; 2) for producing the air-blast; 3) for adding the required anaesthetic vapour to the air-blast.

1), the introducer (fig.1), is a modified direct laryngoscope. It is divided by a septum into two tubes which converge upon the distal aperture. One tube provides an unimpeded view of the glottis. The other serves for the passage of the catheter. It is so arranged that the catheter enters the field of vision just as it reaches the distal aperture of the instrument. When the glottis occupies the field of vision, the catheter, on being advanced is automatically guided into the air-passage, and can be seen clearly passing down the trachea. The necessary light is reflected down the vision tube by a Brünning's electroscope (for oesophagoscopy, etc.). If the primary anaesthesia is satisfactory a rapid, certain and aseptic intubation of the trachea is assured.
2), the apparatus for producing the air-blast (fig.3), comprises an electric motor, a rotary air pump, a rubber gas-bag and an "interrupting" valve. The movement to the air pump and interrupting valve is transmitted by enclosed worm-gearing. The rubber bag is filled with air under pressure, and either delivers this in a steady stream or through the interrupting valve in a series of blasts which correspond in rate to normal respirations. This interrupted air-blast has been found of advantage in permitting a

more complete air exchange in the lungs and in obviating the cardiac risks of a continuous positive pressure within the thorax. (Its use in thoracotomy is of course essential when both pleurae are opened, and is advisable even when only a unilateral pneumothorax is made.) 3), the apparatus for adding the anaesthetic vapour to the air current, is extremely simple. The anaesthetics, both chloroform and ether) are contained in two chambers from which they may be released by needle valves which permit of easy regulation. The drops of anaesthetic are <u>visible</u> as they fall into the vapourising chamber, so that one can see exactly how much is being given. The air enters the apparatus, passes through an electrically heated chamber, through the vapourising chamber, where each drop of anaesthetic is volatilised as it falls, and leaves through a second heating chamber. (The double heating is necessary to ensure proper vapourisation of ether and to counterbalance its cooling effect when this is accomplished.) Pressure regulator, aneroid pressure gauge, and thermometer are fitted. The heating can be regulated.

With such an apparatus warmed, fresh air with any desired proportion of ether or chloroform vapour, or of both, is introduced directly into the trachea in such a way as to simulate normal respiration. In no case has there been any post-operative respiratory complication.

The mode of procedure with the dog is as follows. A preliminary dose of morphia is given to animals over three months of age. (In young puppies the fall of body temperature which morphia causes adds materially to the risks.) The dog is placed under a large bell jar, into which ether is sprayed with an atomiser. When full anaesthesia has developed, the tracheal tube is passed (No.7 catheter for a puppy of 3 - 4 kilos) and fixed to the lip with a stitch. The head support and gag are secured in position, and the animal is placed on the operating table. The delivery tube of the apparatus is connected to the catheter and anaesthesia continued by insufflation. The passage of the catheter in the dog is extremely easy and occupies less than one minute.

For cats I prefer to use chloroform. They tolerate it well, and salivation is much less than with ether. During the transorbital operation the chloroform is given into the pharynx through a catheter which is held in place by a special holder mounted on the gag (fig.8).

C. CRANIOTOMY ON THE DOG.

The operation is conducted with all the care and precautions which belong to modern surgery. A full equipment of sterilized linen, gowns, masks and gloves is necessary.

The animal is placed on the table, on an

Fig. 3. <u>Operating Room</u>, <u>Department of Physiology</u>, <u>Edinburgh University</u>.

Note on the operating-table the head-rest, the head-holder, the electric hot pad, and the movable instrument tray. Beneath the table the intratracheal anaesthesia apparatus is seen. The vertical rod on the distant end of the table is for administration of subcutaneous saline infusion. Note also the multostat, which is used for electrolysis and for supplying the current to the forehead lamp.

2 prints
1 of
whole
1 of
section
showing
shelf &
pump.

2 slides
Same.

Fig.3.

Fig. 4. <u>Special instruments used for craniotomy on the dog.</u>

(Reduced by about one third.)

A. Head-holder. Note the wide gag for depressing the coronoid process of the jaw. With the holder the head may be conveniently rotated during the operation.

B. Brain elevator. Note the special spoon-shaped end.

C. Angled forceps for swabbing, etc.

D. Special angled forceps for manipulating the pituitary gland. This requires to be strong but delicate.

E, E. Special probe-pointed and hooked knives for the deep dural incision. They cut from within outwards.

F. Small, sharp spoon for the removal of the posterior lobe. (It is in reality angled like the other intracranial instruments.)

G. Fine dissector and probe for pituitary manipulations.

H. Self-retaining retractor (Kocher's pattern).

I. Sterilizable sheath for forehead lamp.

Item
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&
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Approx
A4.

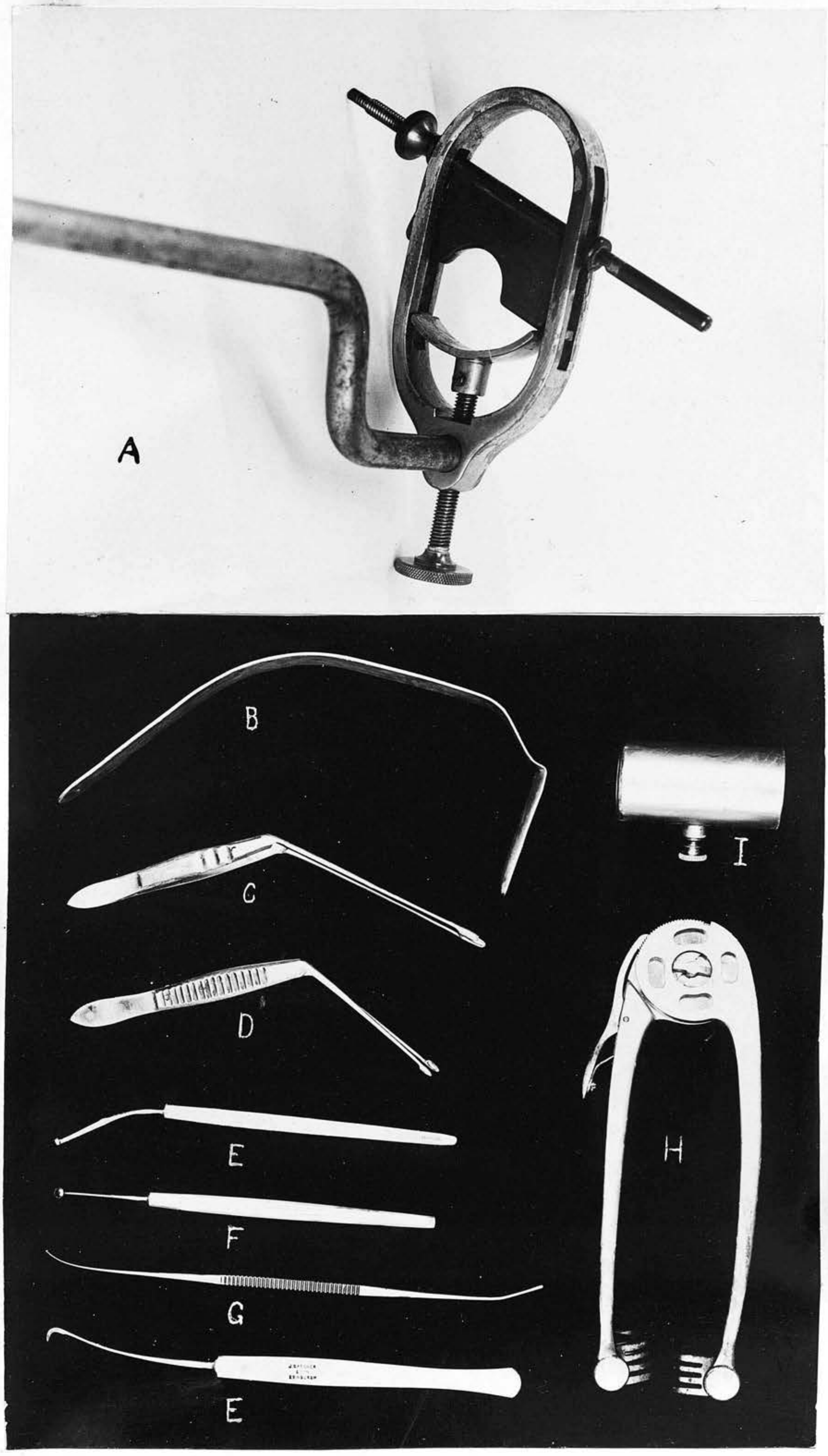

Fig. 4.

Fig. 5. <u>View of the field of operation in exposure of the canine pituitary.</u>

(About life size.)

The skin is completely excluded by a towel fixed to its edges by Michel clips. Observe the reflected temporal muscle, held aside by the self-retaining retractor. The divided posterior end of the zygomatic arch is seen. The bone defect has been made, and the dura incised. The orange coloured pituitary body is seen beneath the tip of the brain elevator.

Fig. 6. <u>Radiographic appearances of the cranial openings and mobilised zygomatic arch.</u>

The X-ray is that of Dog IV (anterior lobe excision). It was taken 7 days after the operation. Note the large openings (outlined). The distant one appears smaller than it really is.

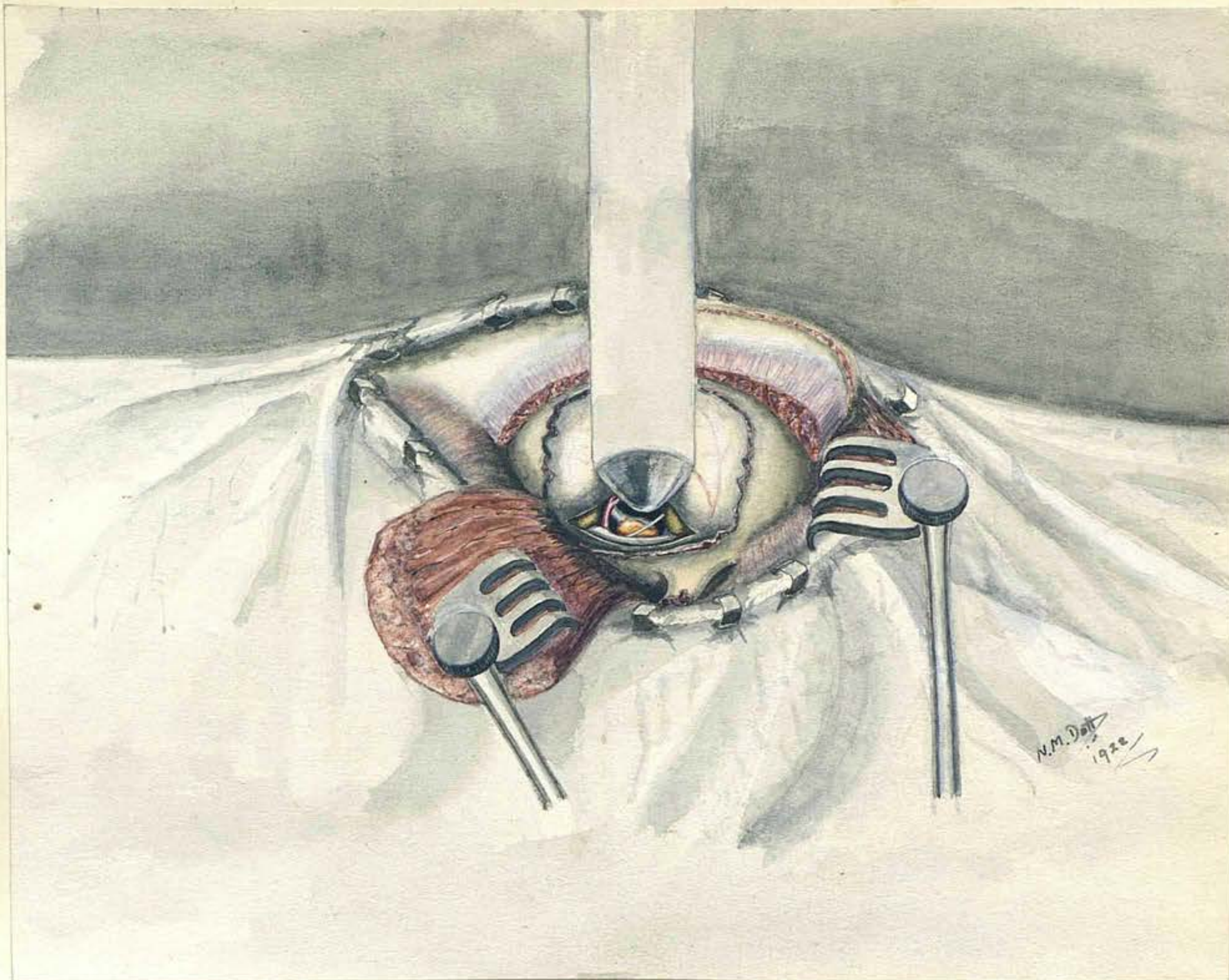

FIG. 5.

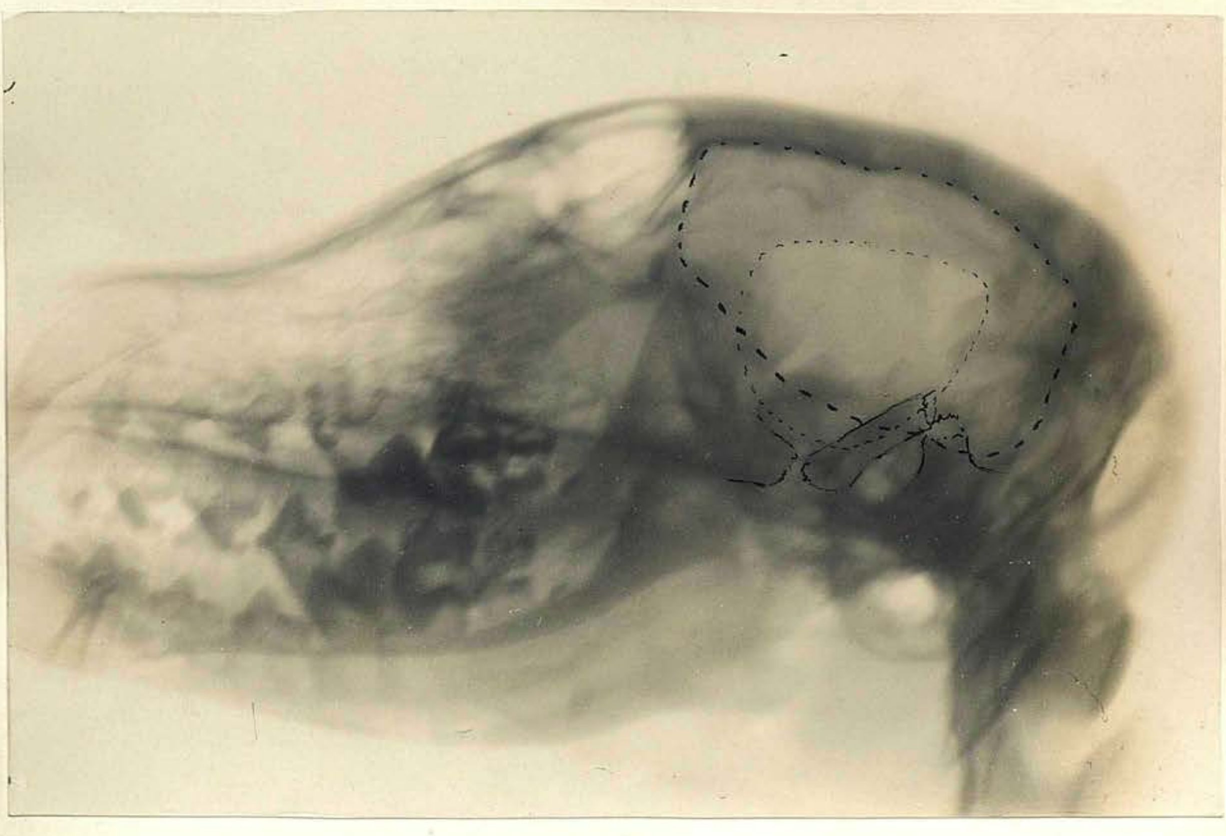

FIG. 6.

electric hot pad, lying on its belly, with the head supported on a hollowed rest (fig.3). It is conveniently controlled by the holder (fig.4) which secures the muzzle and permits of rotation of the head. It is important that the gag should hold the mouth widely opened in order to depress the coronoid process. Sterilized vaseline oil is applied to the eyes (which usually remain open and are liable to injury from drying of the cornea). The field of operation is disinfected with alcohol, followed by a 2% alcoholic solution of picric acid. (Picric acid does not irritate the eyes as does iodine when applied in their neighbourhood.) Sterilized waterproof and towels are secured in position, and the aluminium instrument tray is swung into place over the animal's back. A good forehead lamp is essential for the intracranial work, and it is convenient to have provided a detachable sheath (fig.4) which can be sterilized and permits of adjustment of the lamp during the operation.

The incision passes from the root of the nose in the middle line to the external occipital protuberance and is prolonged for several inches behind that point. (It is immaterial whether the incision is median or curved to the left posteriorly.) A sterilized towel with an opening corresponding to the incision is laid over the wound, and its edges folded round those of the skin, to which it is secured with Michel suture clips. The skin is thus completely shut off from the area of operation (fig.5). Such bleeding as comes from the scalp is controlled by these clips. The occipital muscle is detached from the sagittal ridge and superior curved line on either side, and the scalp tissues are reflected until both temporal muscles come into view. (It is inadvisable to reflect further than this, as an unnecessary space is left in which cerebrospinal fluid may afterwards collect.) On the left side a narrow osteotome is passed down over the temporal fascia to the anterior end of the zygomatic arch, which is divided. The temporal fascia and muscle on either side are divided to the bone from the external angular process of the frontal bone to just below the occipital protuberance and about 5 mm. from the temporal line (to allow material for re-suture). The muscle and periosteum are detached downwards with a raspatory as far as the posterior end of the zygomatic arch and infratemporal crest. A vein from the diploic tissue occasionally requires to be controlled with wax in the lower parietal region. On the left side the bared posterior end of the zygomatic arch is divided just outside the mandibular joint. It can then be displaced forcibly forwards and outwards.

The right side of the skull is now opened with a 1/2" trephine. (The burr is safer in young puppies.) With nibbling forceps the opening is rapidly enlarged. It is unwise to approach nearer than within a centimetre of the superior curved line, which corresponds to the lateral sinus, as the diploic bleeding is here excessive. The bone section may be carried as far in a forward and downward direction as is possible with impunity. In the upper and posterior parietal region diploic bleeding is always free and the application of wax is constantly required to stop it. The defect should measure about 4 cm. long by 3 cm. deep in a puppy of 3 - 4 kilos (fig.6). When all bleeding from the bone has been checked, the dura mater and arachnoid are opened by a triradiate incision - avoiding the main branches of the middle meningeal artery. The temporal muscle is loosely replaced over the defect. Turning to the left side of the skull, a self-retaining retractor (figs. 4, 5) is so placed as to keep the temporal muscle and displaced zygomatic arch well forwards, as good access to the subtemporal region on this side is essential. A bone defect similar to that on the right side is made, but it is carried further into the subtemporal region, till the base of the skull is reached. The dura mater is detached from the floor of the middle cranial fossa by gently packing ribbon-gauze between it and the bone. This should be done slowly, for as it proceeds the brain is dislocated and is partially extruded through the right side of the skull. The dura is easily separated until its trigeminal line of attachment is reached where it adheres to the margins of the sphenoidal fissure, the foramina

Fig. 7. <u>Exposure of the canine pituitary.</u>

Note the brain elevator in place, and the protection afforded to the brain by the dura mater. The margin of the sella turcica stands out, and on it are recognized the anterior clinoid process, the internal carotid artery and the oculo-motor nerve. The brain is seen, bulging in on either side. The pituitary body is at once identified by its anatomical relations and the orange colour of its anterior lobe. The grey-white stalk and posterior lobe are just visible beneath the elevator.

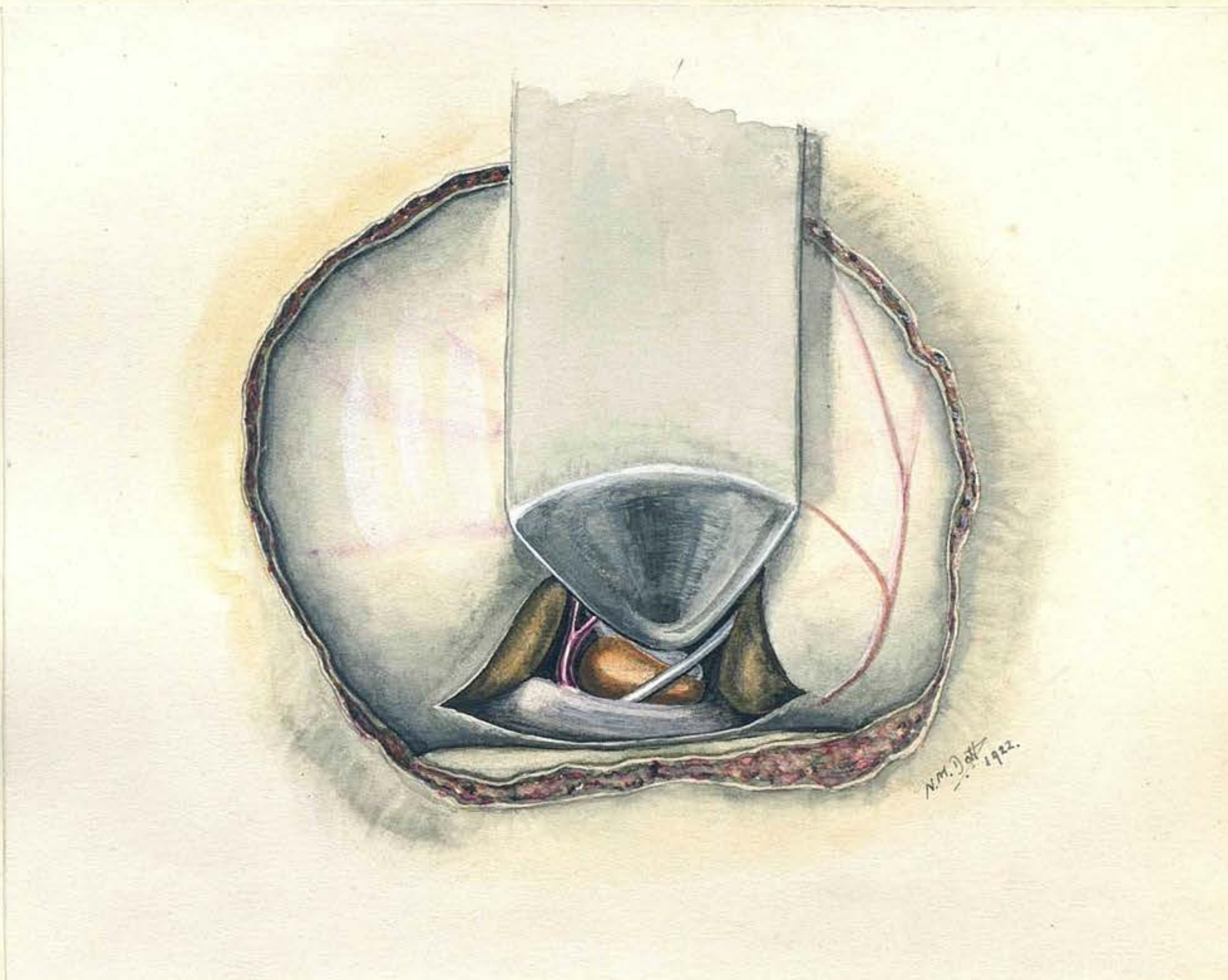

Fig. 7.

rotundum and ovale. As the packing is removed the brain elevator (fig.4) is inserted and the dura pressed upward with it. The anterior border of the divided stump of the zygomatic arch serves as a guide, for the pituitary body lies in a line directly inwards from this point. The dura mater is punctured with a fine knife opposite this point and not less than 5 mm. from its trigeminal attachment. The opening is enlarged forwards and backwards for about 7 - 8 mm. in either direction with the special hooked knife, which cuts from within outwards and obviates the risk of cerebral injury. The elevator is advanced through the opening, and carried across the floor of the middle cranial fossa towards the sella turcica. Great care is necessary to avoid cerebral contusion by keeping the point of the elevator in close contact with the cranial base as it is pushed inwards. The dura mater covering the Gasserian ganglion comes first into view, then the sharp, crescentic, lateral border of the sella turcica (fig.7). The oculomotor nerve is recognized entering this border from behind and above. At the anterior extremity of the sellar margin the eminence of the anterior clinoid process is seen with the internal carotid artery passing up vertically immediately behind it. The elevator is advanced into the interval between the artery and third cranial nerve, over the edge of the sella turcica. By exerting a steady upward pressure the pituitary body is fully exposed to view after the cerebrospinal fluid has been mopped out. The stalk (fig. 7.) passes upwards and forwards to the cerebral base in the interval between the two carotid arteries. The anterior lobe is recognizable by its orange colour. The posterior lobe, barely visible without dissection, is recognized by its grey-white appearance. The desired manipulation having been carried out upon the pituitary body and any blood clot having been cleared from its vicinity, the elevator is withdrawn, the brain resumes its place, and the separated dura is automatically replaced by it on the cranial base. The dura mater on the right side is carefully spread over the subjacent brain, but its suture is unnecessary. Under a stream of warm saline all blood clot and superfluous bone wax is washed from beneath the temporal muscles, and these are replaced. The temporal fascia is accurately sutured with fine catgut. (The gag should be withdrawn to facilitate this.) The occipital muscles and epicranial aponeurosis are approximated in the middle line by suture. The skin is closed by Michel clips and interrupted stitches of silkworm gut. No drainage is employed. The operation occupies about one hour.

For dressing the bismuth and iodoform paste recommended by Sir Harold Stiles as a dressing for infant hernia cases has been found ideal.

Subcutaneous saline is given immediately as a routine procedure (200 - 300 cc. for puppies of 3 - 4 kilos). It is not always necessary, but it serves as an extra fluid supply during the first twelve hours, which, considering the loss of blood and cerebrospinal fluid, is advisable.

TREATMENT OF THE GLAND. It is always well to define the stalk clearly with a blunt probe. To accomplish a total extirpation the gland should first be freed with a fine dissector from the sella turcica, the vascular attachment of the posterior lobe requiring special attention. When the organ is dangling free on its stalk, the latter is seized at the base of the brain with the fine angled forceps, and broken with a twisting movement: the pituitary body can then be removed either in the grasp of the forceps or on a small spoon (fig.4). It is inevitable that a tag of pars tuberalis remains attached to the base of the brain between the tuber cinereum and optic chiasm.

Simple stalk division is done as above. The leash of vessels passing down the anterior surface of the stalk to the anterior lobe may require special attention in order to completely divide them.

Removal of the Posterior Lobe is easily carried out. With the dissector its postero-inferior vascular attachment is broken. The small spoon is then passed forwards under it, shelling it out of the cup-shaped anterior lobe. The spoon is passed up in front of the stalk, and finally is turned backwards against this structure when the base of the brain is reached. It is then removed on the spoon. In this way the posterior lobe and stalk may be excised without injury to the anterior lobe or its blood supply, for if the manipulation is carefully performed the stalk comes away, leaving the vessels passing to the anterior lobe intact. There are no vessels of importance on the posterior surface of the stalk. This procedure permits of an entire ablation of the pars nervosa, the stalk and the pars intermedia. As in total hypophysectomy, the pars tuberalis which is prolonged forwards on the base of the brain remains intact.

Complete removal of the Anterior Lobe alone is an operation of extreme delicacy and difficulty, although large pieces of it may be excised with comparative ease. The anterior lobe is sharply marked off from the posterior by its distinctive colour (fig.7). On the side of the organ which has been exposed (left) a fine dissector is lightly drawn along the line of demarcation. In this way the pituitary cleft is entered. The special forceps is introduced into the cleft while closed, and is permitted to spring open gently, thus widening the gap. At its anterior extremity the anterior lobe is detached from its vascular supply. The stalk and posterior lobe now lie free, suspended across the operative field between the base of the brain and the back of the sella turcica. The anterior lobe occupies the sella turcica, from which it is now freed with the dissector. As large a grasp of it as is possible is taken with the forceps, and it is dragged away from its attachments on the right side. One can hardly guarantee that some minute fragment will not remain on the distant side of the organ. The detachment of a large portion is conducted on the same lines.

OPERATIVE COMPLICATIONS.

1. Sepsis. In one of my first cases an epicranial haematoma became infected. As one can hardly trust the shaved skin of the dog to be perfectly disinfected, I now exclude this from the operative field (fig.5). Since taking the precaution there has been no trouble on this score.

2. Haemorrhage. This has been the only cause of operative mortality in my experiments. Severe bleeding is first likely to be encountered while making the bone defects. Diploic haemorrhage may be extremely free, but is readily controlled with wax. This measure has been necessary in every case. Bleeding from the lateral sinus may occur if the dura of the cranial base is too much stretched in elevating the brain. It is due to tearing of the dural attach-

ment to the upper aperture of the jugular foramen. It may be checked by pushing a small plug of wax into the recess from which it comes. Bleeding from the cavernous sinus is induced if the dural incision is made too near the trigeminal attachment - especially near the sphenoidal fissure. Its control is difficult. Packing and allowing time for coagulation is probably the only available means. The wall of the cavernous sinus is very thin where the carotid artery perforates it, and this area should be avoided lest the dissector should rupture it. The superior petrosal sinus receives a vein at its anterior end from the mid-brain region, and often several irregular veins join it from the temporal lobe. Should the brain elevator be carried too far back rupture of one of these veins is likely to occur. Packing would be the only means of controlling it. Bleeding from a lacerated cortex, while not severe may well cause an operative failure on account of its inconvenience. The middle meningeal artery is not liable to injury on account of its protected position on the cranial base. The internal carotid is also immune by virtue of its strong walls. The manipulations of the pituitary itself cause practically no bleeding.

3. Anaesthesia. With the method used this has never occasioned anxiety.

4. Shock. Apart from haemorrhage there has

been no evidence of this.

5. In elevating the brain a stretching of the third cranial nerve is almost inevitable. In the majority of operations a temporary ptosis, external strabismus and pupillary dilatation have resulted. In one case only have they persisted beyond a few days.

POST-OPERATIVE RECOVERY. When morphia is used the animal will sleep for some hours after the operation. It awakes hungry and will eat freely. If morphia is not employed the dog will take a good meal within 2 - 3 hours of operation. On the following day its condition is practically normal (figs. 18, 29, 33, 36.). In puppies this state is maintained for at least a week, when the further sequence of events depends on the glandular mutilation which has been carried out.

D. TRANSORBITAL ELECTROLYSIS IN THE CAT.

This route for approaching the pituitary body in the cat was suggested to me by Professor Sir E. Sharpey Schafer. He observed that the anatomy of the feline skull was peculiarly adapted to such a procedure, so that when a straight instrument was passed through the orbit and the sphenoidal fissure, it inevitably lodged in the sella turcica, where its progress was arrested by the dorsum sellae.

In practice it is found that a straight instrument so introduced will strike the dorsum sellae accurately in the middle line. It passes close by the side of the pituitary body. A straight hollow trocar is therefore placed in this position, while from a lateral opening in it the electrode is projected into the pituitary body.

Anatomical Considerations. The sphenoidal fissure lies at a considerable depth from the orbital margin (2½ - 3 cm.). Some guide is necessary to ensure the entrance of the trocar into this aperture. The guide is found in the hamulus of the pterygoid process, which can be palpated easily from the mouth. The sphenoidal fissure lies immediately above this landmark. The instrument penetrates the conjunctiva and the orbital fat. On the outer surface of the skull the terminal twigs of the internal maxillary

Fig. 8. <u>Diagram of instrument used to produce electrolytic lesion of cat's pituitary</u>.

(Enlarged three times.)

A. Hollow trocar. Note at <u>a</u> the lateral aperture, and at <u>b</u> the pointer which indicates its position when in operation.

B. Electrode. Note at <u>a</u> the platino-iridium point which is hinged to the steel wire; also the rubber sheath which covers the wire and hinge, leaving only the point bare.
b, screw terminal.
c, pointer to indicate the axis of the hinge when in operation.

C. Diagram to show how the platino-iridium electrode is projected from lateral opening in the trocar, and how it is entirely insulated from it by the rubber sheath.

Fig. 9. <u>Special instruments used for trans-orbital electrolysis on the cat</u>.

A. Head-holder. The lower jaw is held in the ring: the upper jaw is free. Note the tulip-shaped spring clip for retaining the catheter in place, for intra-pharyngeal anaesthesia.

B. Trocar for adult anterior lobe.

C. Trocar for adult posterior lobe.

D. Trocar for kittens'(6 - 8 weeks) anterior lobe.

E. Pituitary electrode with flexible point for cat.
F. Do. for kitten.
G. Eyelid retractor.

H. Flexible finger-protector.

Fig 9.
A

Head
holder.
(for cat!)

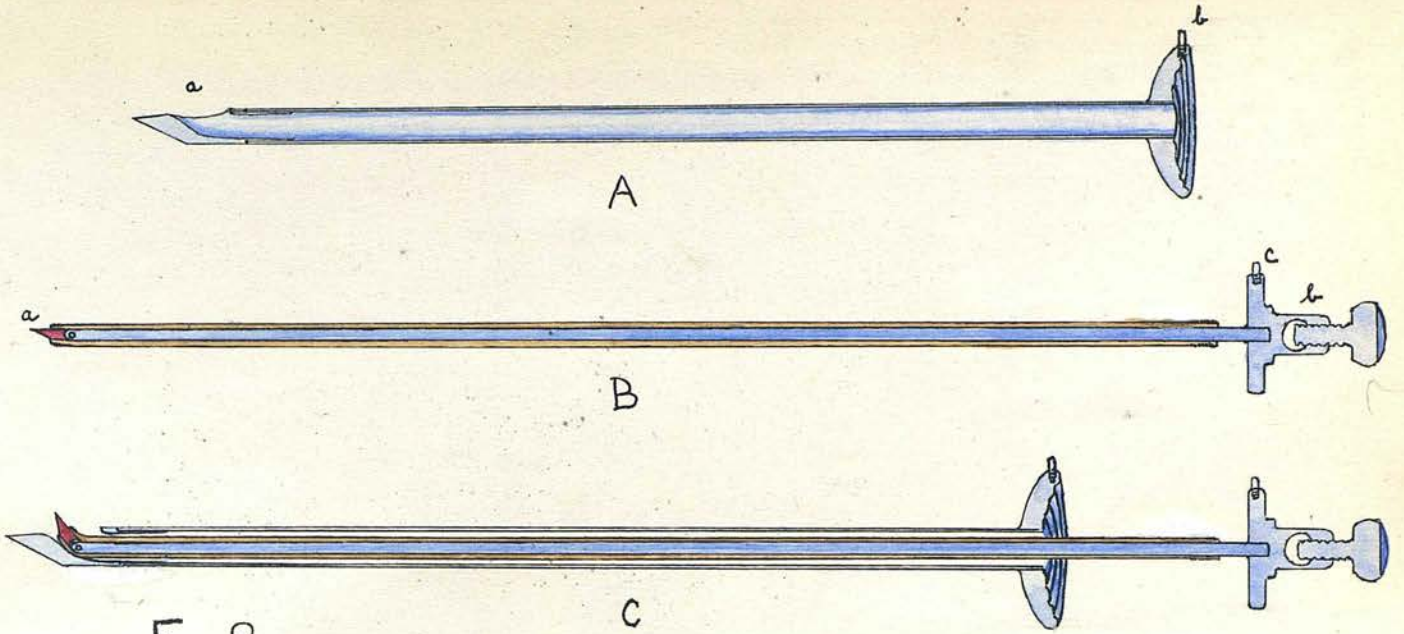

Fig. 8.

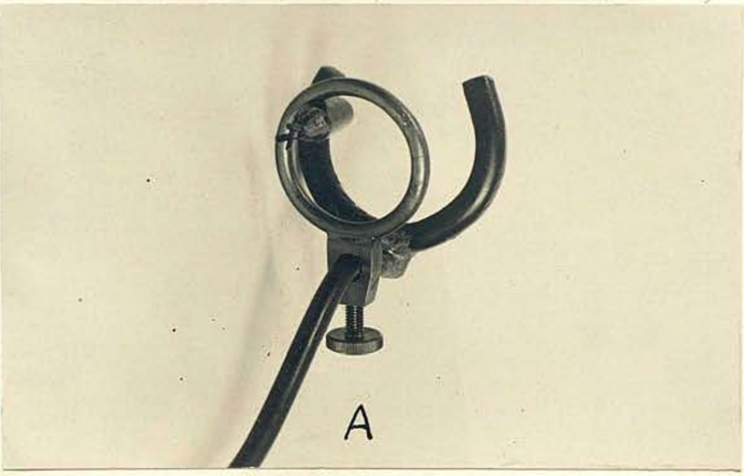

Fig. 9.

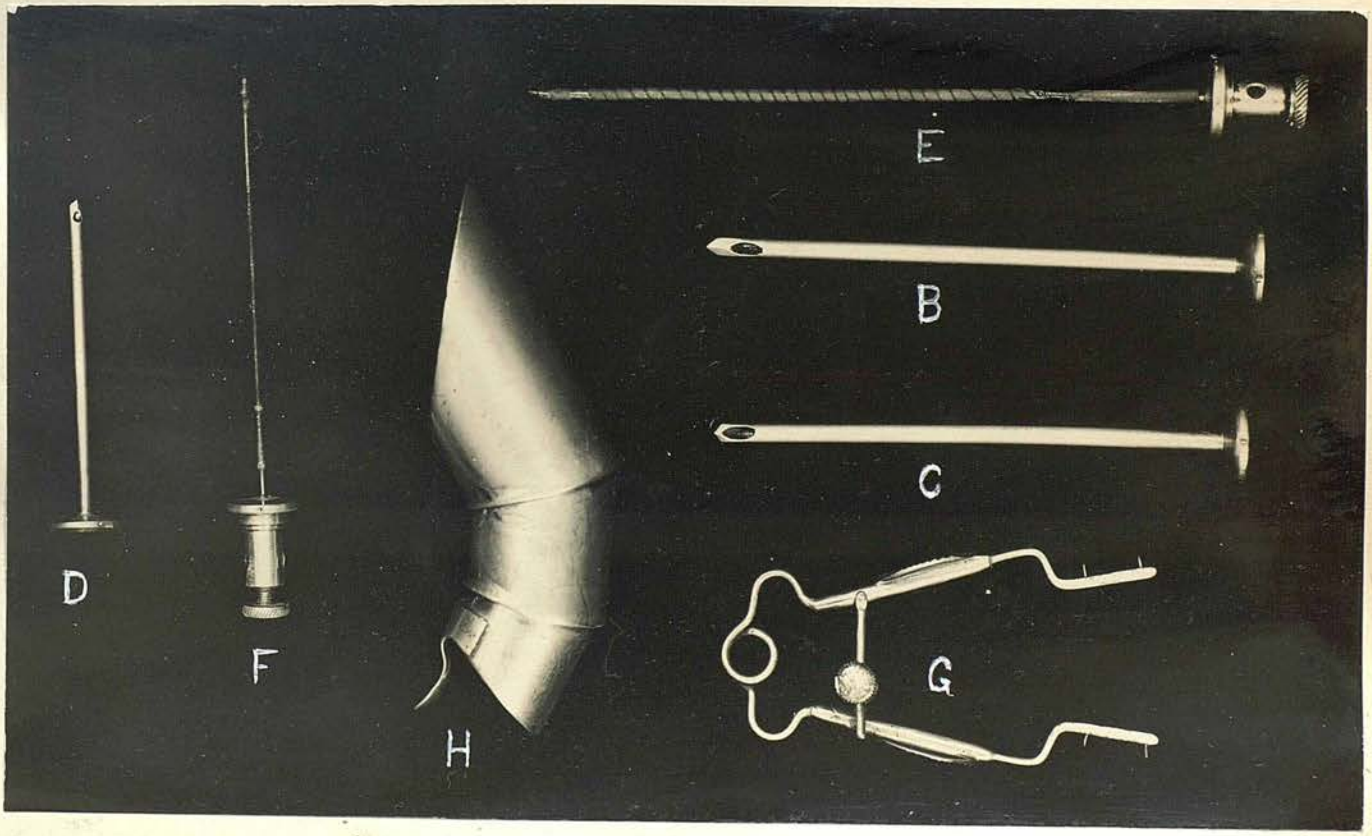

Fig. 10. View of the intracranial anatomy of the transorbital electrolytic operation on the cat.

(Drawn from a specimen × $1\frac{1}{2}$.)

Observe the position of the trocar. It passes through the orbit, the sphenoidal fissure, and lodges with its point touching the dorsum sellae in the middle line. The projecting electrode is seen piercing the anterior lobe of the pituitary body. Note the displaced internal carotid artery. The nerves of the sphenoidal fissure have been removed on the left side in order to fully expose the instrument.

Fig. 11. Radiograph illustrating the transorbital electrolytic operation.

The photograph was taken from the intact cadaver. The trocar lies in place, its point resting against the dorsum sellae. The electrode wire is seen within the trocar. Note the projecting platino-iridium electrode, which has pierced the anterior lobe of the pituitary.

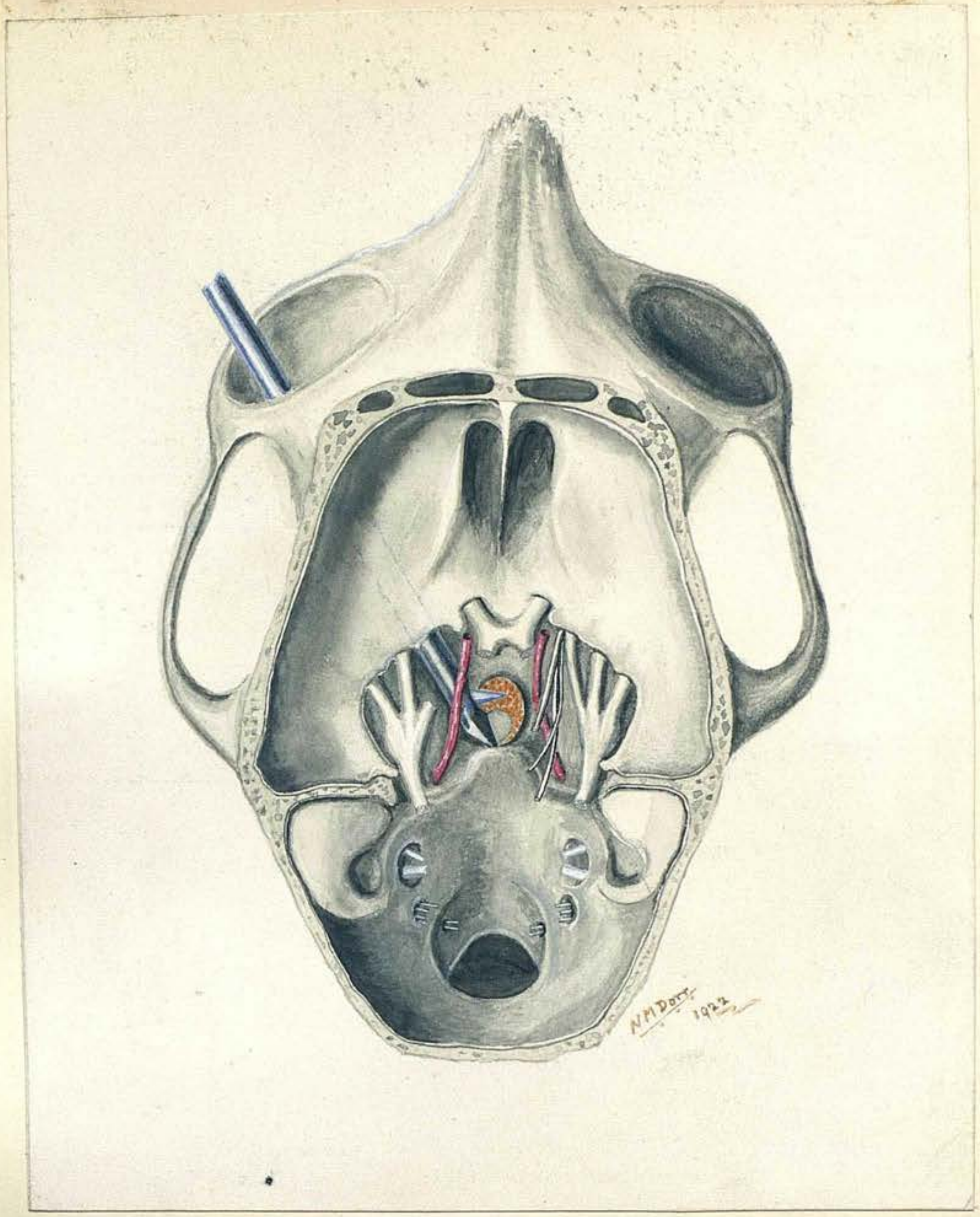

Fig. 10

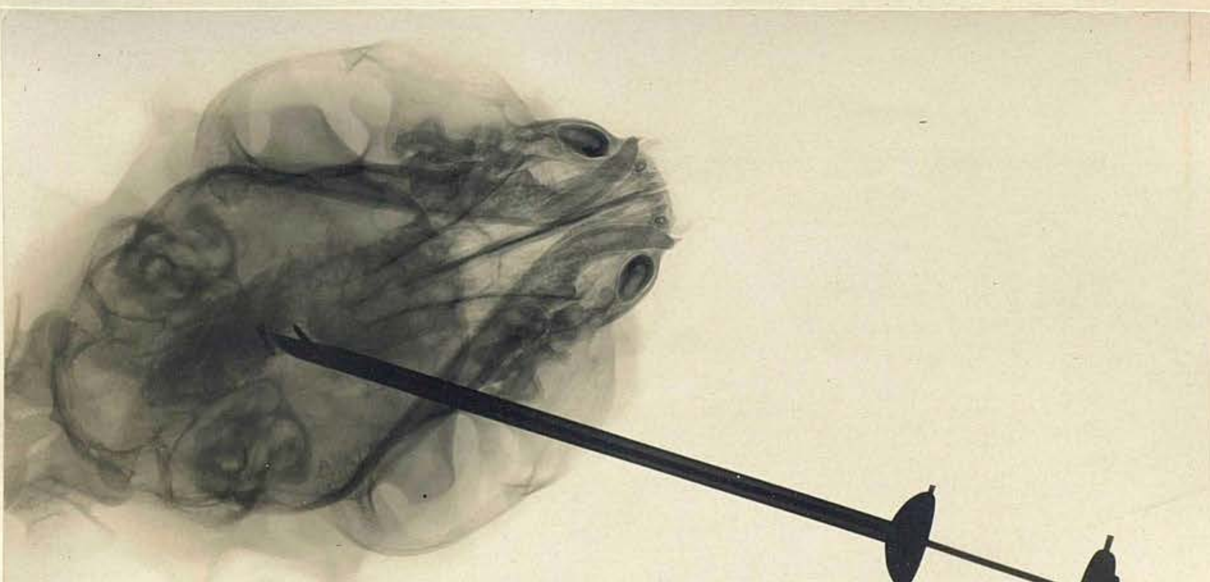

Fig. 11.

artery may be injured. As it enters the sphenoidal fissure the ophthalmic veins are wounded. In the sphenoidal fissure the 3rd, 4th and 6th cranial nerves and the ophthalmic division of the 5th are subjected to pressure against its bony walls as the trocar passes under them. Within the skull the cavernous sinus is traversed (fig. 10). The internal carotid artery is invariably displaced upwards, and escapes injury. Passing the anterior clinoid process, the sella turcica is entered and the instrument comes in contact with the pituitary body. Its progress is definitely arrested by the dorsum sellae. This point of contact with the dorsum sellae is the fixed point which makes accurate operating possible. It is obvious that according as the lateral opening in the hollow trocar is placed close to, or further from its point, so the electrode may be caused to pierce either the anterior or posterior lobe of the pituitary. In this way a lesion mainly affecting one or other lobe may be produced.

The instrument (fig.8) consists of a hollow steel tube with a solid "trocar" point. At a suitable distance from the point is the lateral opening. The lumen of the tube slopes up to the opening, so that the electrode may be directed out at an angle (like a catheterizing cystoscope). On the outer end of the tube a disc is mounted by which it is operated. On the disc a pointer indicates the direction in which the lateral opening is being turned. The electrode is made of platino-iridium; it is 2 mm. long and has a sharp point. It is mounted on a steel wire, to which it is joined by a hinge. The wire joint and all but the point of the electrode are encased in a rubber sheath. On the outer end of the wire is a screw terminal to connect it with the galvanic circuit. Instruments have been devised both for cats and for young kittens.

The other special requisites for the operation are (fig. 9), an eye douche and lotions, an eyelid retractor, a special holder and gag for the animal's head, a finger protector, an apparatus for producing a galvanic current, including a galvanometer and a pad electrode.

<u>The operation</u> is performed as follows:- The cat is placed under the bell-jar and anaesthetized with chloroform. It is transferred to the operating table, where the head is placed on the special rest and the gag inserted. A catheter is passed to the back of the pharynx, and anaesthesia continued with chloroform vapour pumped through the catheter. The latter is retained in place by the special spring clip (fig.9). The eye (left) is thoroughly douched with corrosive sublimate, 1/6000, followed by normal saline. The retractor separates the eyelids. With the left forefinger (suitably protected) in the animal's mouth palpating the hamular process, the

trocar is passed with the right hand. It penetrates the conjunctiva in its lateral and inferior part, and passing outside the globe of the eye, arrives at the hamular process where the left forefinger identifies it. The point is elevated about 5 mm. and pushed onwards, when it is felt to engage in the sphenoidal fissure. Having entered this foramen, the handle of the instrument is brought towards the middle line that the anterior clinoid process may be avoided. The trocar is further advanced, and swung laterally till it is felt to impinge on the dorsum sellae. It now lies in place (fig.10). The pointer is directed inwards and slightly upwards. The electrode is passed, and comes to rest with its point in the pituitary body. The fur of the back (preferably clipped), is moistened with saline solution, and the pad electrode is applied to it. The terminals are connected with the galvanic circuit. The positive pole (which produces a more localized lesion) should be attached to the pituitary electrode. The desired current having been passed, the electrode and trocar are withdrawn and the left eyelids closed with a fine mattress suture.

The operation occupies about ten minutes, and no sterilizing beyond that of the instruments is required.

Operative Complications. None have been encountered.

Post-operative Complications. A paresis of the nerves which pass through the sphenoidal fissure is inevitable. It may be permanent. The only consequence of serious import which may follow such a paresis is dependent on ocular anaesthesia. There is a liability to conjunctivitis and corneal ulceration (Cf. Gasserian ganglion operation in man). The sutured eyelids protect the cornea during the first six days, when the affection is most prone to develop. Scrupulous attention to the toilet of the eyes is essential. The motor paresis may or may not pass off. In any case the unilateral operation causes the animal no inconvenience.

Post-operative recovery is immediate and complete.

Control Experiments. Two adult cats were subjected to the operation - electrolysis being omitted. Both animals recovered without symptoms, beyond ocular disturbances, and survived indefinitely. They were destroyed three months later on account of distemper.

That the products of electrolysis of the pituitary body are not responsible for death or any of the symptoms was proved as follows. In two adult cats the pituitary body was completely destroyed by electrolysis. The débris was aseptically removed from the sella turcica and emulsified in normal saline solution . The emulsions were injected subcutaneously into two healthy cats. These animals showed no symptoms whatsoever consequent on the injections.

The Lesion. It was determined post mortem that a current of 10 milliampères, passed during 10 minutes, produces a complete anatomical destruction of the pituitary body in an adult cat, and that the destructive process does not trespass the limits of the sella turcica - 10 milliampères during 3 minutes produces a similar effect in a kitten of 6 - 8 weeks.

In order to estimate accurately the site and extent of the lesion produced, a series of experiments was carried out. The electrolysis was made at a constant current of 10 milliampères for durations of 3, 5, and 7 minutes - three animals being used in each case. Of the three animals a lesion of the anterior lobe was attempted in two, and of the posterior lobe in one. Thus a series of six anterior lobe lesions and three posterior lobe lesions was attempted with different electrolytic durations. The animals were immediately sacrificed, and the adjacent brain, contents of the sella turcica and base of the skull removed en masse, and subjected to microscopical examination. A definite lesion of the pituitary body was determined in each instance. The lesion was in all cases confined to the sella turcica, the base of which suffered to a varying extent. The minute area of bone which is usually damaged cannot be regarded as of any physiological import. The lesions varied in extent according to the duration of the electrolysis; one-fourth to one-third of the anterior lobe being disorganized with 3 minutes, while the entire lobe was destroyed with 7 minutes. As regards distinctive lesions of the two lobes, a limited lesion of the anterior left the posterior unaffected. An extensive lesion of the anterior always implied a partial lesion of the posterior. No posterior lobe lesion left the anterior lobe entirely unaffected, although its implication was limited to the area immediately surrounding the posterior lobe.

With these data before me, I am able to anticipate the results of an electrolysis experiment with a certain measure of confidence.

The advantages which may be claimed for the method are, that it brings a very useful laboratory animal within the scope of investigation of pituitary function which was formerly not available. It requires much less preparation and occupies less time than the "open" operation as practised on the dog. The operation demands of the investigator less technical skill than does the procedure of craniotomy.

The disadvantage of the operation, as contrasted with the intracranial exposure of the canine pituitary, is that the lesion cannot be so accurately localized to the separate portions of the gland.

Hence in the study of the individual functions of the subdivisions of the pituitary, the electrolytic method is not advisable: the only available means of doing this is to expose the canine gland to vision.

SECTION IV.

GENERAL RESULTS OF OPERATIONS.

A. ACUTE.

In the cat total destruction of the pituitary body *in situ* by the transorbital electrolytic method gives rise to a definite syndrome, referable to absence of the pituitary secretion, which terminates fatally in from three to ten days. The operation was performed on six adult cats and on one kitten. As illustrative of the syndrome (cachexia hypophyseopriva of Cushing[126]) the protocol of one of these animals is given here.

Series B. Kitten 6a. Exp. IV.

22. xii. 21. 7 weeks old. Male. 480 grms.

Operation. Technique as described above. Electrolysis with positive pole, 10 milliampères, during 3 minutes.
No operative complications. Immediate recovery from anaesthetic. Milk taken within an hour of operation.

23. xii. 21. Temperature 102.6°F. (Normal kitten 103°F.) The animal is apparently in a normal condition, taking milk well and playing with its fellows.

24. xii. 21. Temperature 102.4°F. No obvious change in condition.

25. xii. 21. 9 a.m. Temperature 86°F. Very lethargic, and when roused walks unsteadily. Food is refused.
11 a.m. In a condition of partial coma. Can be roused, and responds to handling. Lies in the opisthotonic posture: there is a

Fig. 12. Kitten B, 6a. Apituitarism.

The animal is in a state of deep coma: the higher reflexes have gone. Respiration is less than one per minute (40 per hour).

Fig. 13. Microphotograph of pituitary block from Kitten B6.

(× 20.)

The remains of the pituitary are shown in situ in the sella turcica. The base of the brain is seen to be undamaged. At v is the cavity of the third ventricle. In this case the bone of the sella turcica has not been injured, but the periosteum is partially destroyed.

The pituitary body lies embedded in electrolysed blood clot.

a, the anterior lobe - a mass of coagulated cellular débris. There is not one viable eosinophil cell in the section.

b, Pars nervosa, with its central cavity. In its lower part it is entirely destroyed, while above this some secretion is retained in its meshes.

c, Pars intermedia and

d, pars tuberalis can only be recognized by their anatomical position. They are entirely degenerated and do not stain normally.

e, Pituitary cleft filled with coagulated blood and cellular débris.

It is seen that a complete functional destruction of the pituitary body was produced by the operation, and that the destructive process was limited to the confines of the sella turcica.

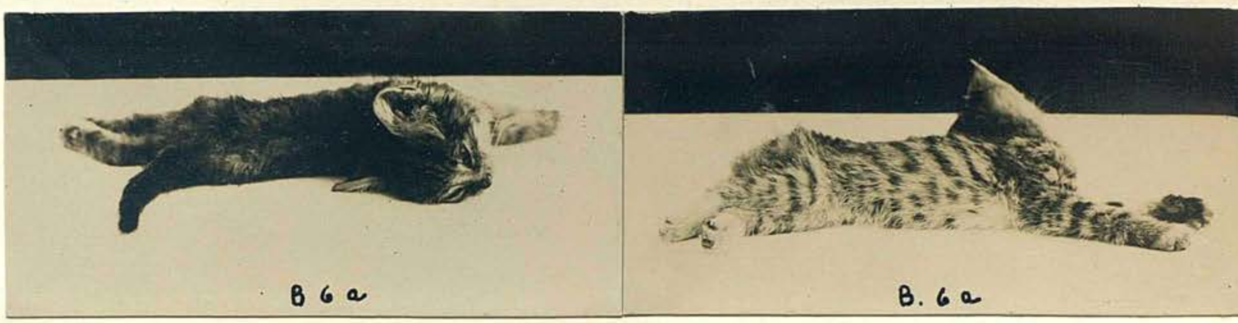

Fig. 12.

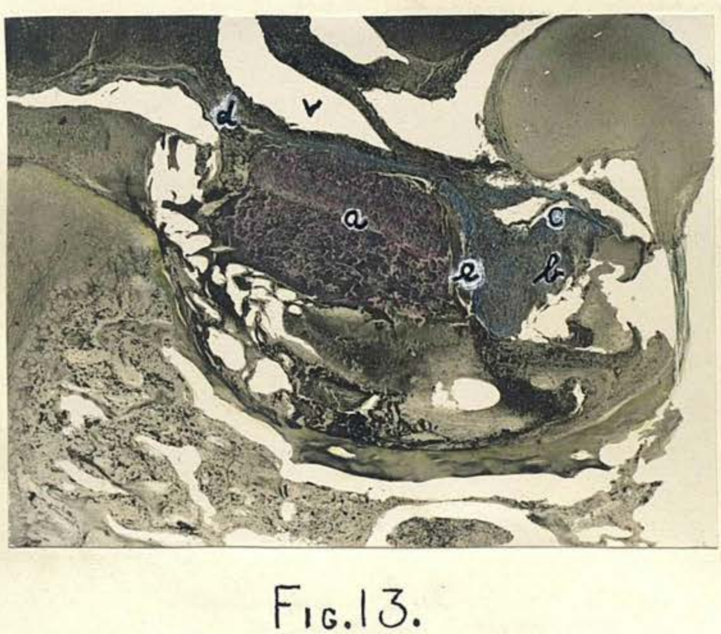

Fig. 13.

constant rhythmic movement of the legs. Temperature 84°F. Respirations 20 per minute. Pulse 110 per minute. Corneal and light reflexes are present. The skeletal muscles retain their tonus. A subcutaneous injection of a boiled extract of anterior lobe ox pituitary was given.

12.30 p.m. Coma is now deeper, though there is still slight response to handling. Temperature 88°F. Respiratinns 6 per minute. Pulse 90 per minute. Corneal reflex absent. Slight light reflex. Muscles retain their tonus. Faeces and urine passed unconsciously.

2 p.m. Deep coma. Cannot be roused. Temperature 90°F. Respirations 2 per minute. Pulse 80 per minute. Corneal and light reflexes gone. Opisthotonic attitude continues, but muscles are less tonic (fig.12). The photograph shows the animal in the condition of deep coma, with absence of the higher reflexes, slow respiration and pulse, and subnormal temperature.

4 p.m. Kitten is now completely flaccid. Temperature 84.2°F. Respirations less than 1 per minute, viz., 40 per hour. Pulse average about 70 per minute. The behaviour of the heart is interesting. Immediately after a respiration the pulse-rate is 100 per minute. As the inter-respiratory interval progresses the rate diminishes until it reaches 45 per minute, and becomes very irregular. It appears to be about to cease. Another respiration is made, and the heart rate again rises and becomes regular. It was during one of these phases that death took place: the respiration being too long delayed, the heart stopped.

5 p.m. Death.

Post Mortem. Brain and meninges show no observable departure from the normal. The base of the skull with sella turcica and adjacent brain were removed *en masse* for microscopic study. The internal organs all appear to be in a healthy state. Rigor mortis did not appear for five hours and was of slight degree (a constant occurrence in these cases).

Microscopic Report (fig.13). Total functional destruction of the pituitary body. No injury to adjacent parts. Other tissues, including the femur, are reserved for future microscopic study.

Comment. The total destruction of the pituitary body in the cat is followed by a period (a few days) of apparently normal existence. The absence of the pituitary function then manifests itself by a very definite sequence of events,- ending in death - usually within twenty-four hours of onset. The symptoms shown are suggestive of a primary effect of apituitarism upon the central nervous system. There appears to be a progressive loss of function in the central nervous system, beginning with its higher and more recently acquired activities and terminating with the lower and more primitive ones. Thus the animal's conscious mentality is probably first affected. Dullness and apathy set in and are succeeded by somnolence and coma. The finer co-ordination of movements suffers next. Inco-ordination is followed by involuntary movements, and lastly by paralysis. The heat regulating nervous mechanism is then gradually put out of action until the animal's temperature may approximate to that of its surroundings. Response to sensory stimuli (pain, pressure, etc.) and the corneal reflex response go. A little later the pupillary light reflex can no longer be evoked, and the bladder and anal sphincters relax. The skeletal muscle reflexes, evidenced by their tonus, disappear. The nervous mechanism of respiration is depressed. The respirations become first deep and slow as the vagus control of the respiratory centre is lost. Later even the carbonic acid stimulus to the respiratory centre begins to lose its effect, and respiration becomes more and more infrequent. The right side of the heart now suffers asphyxial overloading, and this finally causes death. Death, therefore, appears to be due to a loss of response of the nervous mechanism of respiration to the CO_2 stimulus.

Another interesting point illustrated by the case cited is the "thermic reaction" of Cushing[6)]. It consists in the rise of temperature consequent on injection of anterior lobe extract into an animal whose temperature was subnormal as a result of hypopituitarism. This is a point of much significance in clinical diagnosis and therapeutics. The reaction, according to Cushing, is specific, and cannot be elicited except in the presence of hypopituitarism. The injection is, however, powerless to avert death in an animal totally deprived of its pituitary body.

In the dog a similar train of symptoms follows total pituitary extirpation. One puppy (Dog.VIII) has been subjected to this operation by me. He survived the operation for fourteen days, appearing perfectly well during the first week. There was a moderate polyuria and no glycosuria. Fig.39 shows his condition seven days after the operation. During the following week he emaciated rapidly, although his appetite was good; and the syndrome of apituitarism as described for the cat was observed during the last two days. (Crowe, Cushing and Homans[5] describe exactly similar results with puppies.) The case is not given in detail but is reserved for later publication as the histological post mortem findings are not yet available.

Total extirpation of the posterior lobe gave rise to no observable disturbances in the animals' general condition (Dogs V, VII).

Extensive removal of the anterior lobe was well tolerated (much better than I had expected from the literature). Dogs A4, IV, and IX, and Kitten B8 are examples of this. In the dogs no disturbance whatever could be noted during the first few weeks, beyond a temporary polyuria in some cases. Dog IX had a marked degree of somnolence for the first few days, but this has not been the rule. Kitten B8 showed no symptoms for 5 days, after which symptoms of anterior lobe deficiency became evident.

Stalk division is illustrated by Dog A1. The consequences were identical with partial anterior lobe removals.

Subtotal hypophysectomy is illustrated by

Dog VI. The removed pituitary appears to be complete, but the survival of the animal (2 months up to date) indicates that there is a fragment remaining. There was a slight degree of lethargy during the first few days. Dog III also belongs to this category, though a larger fragment of anterior lobe was left. No early symptoms were evident.

B. CHRONIC.

It is as yet too early for me to say much on this subject.

Total extirpation of the posterior lobe has given rise to no observable symptoms over a period of five weeks (Dog.VII). Dog V died of acute lobar pneumonia five weeks after the operation, but had shown no symptoms referable to the removal of the posterior lobe. (The carbohydrate tolerance has not yet been studied.)

Extensive removal of the anterior lobe has been followed by a continuous subnormal temperature and an increased liability to infections. In the cases where sufficient time has elapsed to judge the effect, there has been a retardation of growth, (Dogs A4, IX, and Kitten B8). Dog IV is an exception. Following a very extensive (almost complete) anterior lobe extirpation there has been no fall of temperature: growth has ceased, but, as mentioned later, this may be physiological.

Stalk division was followed by subnormal temperature, retarded growth and dystrophia adiposo-genitalis (Dog A1). The hair was also deficiently replaced on the shaved head, and the skin was thin, dry and wrinkled.

Subtotal hypophysectomy (Dog VI) has been followed by subnormal temperature, marked apathy, arrest of growth, adiposity, diminished resistance to infection, and genital dystrophy (duration two months up to date). In another case (Dog III) there are similar symptoms, but without adiposity (duration three months up to date). In this animal the deficient growth of hair on the shaved head and neck is also striking, and the coat, which was formerly sleek and healthy, has now become dry and poor.

GENERAL RESULTS OF PITUITARY FEEDING.

I insert this merely for the sake of completeness. My data hardly warrant any general statements. Kitten B7 and Dog A2 were subjected to feeding with dried powdered anterior lobe of ox pituitary (supplied by Messrs. Duncan and Flockhart). Both animals showed a definite acceleration in general and skeletal development, as compared with the controls. It is noteworthy that in both cases the smaller animal was selected for feeding, and that it finally outstripped the control animal. The experimental and control animals were kept under exactly similar conditions, and there was no illness in any case.

SECTION V.

SUMMARIES OF INDIVIDUAL EXPERIMENTS, WITH COMMENTS ON RESULTS TO DATE OF WRITING.

Experiment I.

Dog I.

4. xii. 21. 4 months old. Male. 2550 grms.

5. xii. 21. Operation. Partial anterior lobe excision. Intratracheal ether. Duration 95 minutes. Uncontrollable bleeding took place from a ruptured lateral sinus. Operation survived only for two hours. Death due to haemorrhage, and shock from protracted operation. (The animal did not recover consciousness.)

Experiment II.

A litter of three fox terrier puppies; one dog and two bitches. Of these the dog, A1, was selected for operation, the samller bitch, A2, for a pituitary feeding experiment, and the larger bitch, A3, for a control.

Dog A1.

8. xii. 21. 4 months old. Male. 2950 grms. Morphia gr. 0.3. Head shaved and X-ray taken.

9. xii. 21. Operation. Stalk division. Morphia gr. 0.2. Intratracheal ether. Duration 65 minutes. Uncomplicated exposure of the pituitary body. After a futile attempt to separate the anterior lobe (inexperience), it was decided to employ the alternative method of

stalk section. This was done, and the wound closed. Subcutaneous saline infusion 4 ozs. Slept all night (morphia).

10. xii. 21. Fully recovered. Took milk eagerly, and gnawed a bone. Temperature 102.2°F (normal 103°F).

11. xii. 21. Temperature 103.2°F. Excessive polyuria. No glycosuria.

12. xii. 21. Temperature 100°F. Has become very quiet and sleeps much. Still polyuria is evident.

13. xii. 21. Temperature 100.4°F. Polyuria is no longer observed.

19. xii. 21. Weight 2950 grms. The temperature has been about 1°F subnormal. The animal has been much livlier.

3. i. 22. Weight 2970 grms. Temperature has been about 1 to 2°F subnormal. Behaviour quite normal.

17. i. 22. Weight 3000 grms. Temperature has been 1 to 2°F subnormal. Excellent condition.

31. i. 22. Weight 3050 grms. Temperature has been 1 to 2°F subnormal.

13. ii. 22. Weight 3140 grms. Temperature has been 1 to 2°F subnromal.

17. ii. 22. Weight 3140 grms. Experiment terminated.

<u>Observation 69 days.</u>

The animal made a complete and rapid recovery from the operation, and remained in excellent health during the observation period. After four weeks a definite retardation of growth as compared with the control was apparent, and adiposity was becoming recognizable. By the eighth week the limbs were obviously shorter and the body fatter than with the control. The snout was thin and small, and the cranium markedly rounded (an infantile canine characteristic). The animal was always lively and playful, and behaved normally with its fellows. The hair of the shaved area was deficiently replaced. (Observe the neck in fig.16.)

<u>Dog A2.</u>/

Dog A2.

8. xii. 21. 4 months old. Female. 2950 grms. Morphia gr. 0.3. X-ray taken.

9. xii. 21. Pituitary feeding was begun. Dried powdered anterior lobe of ox pituitary was used. 10 grains were administered daily, first thing in the morning (on an empty stomach).

19. xii. 21. Weight 3150 grms.

3. i. 22. Weight 3260 grms.

17. i. 22. Weight 3330 grms.

31. i. 22. Weight 3500 grms.

4. ii. 22. Dose of pituitary substance increased to 15 grains daily.

13. ii. 22. Weight 3710 grms.

17. ii. 22. Weight 3770 grms. Experiment terminated.

Observation 69 days.

The animal remained in excellent health throughout the experiment. The pituitary feeding appeared to cause no digestive disturbance. By the fourth week it was obvious that growth was proceeding faster than in the control. The animal became more solidly built, approaching the adult type more nearly than did the control.

Dog A3. (Control.)

8. xii. 21. 4 months old. Female. 3100 grms. Morphia gr. 0.3. X-ray taken.

19. xii. 21. Weight 3160 grms.

3. i. 22. Weight 3200 grms.

17. i. 22. Weight 3270 grms.

31. i. 22. Weight 3340 grms.

13. ii. 22. Weight 3390 grms.

17. ii. 22. Weight 3400 grms. Experiment terminated.

Observation 69 days.

The animal remained in excellent condition throughout the observation period, and could be regarded as a staisfactory control animal.

The experiment was ended by the administration to the three animals of a lethal dose of chloroform.

Post mortem Examination. (As my data are at present limited, it appears best to give only the salient features of the post mortem examinations in this place.)

In Dog A1 - the operated animal - the cranial operative area was perfectly healed. There was a limited cerebral adhesion to the region of the right temporal decompression (where the dura is left open). The adhesion had given rise to no symptoms during life. The sella turcica was filled with fibrous tissue, and the base of the brain was bound to it slightly by adhesions. The pituitary body was not recognized: no doubt it is embedded in the fibrous tissue. It was not dissected out, but reserved for future microscopical study, being removed with the adjacent brain and bone en masse.

The pituitary bodies of Dogs A2 and A3 were similarly treated. The microscopical findings are not available for description here. But from gross appearances one can have no doubt that the pituitary of Dog A1 had suffered severely from the operation.

None of the animals showed any evidence of incidental pathological conditions.

COMPARATIVE TABLE./

COMPARATIVE TABLE.

	A3. Normal	A1. Hypo-pituitarism	A2. Hyper-pituitarism
At commencement	3100 gm.	2950 gm.	2950 gm.
At termination	3400 gm.	3140 gm.	3770 gm.
	Post mortem Findings.		
Total length (fig.16)	87 cm.	81.5 cm.	88 cm.
General appearance	Normal	Fat and stunted	Abnormally well developed
Skin	Normal	Thin, dry, wrinkled	Normal
Subcutaneous tissue	Normal	Adipose	Normal
Omentum	0.311% of body weight	0.768% of body weight	0.472% of body weight
Thyroid	0.018% of body weight	0.012% of body weight	0.017% of body weight
Generative glands	Normal	? Hypoplastic	No obvious change

Fig. 14. Dogs A1 (2950 grms.), A2 (2950 grms.) and A3 (3100 grms.) at the commencement of the experiment. A3 was in reality slightly the largest.

Fig. 15. Dogs A1, A2 and A3, 69 days after the experiment was begun.

Fig. 16. Dogs A1, A2 and A3 photographed post mortem.

As compared with the control, A3, note the greater length and generally heavier build of A2 (hyperpituitarism); and the deficient length, adiposity and shortness of limbs of A1 (hypopituitarism). The short, small muzzle and rounded cranium of A1 are well seen. The deficient growth of hair upon the neck which had been shaved for operation is also well shown.

A1.	81.5 cm.	3140 grms.
A2.	88 cm.	3770 grms.
A3.	87 cm.	3400 grms.

Fig.14.

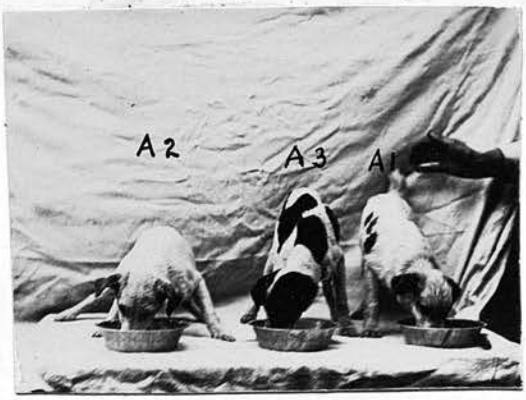

Fig.15.

Fig.16.

tissues is made, but the findings are reserved until more material is available.)

Experiment III.

	Dog II. A mongrel terrier puppy.
19. xii. 21.	5 months old. Female. 4620 grms. Morphia gr. 0.8. Head shaved. X-rayed.
20. xii. 21.	Operation. Extensive removal of anterior lobe. Morphia gr. 0.4. Intratracheal ether. Duration 60 minutes. Uncomplicated operation. The greater part of the anterior lobe was fragmentarily removed. The wound was closed. Subcutaneous saline infusion 4 ozs. Excellent recovery. On the second day following operation an oedematous swelling was noticed under the scalp. On the fourth day it was obvious that infection was present. The animal, however, was perfectly well. It was decided to incise the swelling. Chloroform was given for this purpose, and during its administration the animal died suddenly. Death was due to an overdose of chloroform.

Post mortem Examination. There was a mildly infected haematoma under the scalp. There was no deep infection nor meningitis. Examination of the various organs revealed no gross abnormalities. The tissues are preserved for future study.

Comment. I had no doubt that the cause of infection of the wound in this case was contamination from the exposed skin edges. It taught me the necessity of rigidly excluding the skin from the field of operation. (It appears doubtful to what extent the shaved skin of an animal can be disinfected.)

Experiment IV.

Kitten B.6a.

Total destruction of the pituitary *in situ*. The experiment is detailed on page 81, in the section on acute results of operations.

Experiment V.

Dogs A4 and A5.

Two mongrel collie puppies of the same litter, both male. The heavier and stronger animal, A4, was selected for operation. Dog A5 was intended for a control, but has not proved of much value as such, being weak and suffering from rickets and bronchitis. I have therefore excluded this animal from the present paper, although it is rapidly improving under treatment.

Dog A4.

22. xii. 21. 4 months old. Male. 2650 grms. Morphia gr. 0.25. Head shaved. X-ray taken.

23. xii. 21. Operation. Excision of about 2/3 of anterior lobe.
Morphia gr. 0.2. Intratracheal ether. Duration 75 minutes. Uncomplicated operation. It was possible to remove about 2/3 of the anterior lobe in one piece, leaving the stalk and posterior lobe practically intact (fig.17). The wound was closed. Subcutaneous saline infusion 6 ozs.

24. xii. 21. Complete recovery (fig.18). Food well taken. Temperature 102.2°F.

30. xii. 21. Weight 2670 grms. Temperature has been about 1°F subnormal.

8. i. 22. Weight 2950 grm. Temperature has

been about 1°F subnormal.

16. i. 22.	Weight 3400 grms. Temperature has been about 1°F subnormal.
23. i. 22.	Weight 3550 grms. Temperature has been about 0.5°F subnormal.
30. i. 22.	Weight 3630 grms. Temperature has been about 1°F subnormal.
7. ii. 22.	Weight 3740 grms. Temperature has been about 1°F subnormal.
14. ii. 22.	3800 grms. Temperature has been about 1°F subnormal.
21. ii. 22.	Weight 3860 grms. Temperature has been about 0.5°F subnormal.
28. ii. 22.	Weight 3900 grms. Temperature has been about 0.5°F subnormal.
3.iii. 22.	Acute broncho-penumonia with conjunctivitis developed. Eyes douched. Special diet (Benger's food).
6.iii. 22.	Weight 3150 grms. Temperature failed to rise with the pneumonia, remaining about 1°F subnormal.
8.iii. 22.	Complete recovery. Animal very playful and lively, and is putting on fat again (fig.19).
13.iii. 22.	Weight 3290 grms. Temperature 0.5°F subnormal. Excellent condition.
	Observation 80 days. Experiment not yet terminated.

Comment. This case illustrates a minor degree of pituitary deficiency. The symptoms are:- Retarded growth, a tendency to adiposity, a slightly subnormal temperature, and an infantile appearance.

The dog has grown very little since the operation, the gain in weight being due mainly to adiposity, which is rapidly increasing. He looks and behaves more like a puppy of four months than one of

Fig. 17. Tissue removed at operation from Dog A4.

(Microphotograph × 18.)

a, A large piece of pars anterior. There is a small fragment of pars nervosa, with adherent
b, pars intermedia. The posterior lobe tissue must have been scraped away in freeing the anterior lobe. The gross specimen was estimated to represent about 2/3 of the anterior lobe.

Fig. 18. Dog A4, with Control, A5, 17 hours after operation, showing complete recovery. Note suture line on head.
A4. 2650 grms. A5. 2220 grms.

Fig. 19. A4 , with Control, A5, 75 days after operation. Note the adiposity (reduced by recent pneumonia), the complete replacement of hair on the head, and the generally lively appearance. Apart from adiposity, A4 has grown very little since the operation.

A4. 3290 grms. A5. 2970 grms. A4 should be heavier, having attained 3900 grms. before the attack of pneumonia.

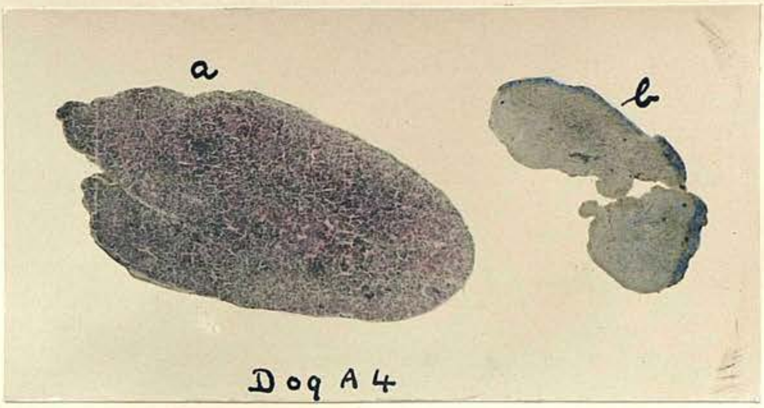

Fig.17.

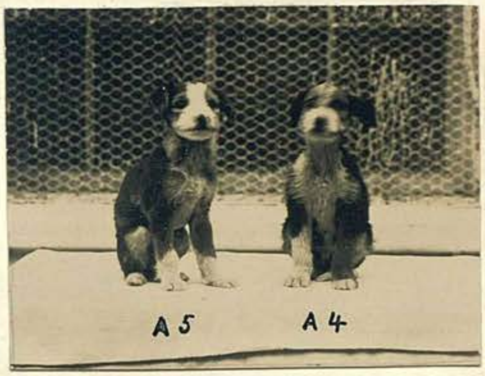

Fig.18.

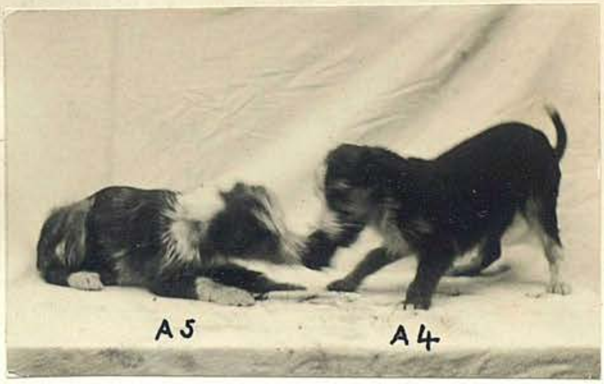

Fig.19.

seven months. He is very lively and playful. The recovery from pneumonia was good. There is no lack of resistance to infection. The hair is well replaced on the head and neck, and the coat is in good condition. I cannot be certain that the testicles are unduly small for a dog of his age.

It is remarkable how well such an extensive excision of the anterior lobe of the pituitary has been tolerated, and how slight the symptoms are following on the operation.

Experiment VI.

28. xii. 21.	Dog III. A mongrel terrier puppy. 4¼ months old. Male. 3100 grms. Morphia gr. 0.4. Head shaved. X-ray taken.
30. xii. 21.	Operation. Subtotal hypophysectomy. Morphia gr. 0.35. Intratracheal ether. Duration 55 minutes. Uncomplicated exposure of the pituitary. About half of the anterior lobe was removed in one piece: the remaining portion was too difficult of access without injury to the stalk and posterior lobe. The stalk was therefore divided and a subtotal excision of the gland carried out (fig.20). A very small fragment of the anterior lobe was left attached to its blood supply, close to the base of the brain. The wound was closed. Subcutaneous saline infusion 4 ozs. The dog was running about and drank milk, within two hours of operation, in spite of the preliminary dose of morphia.
31. xii. 21.	Excellent recovery. Feeding eagerly. Slight left oculo-motor paresis. Temperature 102.6°F. Within three days the paresis had disappeared. There was no gross polyuria.

Jan. 1 - 31. Weight not appreciably altered. Temperature has been between 0.5° and 1°F subnormal. The animal has shown a tendency to be shy, and sleeps much. There is no adiposity.

Feb. 1 - 28. During this month the symptoms of pituitary deficiency have been more noticeable. The weight has altered little - 3150 grms. at the end of the month. The temperature has been about 1.5°F subnormal. The coat has become poor and dry; the skin thin, dry and wrinkled. The hair is deficiently replaced on the head and neck. He has been more retiring and has slept excessively. There have been several attacks of mild bronchitis and conjunctivitis. The appetite has been very good.

March 1-13.

6.iii. 22. A definite bronchitis developed. Weight fell to 2900 grm. Temperature 104.2°F.

7.iii. 22. Bronchitis worse. Temperature 102.8°F.

8.iii. 22. Broncho-pneumonia. Temperature 101.4°F. Very apathetic. Back arched. Respiration slow (12 per minute). It is obvious that he is entering on the state of acute pituitary deficiency. Food is refused. A subcutaneous injection of an extract of anterior lobe of ox pituitary was administered, and he was fed with the stomach tube.

9.iii. 22. His condition is much improved. The temperature has risen to 103.2°F, and food is taken voluntarily (fig.22 - photograph taken on this day).

10.iii.22. Improvement continued. Temperature 102.6°F. Injection of anterior lobe extract repeated.

11.iii.22. Temperature 103.1°F. Recovery from pneumonia now complete.

13.iii.22. Weight has fallen to 2700 grm. He remains well. (He has since improved greatly with pituitary feeding, has become quite normally playful and is putting on weight.)

<u>Observation 73 days</u>. Experiment not yet terminated.

Comment. This case exhibits several interesting features. As the result of a subtotal hypophysectomy bodily growth has been entirely arrested; the size is the same now, at 6½ months, as it was at 4½ months. The temperature is subnormal. The condition is one of mental apathy and somnolence. The hair is poor and dry; the skin thin, scaly and wrinkled. The testicles are very small. There is a diminished resistance to infection. There is as yet no adiposity.

These symptoms have been progressive, and this suggests a progressive interference with the remaining glandular fragment by contracting scar tissue.

Of special interest was the response of the animal to organo-therapy. Symptoms of acute glandular deficiency were precipitated by an attack of broncho-pneumonia. The condition appeared hopeless, but was successfully tided over by administration of pituitary extract. The recent improvement in general and mental condition with pituitary feeding has been very striking.

The thermic response to the injections is clearly shown.

The animal now exhibits a severe degree of pituitary deficiency, moderated in its effects by pituitary feeding.

Experiment VII.

Fig. 20. <u>Tissue removed from Dog III at operation</u>.

(Microphotograph × 10.)

a, The major portion of pars nervosa, with adherent investment of pars intermedia.

b,b,b,b,b, are considerable fragments of pars anterior. It was estimated that a subtotal hypophysectomy had been carried out, leaving a small fragment of pars anterior.

Fig. 21. <u>Dog III</u>. Photograph taken on the day preceding operation. Weight 3100 grms.

Fig. 22. <u>Dog III</u>. 69 days after operation. He is here just recovering, under organo-therapy, from an attack of pneumonia. His size has not appreciably altered since the operation. The recent pneumonia accounts for the fall in weight to 2900 grms.

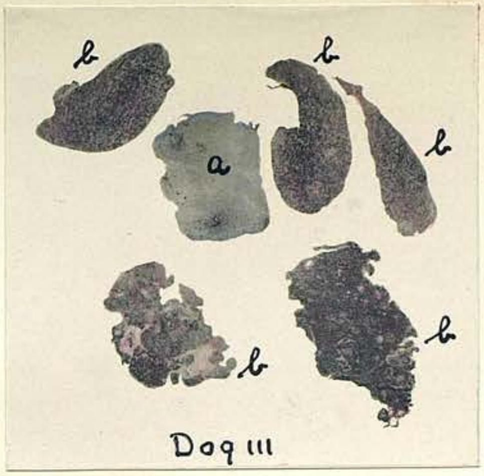

FIG. 20.

FIG. 21.

FIG. 22.

Experiment VII.

Kittens B6, B7 and B8 (fig.23).

A litter of three kittens, 8 weeks old, one male and two female. Of these the larger female, B6, was selected for a control; the smaller female, B7, was subjected to pituitary feeding; in the male, B8, a pituitary lesion was produced.

Kitten B8.

29. xii. 21. 8 weeks old. Male. 460 grms. X-rayed under chloroform anaesthesia.

30. xii. 21. Operation. Transorbital electrolysis of pituitary.

Chloroform followed by ether. Duration 10 minutes. Trocar passed into sella turcica through left sphenoidal fissure. Electrolysis with positive pole, at 10 milliampères, during 2 min. 45 sec.

Immediate recovery from operation. Took milk within an hour of operation. During the first three days no symptoms referable to the operation were seen. The temperature remained normal.

3. i. 22. Temperature 100.6°F (normal 103°F). There is a slight unsteadiness of gait. Apparently the condition of acute glandular deficiency is impending. Subcutaneous injection of anterior lobe of ox pituitary extract. Within three hours the temperature had risen to 102.4°F.

4. i. 22. Condition much improved. Temperature 103.2°F. There is no unsteadiness. Animal lively and eats well.

For the next week the condition remained much the same; the temperature, however, fell progressively, and there was a mild conjunctivitis.

13. i. 22. Weight 470 grms. Very quiet and does not play.

14. i. 22. Temperature 100.8°F. There is a slight nasal catarrh. Keeps close to the fire all day.

15. i. 22. Temperature 97.4°F. Weak and unsteady in walking, and does not eat well. Acute glandular deficiency is obviously setting in again. Respiration is not yet affected.

16. i. 22. Experiment terminated.

Observation 17 days.

Apart from the evidences of glandular deficiency, the animal remained in good health during the experimental period, taking food well. Growth was entirely arrested as a result of the operation.

Kitten B7.

29. xii. 21. 8 weeks old. Female. 420 grms. X-rayed under chloroform anaesthesia.

1. i. 22. Pituitary feeding begun. 5 grains of the dried, powdered anterior lobe of ox pituitary was given daily, first thing in the morning, on an empty stomach, until the termination of the experiment.

13. i. 22. Weight 600 grms.

16. i. 22. Experiment terminated.

Observation 16 days.

During the experimental period this kitten remained in excellent health. After one week it was obvious that she was overtaking her larger sister in bodily growth.

Kitten B6. (Control.)

29. xii. 21. 8 weeks old. Female. 460 grms. X-rayed under chloroform anaesthesia.

13. i. 22. Weight 550 grms.

16. i. 22. Experiment terminated.

Observation 17 days.

During the experimental period the animal remained in good health, and could be regarded as a satisfactory control.

Post mortem Examinations. On 16.i.22 a lethal dose of chloroform was administered to the three animals.

Kitten B8.

Gross Examination. A small, thin animal. Total length 30 cm. Weight 460 grms. (fig. 24). Brain and meninges normal. Pituitary reserved for microscopic study. The thyroid lobes were obviously small. The thymus was very small. No other abnormality except a slight conjunctivitis was noted.

Microscopical Examination. The pituitary body is extensively destroyed and degenerated (fig. 25). The thyroid is definitely atrophic; the epithelium is low, and small growing vesicles are relatively few in number (fig. 26). The thymus is strikingly depleted of lymphoid tissue and relatively rich in Hassal's corpuscles. The latter are very well developed; their cells are swollen and active in comparison with the control. The suprarenals, pancreas, spleen and liver show no recognizable changes. It is regrettable that no male control for comparison of testis was available. No gross changes were observed in this organ.

Kitten B7.

Gross Examination. A large, heavily built kitten. Total length 33.5 cm. Weight 640 grms. (fig. 24). The thyroid lobes looked large and pale, suggesting hyperplasia. The ovaries were strikingly large as compared with those of the control. No other abnormality was noted.

Microscopical Examination. The pituitary body presents a normal appearance. The thyroid is slightly but definitely hyperplastic as compared with the control. The epithelium is deeper, and small growing vesicles are more widely distributed (fig. 26). The ovaries are strikingly more mature in their development (fig. 27). The thymus, suprarenals, pancreas, spleen and liver show no recognizable deviation from the normal.

Kitten B6.

Gross Examination. A normal kitten. Total length 32.5 cm. Weight 570 grms. (fig. 24). Nothing abnormal was discovered.

Microscopical Examination. Pituitary body normal (fig. 25). Thyroid normal (fig. 26).

Ovaries normal (fig. 27). The thymus, suprarenals, pancreas, spleen and liver show no recognizable deviation from the normal.

The bone changes are described in Section VI.

COMPARATIVE TABLE.

	B6. Control	B7. Hyper-pituitarism	B8. Hypo-pituitarism
At commencement	460 gm.	420 gm.	460 gm.
At termination	570 gm.	640 gm.	460 gm.
	Post mortem Findings.		
Length of body	32.5 cm.	33.5 cm.	30 cm.
General appearance	Normal	Abnormally well developed	Small and thin
Thyroid	Normal	Hyper-plastic	Hypo-plastic
Generative glands	Normal	Hyper-plastic	? (No control)
Bones (Section VI)	Normal	Accelerated growth	Retarded growth

Comment. The consequences of hyper- and hypopituitarism upon a growing animal are well illustrated by this experiment. Pituitary feeding induced a striking and harmonious acceleration in bodily development. The animal subjected to it was originally the samllest of the three; but she outstripped the control both in length and weight. Ovarian development was simultaneously accelerated. I have the impression that the thyroid was definitely hyperplastic, but do not lay much stress on this from one experiment only.

The animal exhibiting a severe degree of pituitary deficiency ceased to grow. The thyroid atrophy was very striking. Other symptoms associated with pituitary deficiency exhibited by this animal were subnormal temperature, mental apathy, and diminished resistance to infection. The changes noted in the thymus were probably referable to the mild conjunctivitis and nasal catarrh which were present.

It is obvious that while the bone changes (Section VI) were associated with hyper- and hypopituitarism, one must consider the secondary thyroid changes in this relation. Experimentation directed to the elucidation of this point is indicated.

The marked acceleration of sexual development in the feeding experiment presages an early arrest of growth. It leads one to speculate on the possibilities of pituitary feeding to a castrated animal in producing actual gigantism. Research in this direction is certainly suggested by the findings of this experiment.

<u>Experiment VIII</u>.

Fig. 23. Kittens B6, B7 and B8 at the commencement of the experiment.

B6. 460 grms.
B7. 420 grms.
B8. 460 grms.

Fig. 24. Kittens B6, B7 and B8 photographed post mortem at the termination of the experiment.

B6. 570 grms.
B7. 640 grms.
B8. 460 grms.

Note the dwarfism of the operated animal, and the massive build of the pituitary-fed kitten, which more nearly approaches the adult type than does the normal control. These effects are enhanced by the facts that the operated animal is a male, and the pituitary-fed subject was originally smaller than the control.

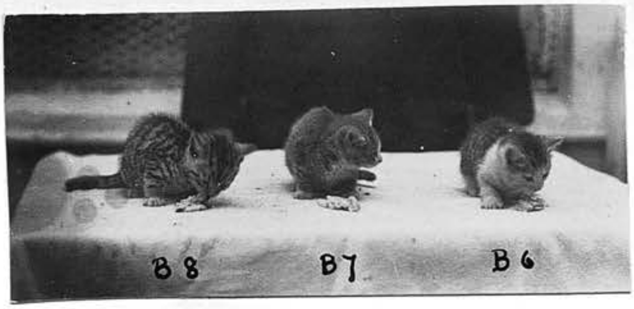

Fig. 23.

Control Hypopituitarism Hyperpituitarism

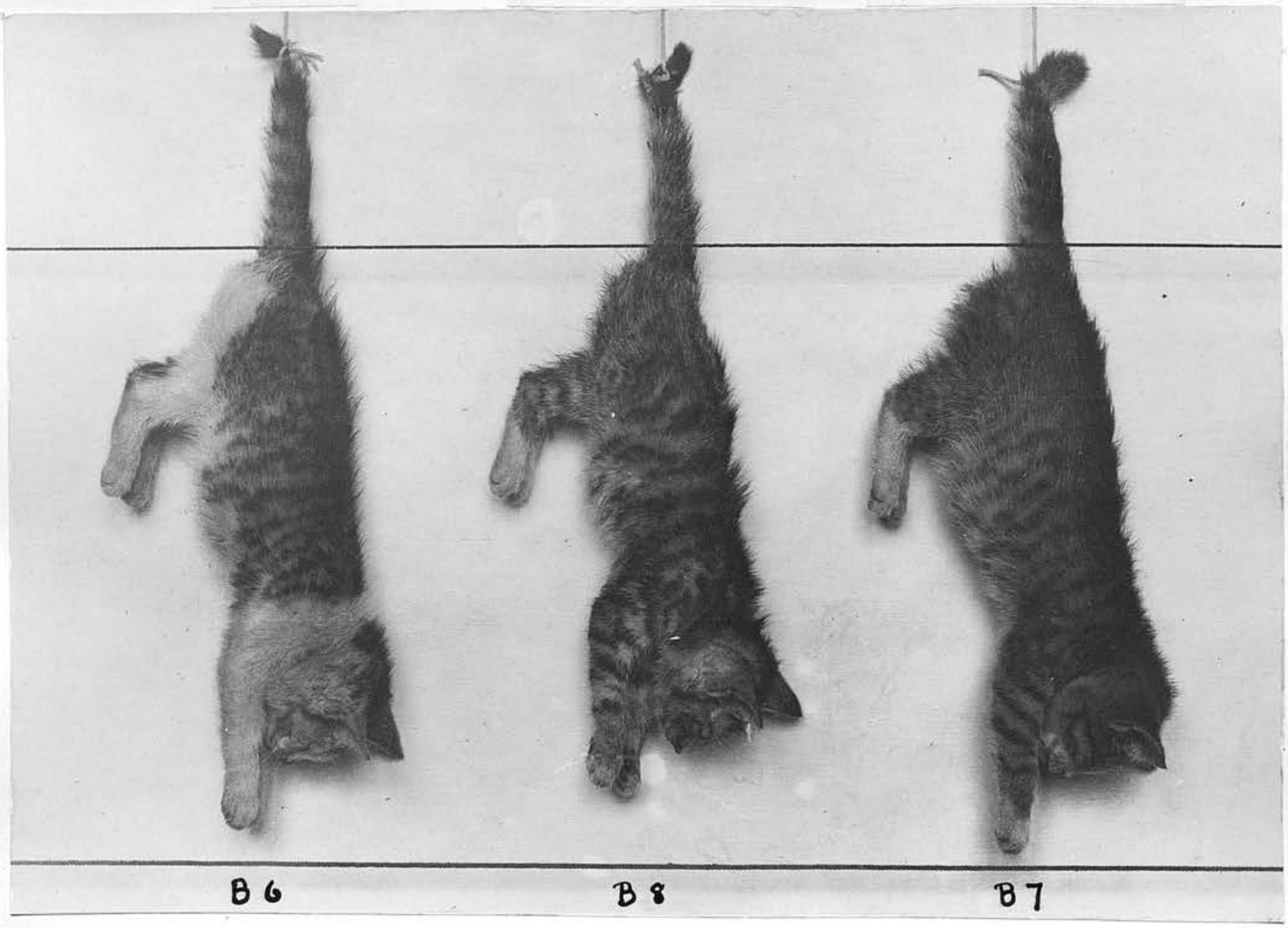

Fig. 24.

Fig. 25.

Pituitary blocks of Kittens B6 and B7.
(Microphotograph × 28.)

The sections include the body of the sphenoid bone, the pituitary and the adjacent brain.

B6. The normal kitten's pituitary.

a, anterior lobe: b, posterior lobe: c, cleft:
d, pars tuberalis: e, third ventricle of brain:
f, bony floor of sella turcica.

Observe the deeply staining, compactly built anterior lobe, the thick investment of pars intermedia on the posterior lobe, and the pars nervosa filled with secretion, which gives it a solid appearance.

B8. Electrolytic lesion of the pituitary.

The various parts are lettered as in B6. At g, a large coagulum mixed with cellular débris of the anterior lobe. The cells of the surviving portion of the anterior lobe are markedly shrunken and stain poorly. Their blood supply is interefered with by the coagulum, which interrupts the vascular leash to the anterior lobe. At h, is another coagulum, with pars intermedia débris. A little degenerated pars intermedia is recognisable at the stalk, while that portion which should invest the posterior lobe is completely destroyed. At b, is the pars nervosa, barely distinguishable from the surrounding blood clot. Its interstices contain no secretion. The sella turcica is filled with organising blood clot, which surrounds the pituitary below. The brain is intact. The periosteum of the sellar floor is destroyed, and a fragment of necrosed bone is seen at i. The lesion is severe as regards the pituitary, but is completely localized, no other structure of importance being injured.

Fig. 26.

Thyroid tissue of Kittens B6, B7 and B8.
(Microphotograph × 55.)

B6 represents the normal condition.

B7 (hyperpituitarism) shows a slight relative hyperplasia (make allowance for denser plate in normal). B8 (hypopituitarism) shows a very marked thyroid atrophy.

Fig. 27.

Ovaries of Kittens B6 and B7.
(Microphotograph × 20.)

B6 represents the normal condition.

B7 (hyperpituitarism) shows a striking acceleration of ovarian development. (Although it does not appear in the sections, the ovary of B7 was in reality considerably the larger.)

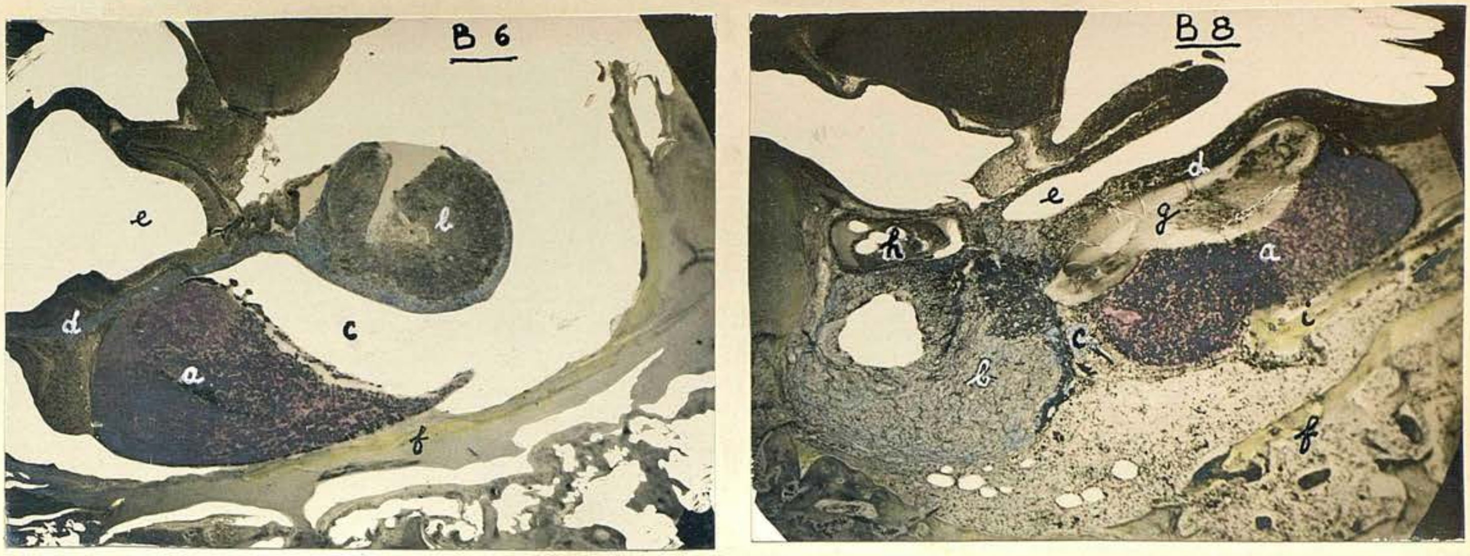

Fig. 25.

Control Hyperpituitarism Hypopituitarism

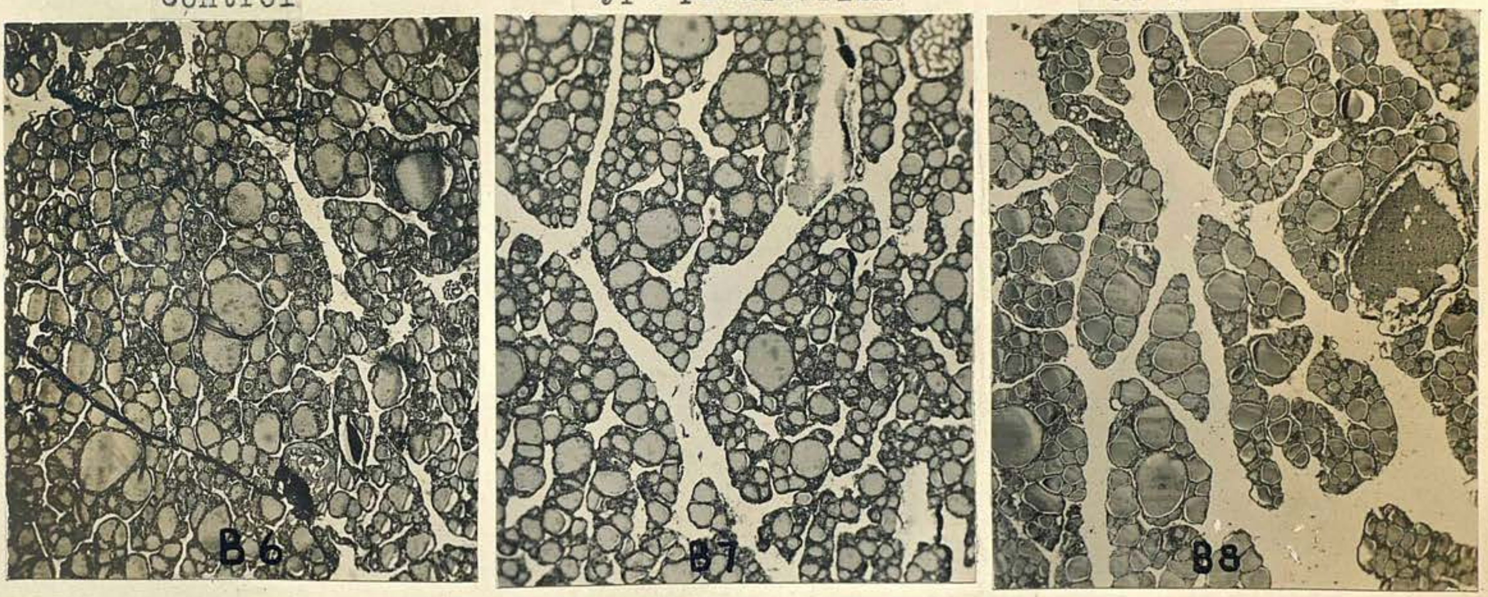

Fig. 26.

Control Hyperpituitarism

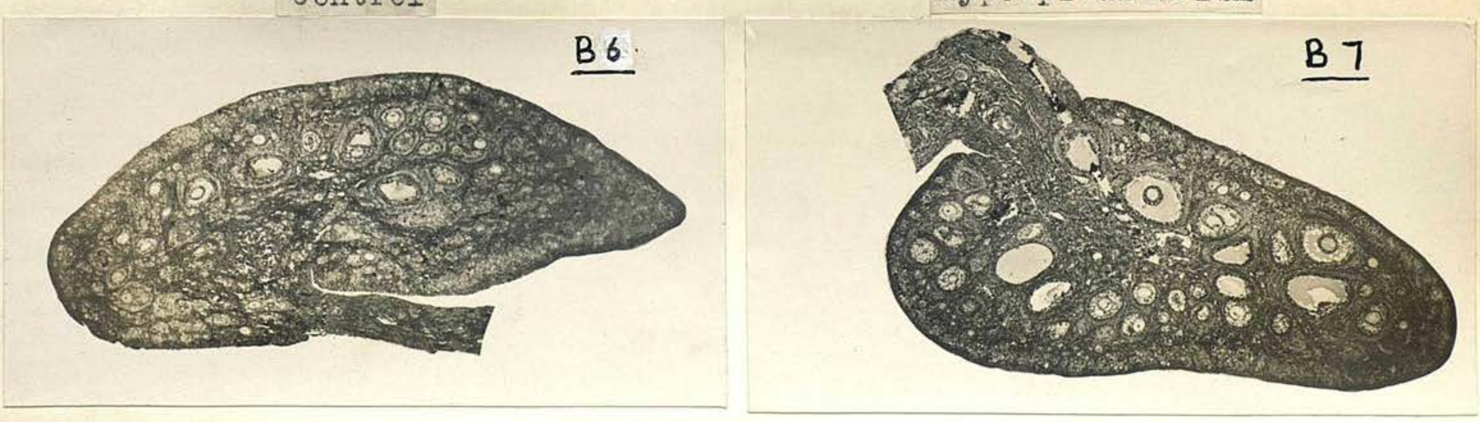

Fig. 27.

Experiment VIII.

Dog IV. A mongrel terrier.

20. i. 22. ? 4¼ months old. Female. 5270 grms. Morphia gr. 0.5. Head shaved. X-ray taken.

23. i. 22. Operation. Excision of anterior lobe. Intratracheal ether. Duration 50 min. Uncomplicated exposure of pituitary. The anterior lobe was removed in one piece, the posterior lobe and stalk being left intact. The specimen appeared almost complete, but a minute fragment of anterior lobe was probably left adherent to the distant side of the stalk. Tissue removed is shown in fig. 28. The wound was closed. Subcutaneous saline infusion 4 ozs.. Rapid recovery. Running around and taking milk within three hours of operation.

24. i. 22. Excellent condition. The dog gnaws a bone vigorously. There is a slight oculo-motor paresis. Temperature 104°F (see fig. 29: photo taken 15 hours after operation).

25. i. 22. There is obvious polyuria. Drinks freely, and keeps rather quiet. Temperature 104.2°F. Wound area in perfect condition.

26. i. 22. Quite bright and playful again. Polyuria persists. Temperature 103.4°F.

28. i. 22. Polyuria has disappeared. Oculo-motor paresis has entirely passed off. The animal is in excellent condition. Temperature 102.6°F.

30. i. 22. Morphia gr. 0.5. Sutures removed. X-ray photograph of skull taken (fig.6). Temperature 103°F. Weight 5260 grms.

6. ii. 22. Temperature has ranged 0° to 0.5°F subnormal. Weight 5310 grms.

13. ii. 22. Temperature has ranged about normal. Weight 5340 grms.

20. ii. 22. Temperature has been normal. Weight 5360 grms.

27. ii. 22. Has had proctitis - temperature therefore not taken. Weight 5370 grms.

6. iii. 22. Has had a nasal catarrh. Temperature about 1°F above normal. Weight 5370 grms.

13. iii. 22. Quite well again. Temperature normal Weight 5390 grms.

Observation 49 days. Experiment not yet terminated.

Comment. This experiment brings out the tolerance of extensive anterior lobe resections. From it one can have no doubt that Nature has provided a large "safety-excess" of anterior lobe pituitary tissue, as is well known to be the case with other vital tissues. The animal has certainly been deprived of a large proportion of the anterior lobe but shows no resultant symptoms whatever. The temperature is not depressed; the hair is growing naturally; the dog is strong and playful.

Certainly there has not been much increase in growth during the 49 days of observation; but I am very doubtful of the reputed age. The X-ray of the epiphyseal regions at the knee joint suggests an almost mature animal.

The operation was unusually easy of accomplishment, and there was an entire absence of bleeding in the neighbourhood of the sella turcica; so that the remaining fragment of anterior lobe is, no doubt, in an ideal condition to maintain its functions.

Experiment IX.

Fig. 28. Tissue removed from Dog IV at operation.

(Microphotograph × 18.)

The section shows a large portion of pars anterior alone. The anterior lobe tissue was cleanly removed in one piece in this case, and was estimated to represent almost the entire lobe.

Fig. 29. Photograph of Dog IV. 15 hours after operation.

Weight 5270 grms.

Fig. 30. Photograph of Dog IV. 44 days after operation.

Weight 5390 grms.

Observe the complete replacement of hair on the head and neck.

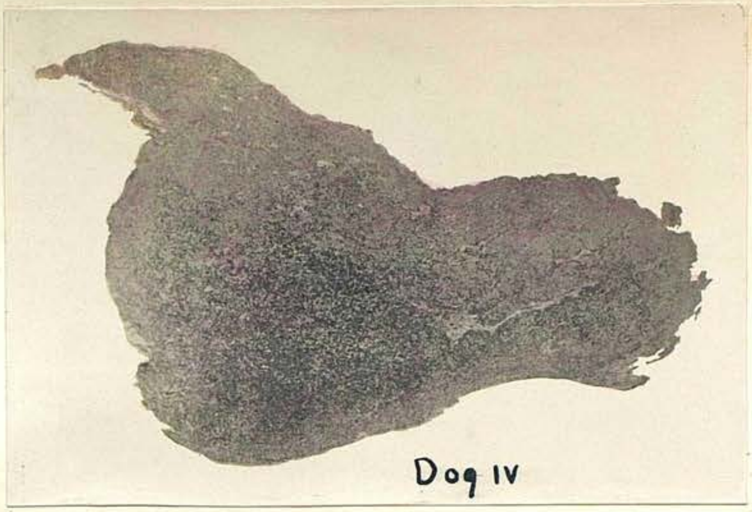

Fig. 28.


Fig. 29.


Fig. 30.

Experiment IX.

Dog V. A mongrel terrier puppy.
25. i. 22. 4 months old. Male. 4180 grms.
Morphia gr. 0.5. Head shaved.

27. i. 22. Operation. Posterior lobe removal. Morphia gr. 0.3. Intratracheal ether. Duration 60 minutes. Uncomplicated exposure of pituitary. The posterior lobe was accurately shelled out of the anterior, the stalk divided and the posterior lobe removed intact (see fig. 31). The leash of vessels to the anterior lobe was not injured. The wound was closed. Subcutaneous saline infusion 6 ozs. Rapid recovery from operation.

The temperature ranged about 0.5°F subnormal during the first four days, and then became normal.

On the second day after operation there was bad conjunctivitis; bronchitis and diarrhoea followed. It was recognized that he had distemper. By careful dieting and treatment of the eyes, he appeared quite cured in 10 days.

Good health continued until
25. ii. 22. when a tape worm infection was discovered to be present. This was successfully treated; however the general condition was rendered poor by the attack of distemper and the worm infection. The animal had lost 500 grms. since the operation.

1. iii. 22. He took acute lobar pneumonia.

2. iii. 22. Died of this.

Observation 34 days.

Post mortem Examination. The cranial operation area was in perfect condition. There was a cerebral adhesion at the right temporal decompression, which had occasioned no symptoms during life.

No special changes were noted on gross examination of the various organs, beyond those associated

Fig. 31. <u>Tissue removed from Dog V at operation</u>.

(Microphotograph × 18.)

The section shows the posterior lobe (i.e., pars nervosa with its investment of pars intermedia) cleanly removed, alone and intact.

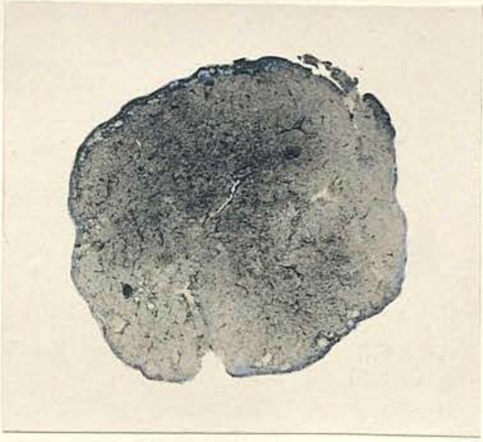

FIG. 31.

with a double lobar pneumonia. The thymus was strikingly small: this change was probably associated with the pneumonic infection.

The tissues have been preserved for microscopical study.

Comment. Little can be deduced from an experiment so complicated by a series of accidental illnesses. However, no symptoms were observed which could be attributed to the operative removal of the posterior lobe of the pituitary body.

Experiment X.

	Dog VI. A mongrel terrier puppy.
30. i. 22.	3¼ months old. Male. 2750 grms. Morphia 0.4 gr. Head shaved. No X-ray was taken, as morphia was not well tolerated.
31. i. 22.	Operation. Subtotal hypophysectomy. Intratracheal ether. Duration 50 minutes. In opening the dura mater on the left side, the sphenoidal fissure was too closely approached and the cavernous sinus was slightly injured. The oozing from this injury rendered a good exposure and dissection of the pituitary body impossible. A glimpse of the organ having been obtained, it was seized with forceps and removed, apparently entire (fig. 32). Bleeding was then controlled by packing, and time for coagulation allowed. When the pack was removed bleeding had been permanently arrested by clotting. The wound was closed. Subcutaneous saline infusion 6 ozs. Milk taken within three hours of operation.
1. ii. 22.	Good recovery (fig. 33). Temperature

103°F. Severe oculo-motor paresis.
The temperature remained normal (103°F) for four days. During this period the animal was a little lethargic, but fed well and responded to petting.

5. ii. 22. Temperature fell abruptly to 99.8°F. During the following week it remained 2° - 3°F subnormal.

11. ii. 22. Temperature 100.8°F. Weight 2740 grms. Appears quite well, but rather slow and dull.

12. ii. 22. Temperature 101.8°F. Does not look well. There is a slight cough and conjunctivitis. Eyes bathed.

13. ii. 22. Temperature 105.5°F. Has bronchitis.

14. ii. 22. Temperature 103.6°F. Appears rather better, but has diarrhoea and melaena. Special diet (Benger's Food).

16. ii. 22. Much better. Temperature 101.8°F.

18. ii. 22. Temperature 103.2°F. Cough and nasal catarrh. Weight 2680 grm.

20. ii. 22. Temperature 105°F. Broncho-pneumonia. Very ill, and refused food. 8 ozs. Benger's Food were therefore given by stomach tube, twice in the day. Subcutaneous injection of anterior lobe pituitary extract.

21. ii. 22. Temperature 105°F. Same condition. Benger's Food by stomach tube. Injection of anterior lobe extract repeated.

22. ii. 22. Much better. Temperature 103.8°F. Took a little food, but the tube was used again.

24. ii. 22. Temperature 102.2°F. Much better, and now takes food eagerly. Very inert except at meal times, when he wakes up.

27. ii. 22. Temperature 102.2°F. Weight 2890 grms. Rapidly growing fat.

6. iii. 22. Temperature has ranged about 2°F subnormal. Weight 2970 grms.

13. iii. 22. Temperature has ranged about 2°F subnormal. Weight 3140 grms. He is growing obese. The testicles are very small, and I think they are smaller than they were before operation. His behaviour is curious. He remains very inactive until food is seen, when he becomes quite lively. When the food is finished, the apathetic state is resumed. Oculo-motor paresis has quite passed off now.

Observation 41 days. Experiment not yet terminated.

Comment. This animal illustrates well the experimental counterpart of the clinical syndrome dystrophia adiposo-genitalis of Fröhlich. The temperature is considerably depressed. There is a rapidly increasing adiposity. The testicles are hypoplastic and have, I think, actually retrogressed in size. The animal is somnolent and mentally deficient. His stature has not perceptibly increased since the operation, the gain in weight being entirely due to the commencing adiposity. There is a diminished resistance to infection. The hair is deficiently replaced on the head and neck.

It is of interest that an attack of bronchopneumonia, which it appeared must terminate fatally, was successfully tided over by means of organotherapy and artificial feeding.

Experiment XI.

Fig. 32. Tissues removed from Dog VI at operation.

(Microphotograph x 18.)

The lobes came apart during fixation and have been separately sectioned.

a, the entire posterior lobe with a fragment of anterior lobe adherent to it.

b, the cup-shaped, apparently entire, anterior lobe. From the facts of the case, however, one is forced to assume that a small fragment of pars anterior remains.

Fig. 33. Photograph of Dog VI taken 16 hours after operation.

Note the suture line and paste dressing. He is making a vigorous attack on a bone. Weight 2750 grms.

Fig. 34. Photograph of Dog VI taken 36 days after operation.

Weight 3140 grms. There is commencing adiposity. He has not increased in stature. The hair is not growing well on the shaved area of the head and neck.

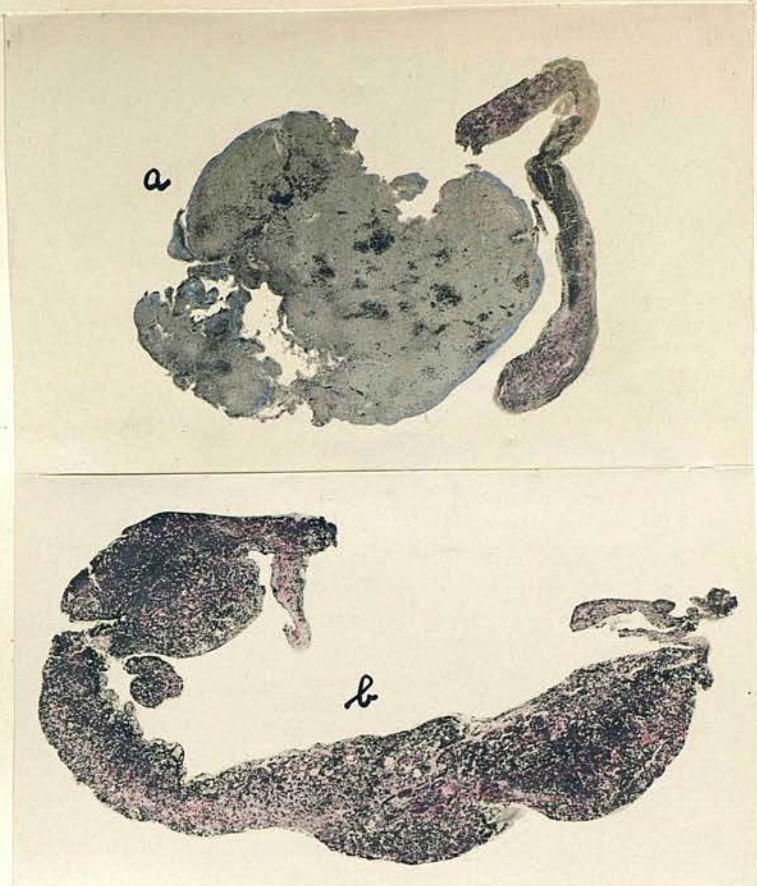

Fig. 32.

Fig. 33.

Fig. 34.

Experiment XI.

	Dog VII. A mongrel collie puppy.
6. ii. 22.	4¼ months. Female. Weight 3400 grm. Morphia gr. 0.45. Head shaved. X-ray taken.
7. ii. 22.	Operation. Excision of posterior lobe and stalk. Intratracheal ether. Duration 65 minutes. Uncomplicated exposure of the pituitary body. The posterior lobe was accurately shelled out of its bed in the anterior lobe, and removed entire. As it was my aim to remove as completely as possible the pars nervosa and intermedia also, the stalk was followed to the tuber cinereum, and the anterior lobe vessels having been carefully separated forward, it was removed from the base of the brain (fig. 35). In this way most of the pars tuberalis was also removed. I do not think the third ventricle was opened into. The anterior lobe and its blood supply were certainly left intact. The wound was closed. Subcutaneous saline infusion 3 ozs. Rapid recovery. The animal drank 6 ozs.of Benger's Food within two hours of the operation.
8. ii. 22.	Excellent recovery (fig. 36). There is a slight oculo-motor paresis. Temperature 102.8°F. No marked polyuria was observed. The temperature remained about 0.5°F subnormal during the first week. There were no other observable consequences of the operation. The oculo-motor paresis had disappeared in 2 days.
14. ii. 22.	Temperature 103°F. Very frisky and takes food well. Weight 3400 grms.
21. ii. 22.	Temperature has been normal. There has been a very mild conjunctivitis and cough, from which she has now recovered completely. Weight 3460 grms.
28. ii. 22.	Temperature has been normal. Weight 3500 grms. Excellent condition.
6. iii. 22.	Temperature normal. Weight 3550 grms.

Fig. 35. <u>Tissue removed from Dog VII at operation</u>.

(Microphotograph × 18.)

The section shows the clearly shelled out and intact posterior lobe, a. The small fragment, b, represents the infundibular stalk, which was separately removed. Adherent to the stalk (which was sectioned as high as possible) is a portion of the pars tuberalis. It is estimated that in this case the entire pars nervosa and stalk were removed, and almost all the pars intermedia. No doubt the anterior extremity of the pars tuberalis remains.

Fig. 36. <u>Photograph of Dog VII taken 17 hours after operation</u>.

Note the suture line and paste dressing. Recovery is complete. The animal is about to make a good meal. Weight 3400 grms.

Fig. 37. <u>Photograph of Dog VII taken 28 days after operation</u>.

Weight 3820 grms. The dog is gnawing normally, and exhibits no symptoms of dyspituitarism.

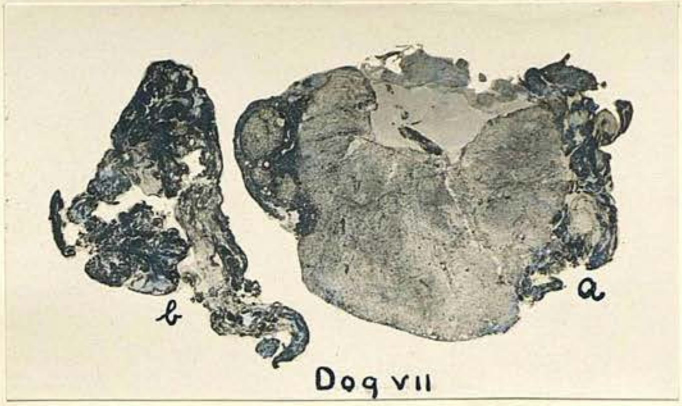

Fig. 35.

Fig. 36.

Fig. 37.

13. iii. 22. Temperature has been normal. Weight 3820 grms. The animal is bright, intelligent and playful; and perfectly normal. The hair is growing well on shaved area.

Observation 33 days. Experiment not yet terminated.

Comment. This animal shows no symptoms whatever referable to the operation of posterior lobe and stalk extirpation. Growth is normal, the hair is healthy, the temperature unaffected, and the mental condition good. From the literature one would expect in such an experiment that adiposity might develop. It is as yet too early to judge of this, but so far there is no suggestion of obesity. In Experiments II and XIII commencing adiposity was obvious within three weeks and one week respectively.

Experiment XII.

13. ii. 22. Dog VIII. A mongrel terrier puppy. 4 months old. Male. 3320 grms. Morphia gr. 0.4. Head shaved.

15. ii. 22. Operation. Total hypophysectomy. Intratracheal ether. Duration 65 min. Uncomplicated exposure of the pituitary body. The organ was removed fragmentarily but completely (fig. 38). In removing the stalk, with all possible pars intermedia, from the tuber cinereum, the third ventricle of the brain was deliberately opened. The wound was closed. Subcutaneous saline infusion 4 ozs. The animal was well recovered within three hours.

16. ii. 22. Complete recovery. There is an oedematous swelling on the left side of the head, due to exudation of

cerebrospinal fluid. No ocular paresis. Temperature 103°F.
During the first week the temperature was about 0.5°F subnormal. He was rather shy and somnolent, and appeared nervous when disturbed. He took food well. Weight 22. ii. 22, 3250 grms.

23. ii. 22. Quite bright and playful. Temperature 102.2°F. Fig. 39 is a photograph taken on this day.

24. ii. 22. Temperature 101.2°F. He is becoming thin, in spite of a good appetite. More lethargic to-day, nervous when disturbed, and a little unsteady in gait. Subcutaneous injection of 1 cc. boiled extract of anterior lobe of ox pituitary.

25. ii. 22. Temperature 103.2°F. Seems rather brighter.

26. ii. 22. Temperature 102.4°F. Now very thin, and does not take food well. Quite unsteady in walking.

27. ii. 22. Temperature 101.4°F. Same condition. Subcutaneous injection of anterior lobe extract repeated.

28. ii. 22. Temperature 102.2°F. Condition has not altered perceptibly in consequence of last injection. Weight 2570 grm.

1. iii. 22. Temperature 96.8°F. Respirations 9 per minute. Pulse 64 per minute. Acute glandular deficiency is obviously setting in.

2. iii. 22. Died this morning.

<u>Observation 14 days</u>. Death from acute apituitarism.

<u>Post mortem Examination</u>. Rigor mortis is deficient. Cranial wound area is perfectly healed. The brain and meninges show no abnormality beyond a small adherent area within the sella turcica. The whole body is dry and emaciated. The thyroids ap-

pear distinctly small. The thymus is small. The suprarenal glands show no gross abnormality. The testicles are of course immature. The pancreas appears to be acutely degenerated. It is of a peculiar greenish-grey colour. The liver shows obvious fatty degeneration, and its lower surface is deeply bile-stained all over. The bile-staining penetrates two or three millimetres from the surface.

The spleen is soft and rather small. The stomach and intestines are soft and atrophic. The lungs show a few small patches of broncho-pneumonia at the bases.

The tissues have been preserved for microscopical study. They include the usual block from the pituitary region, and the femur.

<ins>Comment</ins>. This experiment illustrates the state of acute apituitarism in the young dog. There was a period of seven days following the total removal of the gland during which the animal's condition was practically normal. The syndrome consequent on an absence of the pituitary function was then seen. Prominent symptoms were mental apathy, inco-ordination of movements, subnormal temperature, slow respirations, and emaciation. Unfortunately I was unable to observe the terminal stages in this case, but by analogy from the similar condition in the cat, I have no doubt that death was due to paralysis of the respiratory centre.

Fig. 38. Tissue removed from Dog VIII at operation.

(Microphotograph × 10.)

a, Complete posterior lobe, with an adherent fragment of anterior.

b,b,b, Fragments of anterior lobe.

c,c,c, Fragments of cerebral tissue with adherent pars tuberalis.

The sella turcica was completely cleared. It was estimated that a complete though fragmentary hypophysectomy had been carried out.

Fig. 39. Photograph of Dog VIII taken 7 days after total hypophysectomy.

He is in an apparently normal condition, and is dragging eagerly at the bone.

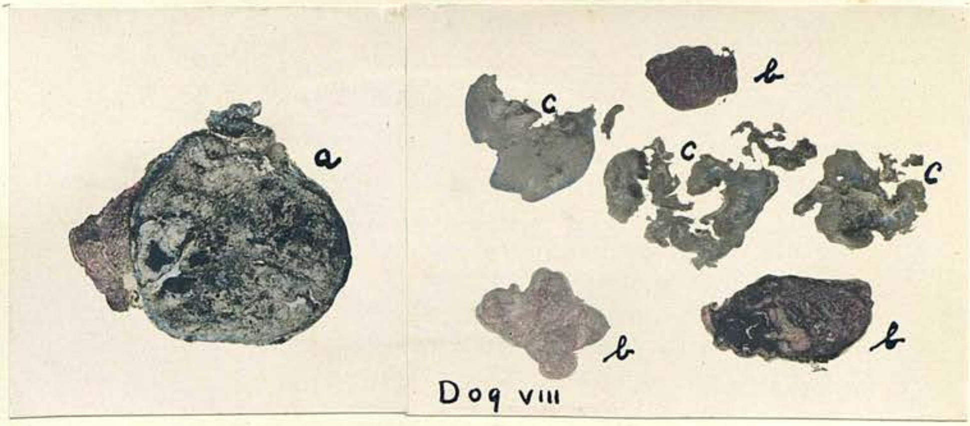

Fig. 38.

Fig. 39.

In the early stages the thermic response to an injection of anterior lobe extract was striking, and the general condition was markedly improved by it. Later the thermic response was slight and no improvement in general condition was noted. Injection of the extract did not suffice to avert the fatal consequence of total removal of the pituitary body.

Experiment XIII.

20. ii. 22.	Dog IX. A mongrel terrier puppy. 3 months old. Female. 4000 grms. Morphia gr. 0.35. Head shaved. X-ray taken.
22. ii. 22.	Operation. Extensive anterior lobe excision. Intratracheal ether. Duration 65 minutes. Uncomplicated exposure of the pituitary body. The major portion of the anterior lobe was removed in one piece. The stalk was but slightly contused. The microscopic examination of the removed tissue shows that a minute fragment of the pars posterior was scraped off during the dissection (fig. 40). The wound was closed. Subcutaneous saline infusion 4 ozs. Rapid recovery. Six ounces of milk food taken within two hours of operation. During the first three days the temperature remained about normal. The animal was very lethargic, but when roused took food well. There was a transient oculo-motor paresis. Polyuria was marked, and persisted for seven days. There was no glycosuria.
26. ii. 22.	The temperature fell abruptly to 100°F (3°F subnormal). Growing very fat.
28. ii. 22.	Temperature 100°F. Weight 4350 grms.
6. iii. 22.	Temperature has ranged about 2°F sub-

normal. Has become quite lively and playful again. Weight 4620 grms.

13. iii. 22. Temperature has ranged about 2°F subnormal. In excellent condition and very fat. Weight 4870 grms.

<u>Observation 19 days</u>. Experiment not yet terminated.

<u>Comment</u>. This animal exhibited a period of lethargy immediately following the operation. This has not been the rule, and was possibly accidental. Transient post-operative polyuria was very marked. The gain in weight of 870 grms. in 19 days is very striking, and the obesity is already pronounced. The temperature has been <u>earlier</u> and more strikingly depressed than was the case in the previous anterior lobe excisions.

Fig. 40. Tissue removed from Dog IX at operation.

(Microphotograph × 18.)

a, a large portion of anterior lobe.

b, a smaller fragment of same.

c, a minute shred of pars nervosa with covering of intermedia cells.

It is estimated that about 3/4 of the anterior lobe was removed, the posterior lobe being but slightly interfered with.

Fig. 41. Photograph of Dog IX taken 16 hours after operation.

Note the somewhat sleepy appearance. Weight 4000 grms.

Fig. 42. Photograph of Dog IX taken 14 days after operation.

She is growing very fat, but is quite lively and playful. Weight 4730 grms.

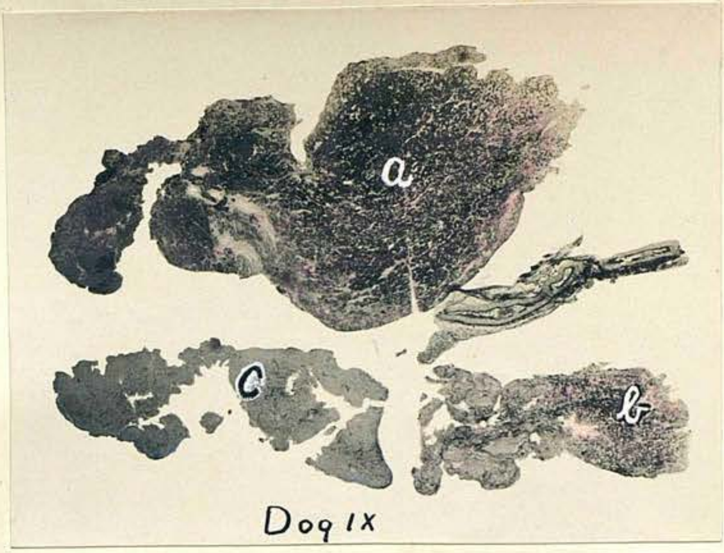

Fig. 40.

Fig. 41.

Fig. 42.

SECTION VI.

INFLUENCE OF HYPER- AND HYPOPITUITARISM ON THE DEVELOPMENTAL GROWTH OF BONE.

(From Experiment VII.)

The epiphyseal region of the lower end of the femur has been selected for the study of this subject. In order to have satisfactory control observations of the bones during life the X-rays were used, while the bones are examined histologically *post mortem*.

A complete study of this nature is at present available from Experiment VII only. In this experiment on three kittens of the same litter B6 was retained as a normal control, B7 was used for experimental hyperpituitarism, B8 was used for experimental hypopituitarism.

X-rays. Fig. 43. shows the radiographs of these animals taken at the commencement of the experiment. The bones and their epiphyseal cartilages are seen to be exactly similar in the female animals, B6 and B7, while they are slightly larger in the male, B8.

Fig. 44 shows the radiographs taken at the termination of the experiment. The changes induced by the experimental conditions are very striking. They are seen in the epiphyseal cartilage and the adjacent diaphysis (metaphysis of Lexer). In B7 (hyperpituitarism) as contrasted with B6 (normal), the epiphyseal cartilage is strikingly thick. Its growing surface (metaphyseal) is seen to have a more indefinite or "woolly" appearance - an indication of more active growth (see histologic findings). The spongy bone of the metaphyseal region is more strongly developed. The whole femur has grown 1 mm. more in length than the control bone during the experiment.

In B8 (hypopituitarism) as contrasted with B6 (normal) and a fortiori with B7 (hyperpituitarism) the epiphyseal cartilage is extremely thin. Its growing surface (metaphyseal) is strikingly sharp in definition - an indication of arrested or retarded growth (see histologic findings). The spongy bone of the metaphyseal region is less well developed (making allowance for denser negative and print). The whole femur has grown 1 mm. less than the control bone during the experiment.

Histological Findings. Fig. 44 shows the epiphyseal region in B6 (normal), B7 (hyperpituitarism), B8 (hypopituitarism). It is well to define the terms I use: for this purpose I refer to the photograph and lettering of B6.

a) The resting zone of the epiphyseal cartilage which has the structure of normal hyaline cartilage and is the reservoir of supply for the cartilage cells concerned in epiphyseal bone growth.

b) The proliferating area, where the cells are arranged in parallel rows. The cells are flattened and small, and their nuclei stain deeply. They are in process of active division and multiplication.

c) The area of enlarged cells. They are still arranged in rows, but have become greatly enlarged: they have assumed a spherical or oval shape. The nuclei are large and stain less deeply. The cells have enlarged at the expense of the cartilaginous matrix, which is now represented by thin trabeculae between the individual cells, and cell rows. These changes are doubtless concurrent with the active deposition of calcium salts in the cartilaginous matrix.

d) The erosion line, where the vascular loops of the diaphysis actually meet the advancing rows of cartilage cells. Here most of the cartilage cells disappear; whether by complete destruction or by metamorphosis into osteoblasts I do not know. Certainly they are largely disintegrated and as cartilage cells they disappear.

e) The metaphysis, an area where cartilaginous tissue and true bone are intermingled. The former is preponderant close to the epiphyseal cartilage, and fades away as the distance from that structure is increased until it disappears entirely and the true spongy bone of the diaphysis is reached. In this area the trabeculae of cartilage enclose spaces - areolae - which are filled with capillaries and lined with osteoblasts. The osteoblasts deposit true bone upon the cartilaginous trabeculae, so that these become enclosed. They become absorbed completely as the metaphysis ends and the area of true bone is reached. It is an extremely vascular area and represents the place in which the true bone actually grows in length.

<u>Kitten B7</u>. (Hyperpituitarism.) At a glance one sees that the epiphyseal cartilage is increased as a whole, and that the spongy tissue of the meta-

physis is strikingly more compact in structure. Examining the various zones individually, the following points are brought out.

a) The resting zone shows no recognizable change.

b) The proliferating zone. Here the cells are slightly more flattened and closely packed. This zone is ~~not~~ increased in width.

c) Zone of enlarged cells. In this area the increase in thickness of the cartilage is mainly brought about. It is markedly deeper than the corresponding zone in B6 (normal). The increase in thickness of this area is due to the greater number of active, enlarged cartilage cells.

d) The erosion line is quite regular, but is less obvious on account of the greater density of the adjacent metaphysis. The vascular loops are here more closely packed.

e) The metaphyseal region. It is here that the most striking changes occur. The cartilaginous trabeculae are much more numerous and are thicker near the epiphyseal cartilages. Consequently the areolar spaces enclosed by them are much smaller and more numerous; the whole appearance being that of denser tissue. On the cartilaginous trabeculae and lining the areolae the osteoblasts are much more numerous and true osteoblastic bone is more heavily deposited. In spite of this the cartilaginous tissue is recognizable at a greater distance from the epiphysis: the metaphyseal region is strikingly enlarged - a clear indication of more rapid growth. The whole area is more vascular. These changes explain the "woolly" radiographic appearance.

<u>Kitten B8</u>. (Hypopituitarism.) One is at once struck with the thinness of the epiphyseal cartilage and the deficiency of the spongy bone.

a) The resting zone shows no recognizable change as compared with the normal (B6).

b) The area of proliferating cells is very much diminished in thickness. The individual cells in this area are strikingly altered. They show little or none of the characteristic flattening, but are quite rounded. Their nuclei are large, and stain faintly. They suggest cells in an inactive, resting stage.

c) The area of enlarged cells is also diminished in thickness, and most of the cells here retain the character of the preceding zone. The individual cells are smaller than the corresponding elements of the normal bone, and near the erosion line they remain well preserved, with distinct nuclei and intact protoplasm, in contrast to the disintegrated condition of the normal cells in this position.

d) The erosion line is well defined and stands out prominently on account of the deficient metaphyseal tissue.

e) The most striking change of all affects the metaphysis. Here the cartilaginous trabeculae are very slender and wide apart, enclosing large, open areolae. The osteoblastic lining of these spaces is very deficient, as is their vascularity. The deposition of true bone on the trabeculae is very slight. The sharp definition of the metaphysis in the radiograph is readily understood in the light of these facts.

The epiphyseal region in hyperpituitarism presents a consistent picture of hyperactivity and acceleration of the process of bone growth. In hypopituitarism the whole picture is that of depressed activity and a marked retardation of the process of growth. It is important that these changes are recognizable <u>during life</u> by means of radiology.

The deposition of periosteal bone is much less markedly affected by the experimental conditions.

One gains the impression, however, that in the animal subjected to hyperpituitarism the compact cortex of the shaft is slightly better developed than in the control. In the animal subjected to hypopituitarism it is slightly less well developed than in the control. The differences are very slight, and one cannot lay much stress on them from a single experiment.

Fig. 43. Radiographs of femurs of kittens B6, B7 and B8 taken at the commencement of the experiment.

B6 (female) 52 mm.
B7 (male) 52 mm.
B8 (male) 55 mm.

The male animal has of course larger bones.

Fig. 44. Radiographs of femurs of kittens B6, B7 and B8 taken at the termination of the experiment.

B6. 56 mm.
B7. 57.mm.
B8. 58 mm.

Note the changes in the epiphyseal cartilages and metaphysis (see text). It is significant that in B6 (normal) the femur increased in length by 4 mm. during the experiment; the femur of B7 (hyperpituitarism) by 5 mm.; and the femur of B8 (hypopituitarism) by 3 mm.

Fig. 45. Microphotographs × 55.

The photographs depict the central regions of the epiphyseal cartilages of the lower ends of the femurs of Kittens B6 (normal), B7 (hyperpituitarism), and B8 (hypopituitarism).

a, the resting zone.
b, the area of proliferating cells.
c, the area of enlarged cells.
d, the erosion line.
e, the metaphysis.
(For description of changes see text.)

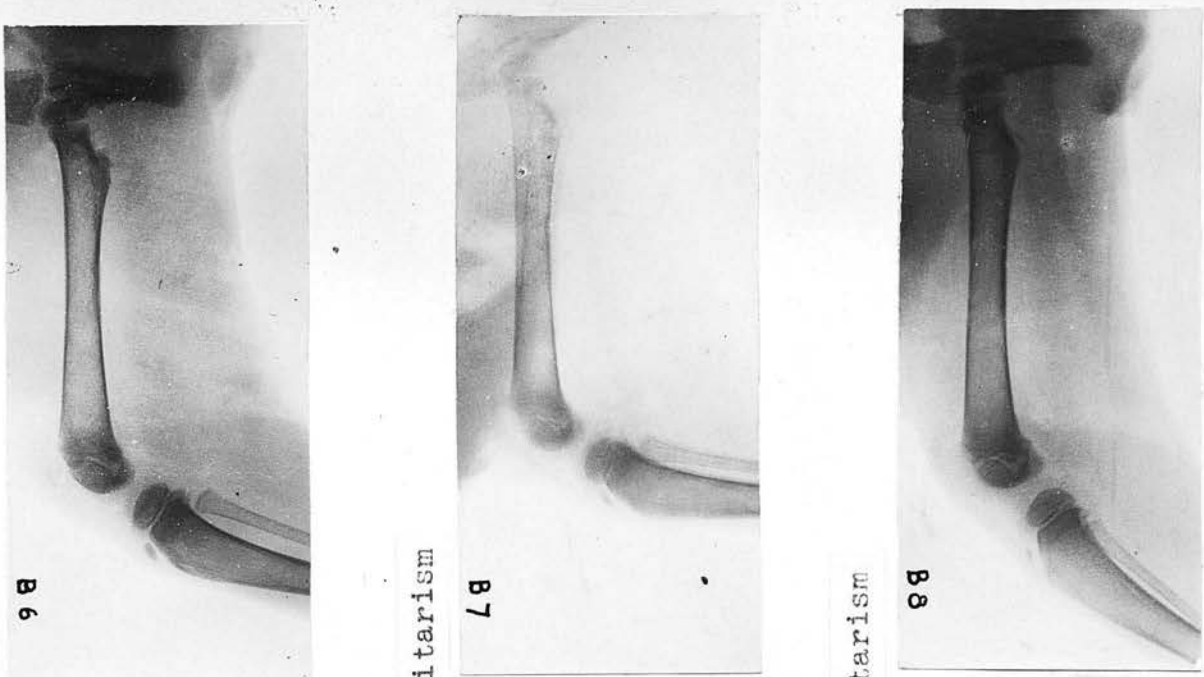

Fig. 43.

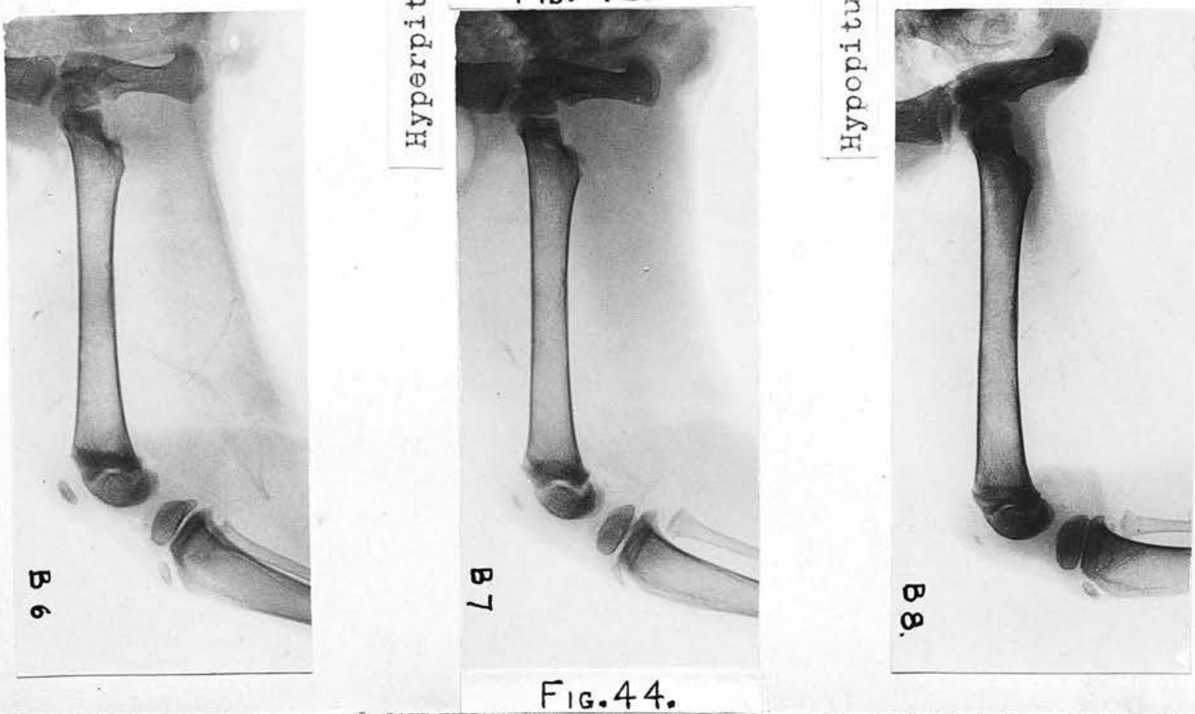

Fig. 44.

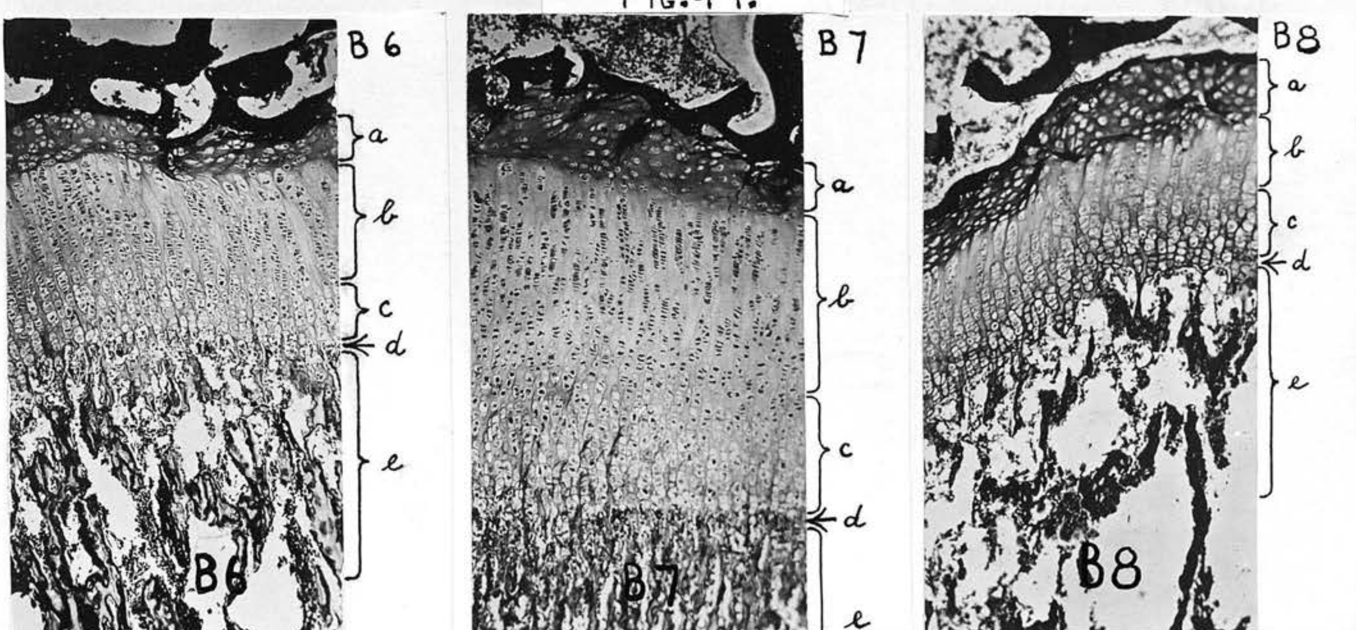

Fig. 45.

From Experiment II.

A study of the developmental growth of the bones of Dogs A3, A2 and A1 is represented by figs. 45, 46, 47 and 48. In comparing the changes observed in the bones of these animals with those just described in Kittens B6, B7 and B8, one finds the two series are consistent but are modified by the fact that the dogs were relatively older and their epiphyseal cartilages were approaching termination of their function and final disappearance, at the end of the experiment.

A3 was the control. A2 was subjected to pituitary feeding. In A1 the infundibular stalk, with the blood supply to the anterior lobe of the pituitary, had been divided at operation.

The radiographs show that the experimental hyperpituitarism caused a remarkable acceleration of increase in length of the femur, and the corresponding appearance of the epiphyseal cartilage is demonstrated. Experimental hypopituitarism induced an arrest of growth in the femur and the corresponding epiphyseal line presents a characteristic appearance.

The microscopical study of the bones shows that in A3 (control) the femur is nearing the mature condition, for the epiphyseal cartilage is narrow, and its resting zone has been exhausted and has almost disappeared. The remaining cartilage and the metaphysis are completing their function of increasing the length of the bone in a normal manner.

In A2, under the influence of hyperpituitarism, the epiphyseal cartilage and metaphysis present a picture of extraordinary activity. This bone is also nearing maturity, as shown by the exhaustion of the resting zone in the cartilage. The cartilage is, however, thick on account of hyperplastic changes. In the metaphysis the small areolar spaces where osteoblastic bone is being deposited upon the cartilaginous trabeculae are well seen. This feature tells of active growth and gives rise to the typical X-ray appearance. The marrow of the spongy bone is very vascular and contains but little fat. The whole appearance is that of a bone which, though approaching the period at which growth in length ceases, is growing with great rapidity.

In A1, under the influence of hypopituitarism, the functions of the epiphyseal cartilage and metaphysis have been suspended. The bone is in a less advanced stage of development than that of the control, as shown by the well preserved resting zone in the epiphyseal cartilage. The cellular elements of the cartilage which should be active, present passive appearances. In the metaphysis the osteoblastic deposition of bone is deficient and gives rise to the typical X-ray picture associated with suspended growth. The marked fatty infiltration of the marrow is interesting as it may bear some relation to the pathological adiposis which the animal exhibited. The whole impression is that of a bone whose development has been interrupted, which retains the characteristics of immaturity which it possessed when the state of hypopituitarism affected it; and whose growing elements are in a condition of inactivity and hypoplasia.

Fig. 46.

Radiographs of femurs of Dogs A3, A2 and A1 taken at the commencement of the experiment.

Note that the bones of A1 (male) and A2 (female) are exactly similar. The bone of A3 (female) is larger and of a distinctly heavier construction. The animals were not pure bred, and it is obvious that A3 shows hereditary tendencies to a larger type, while A1 and A2 incline to follow their smaller parent in size. Unfortunately A1 has moved during the exposure, but it may be gathered that the epiphyseal lines show a similar stage of development.

Lengths. A3 110 mm. A2 104 mm. A1 104 mm.

Fig. 47.

Radiographs of femurs of Dogs A3, A2 and A1 taken at the termination of the experiment.

Lengths. A3 (normal) 115 mm. A2 (hyperpituitarism) 115 mm. A1 (hypopituitarism) 105 mm. Increase in length of femur subjected to

Normal Conditions	Hyperpituitarism	Hypopituitarism
5 mm.	11 mm.	1 mm.

It is of interest that, while pituitary feeding has caused an acceleration of growth in length in the femur of A2, so that it finally equalled that of A3, there is not a corresponding increase in girth of the bone. The facts suggest that possibly during the growing period the more active bone growth at the epiphyseal cartilage is affected by the pituitary hormone to a greater extent than the less active periosteal bone formation.

The epiphyseal line at the lower end of the femur of A3 (control) is that of a normal animal whose skeleton is nearing mature completion. The line of cartilage is thin. The cartilage of A2 (hyperpituitarism) is thick by comparison and its metaphyseal surface is seen to be more indefinite and woolly in appearance. The cartilage of A1 does not differ appreciably in thickness from that of the control, but the sharper definition of the metaphyseal surface is obvious. The interpretation of these observations is made clear by microscopical study.

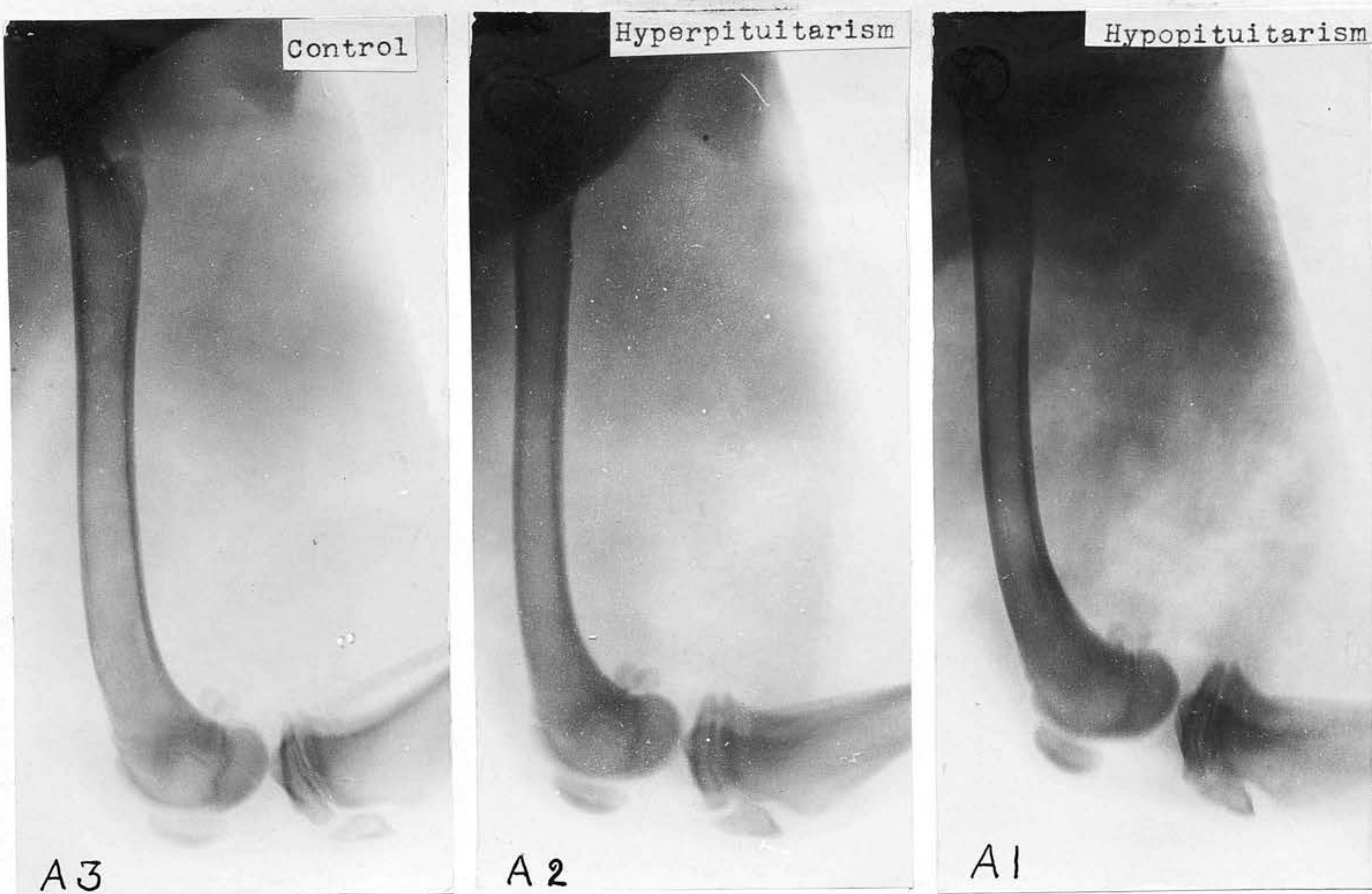
Control
Hyperpituitarism
Hypopituitarism
A3
A 2
A1

FIG. 46.

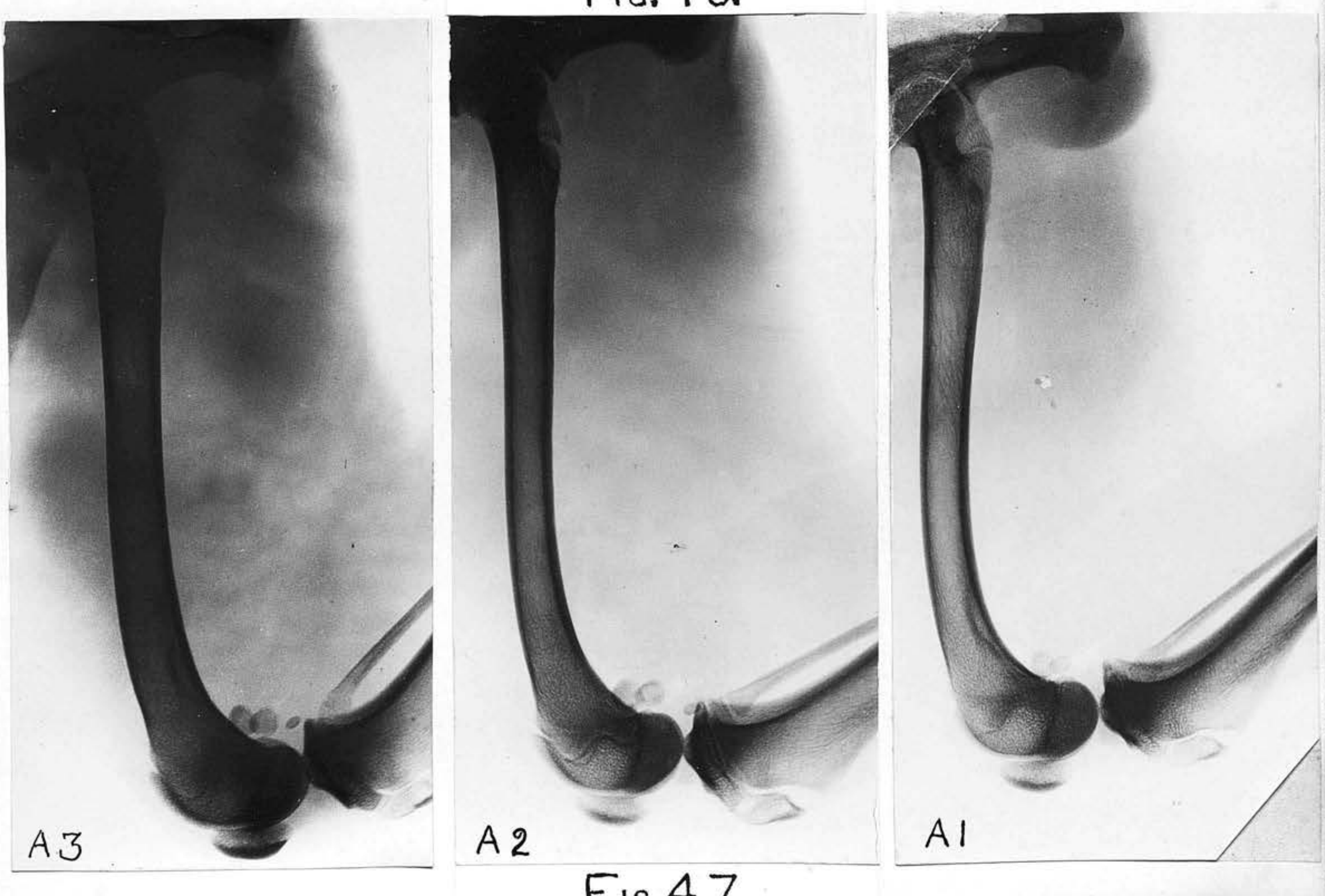
A3
A 2
A1

FIG. 47.

are slightly less regularly arranged than in the normal specimen - no doubt on account of their extremely rapid formation. The marrow is vascular, and there are very few fat sapces. In A1 the cartilage is narrow on account of deficient activity. The spongy bone is ill formed, its trabeculae being thin and irregularly arranged. The marrow shows a gross fatty infiltration almost up to the erosion line.

Fig. 48.

Microphotographs of the epiphyseal cartilages at the lower ends of the femurs of Dogs A3, A2, A1. (× 80.)

A3 (normal). a Resting zone which has almost disappeared: b area of proliferating cells: c area of enlarged cells: d the erosion line: e the metaphysis.

A2 (hyperpituitarism). a Resting zone which has almost disappeared: b the zone of proliferating cells: This area is considerably increased in thickness, while the individual cells are more closely packed (i.e., more rapidly proliferating). c the zone of enlarged cartilage cells is very greatly increased in depth. So closely are the cells packed that little intervening matrix is left: d the erosion line is ill defined on account of the density of the adjacent metaphysis: e the metaphysis is very vascular. The areolar spaces are small. They are richly lined by osteoblasts and on the cartilaginous septa the deposition of osteoblastic bone is far in excess of the normal.

A1 (hypopituitarism). a Resting zone. It is well preserved, and contains many groups of resting cells. Its presence indicates the immature condition of the bone: b the zone of proliferating cartilage cells (a misnomer in this case). The cells here are not closely packed. They are less flattened, and represent cells in an inactive condition. c the zone of enlarged cartilage cells. Here the cells present almost the same appearances as in the preceding area. They are not so large as the corresponding elements of the normal bone. At d, the erosion line, they show no tendency to disintegration and their nuclei here remain well preserved. They are obviously in a state of suspended activity. Thus the thinness of the cartilage is due to a hypoplastic condition of its active parts and not to approaching maturity. e The metaphysis exhibits a poor vascularity. The areolar spaces are wide and irregular and the deposition of osteoblastic bone on the cartilaginous septa is deficient.

Fig. 49.

Microphotographs of the above epiphyseal cartilages, together with the adjacent diaphysis. (× 25.)

A3 shows the normal condition with thin cartilage, well formed and well arranged bony trabeculae in the adjacent spongy bone. The marrow is moderately infiltrated with fat. In A2 the cartilage is unduly wide. The areolar spaces of the metaphysis are small and filled with blood vessels. The trabeculae present a more vigorous deposition of bony tissue. The adjacent spongy bone is well formed, and the trabeculae

(OVER.)

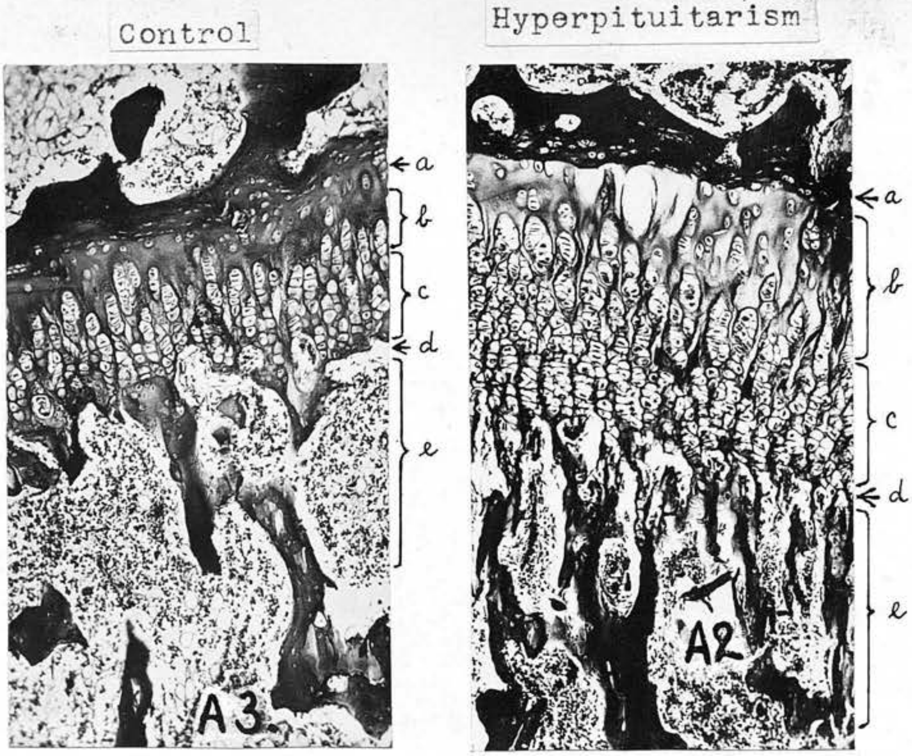
Control
Hyperpituitarism
Hypopituitarism
a
b
c
d
e
A3
A2
A1.

Fig. 48.

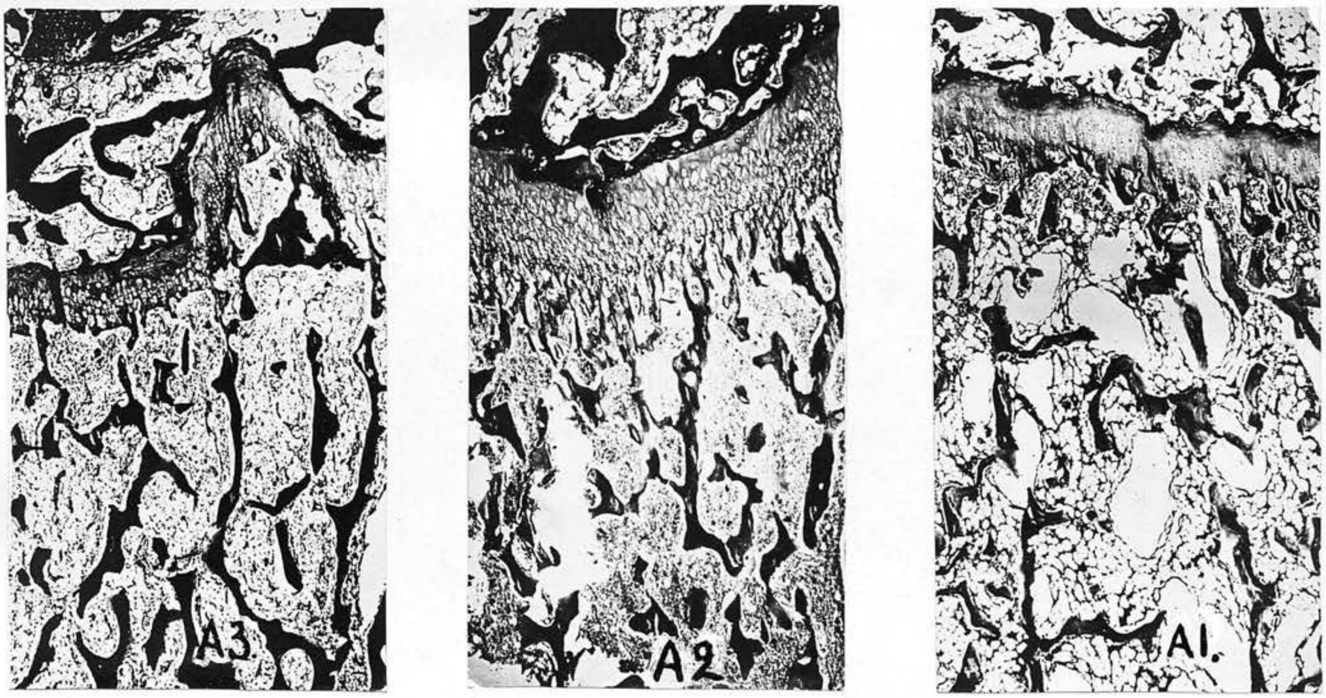
A3
A2
A1.

Fig. 49.

It does not appear justifiable to draw any general conclusions from experiments so incomplete and so few in number as those described above. However, the results so far obtained are of sufficient interest to warrant a more detailed study in the future. They suggest means of approaching the problems of the interrelationship of the pituitary body, the thyroid and the sex glands in their association with pathological states.

Of considerable clinical interest is the accurate reproduction of clinical states of hypopituitarism in the experimental animal, and the striking response to organo-therapy exhibited. A further study of the "thermic reaction" and of the radiographic appearances in the experimental state might render them valuable diagnostic aids in clinical practice.

My thanks are due to Professor Sir Edward Sharpey Schafer for the valuable advice and the many facilities afforded me during this research; to Mr. John Fraser, F.R.C.S., for suggestions, and access to unpublished work of his own; and to Mr. E. Dott, who has acted as anaesthetist throughout.

Mr. F. Pettigrew, of the Surgery Department, took the photographs of the animals; the histological preparations are the work of Mr. W. Henderson, of the Histology Laboratory; and the microphotography has been done by Mr. Chisholm, of the Animal Breeding Research Laboratory.

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