

**THE GROWTH FUNCTION OF THE PITUITARY GLAND
ITS EFFECT UPON THE BRAIN AND BRAIN WEIGHT-BODY WEIGHT RELATIONS**

By
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To Professor Carl L. Davis, gentleman and scholar, who served so untiringly as my teacher, so sincerely as my friend and so valuably as my adviser, this thesis is gratefully dedicated.

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H. S. Rubinstein

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THE GROWTH FUNCTION OF THE PITUITARY GLAND
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PART ONE

INTRODUCTION

Man has interested himself in growth and its abnormalities for so long a time that many of the early classics refer to the gigantic or dwarfed stature of their characters. Thus, the giants of Genesis (VI, 4), Og, king of Bashan (Deuteronomy III, II) and Goliath of Gath (I Samuel XVII, 4) are only a few of the biblical allusions to gigantism. Antaeus the antagonist of Hercules and Polyphemus the gigantic cyclope blinded by Ulyses (Aeneid) are among the myths of the early Greeks. In like manner, the references to the dwarfed gods of Egypt and the early court dwarfs bespeak the attention which these diminutive persons attracted.

The factor responsible for growth, both normal and abnormal, was entirely unknown to the ancients. It remained for the 19th century investigators to correlate this phenomenon with the pituitary gland.

Although the pituitary gland was known to Galen, it was first described by Vesalius (1543) who, because the structure was believed to secrete

the mucous of the nose, named it from "pituita" the Latin for "clammy moisture." This function, however, was disproved by Conrad Victor Schneider (1660) and the gland redescribed by Sommering (1778) who named it from the Greek $\nu\pi\omicron$ under, and $\phi\epsilon\iota\upsilon$ to grow, presumably because of its position beneath the brain (Garrison 1922).

The first instance of abnormal form attributed to the pituitary gland was reported by Bernard Mohr (1840) when he described the case of a patient suffering from obesity, imbecility, loss of memory, somnolence, and visual disturbances who at autopsy showed a tumor of the pituitary gland. Credit for establishing the relationship of the pituitary gland to body length is usually given to Lorain who in 1871 described the first case of infantilism. A study of the literature, however, leads one to the conclusion that such a relationship must have been established only later.* In 1891, Paltauf described the case of a dwarf who possessed an abnormally large sella turcica but he too failed to attribute the dwarfism to hypophyseal pathology.

*Footnote: Some authors (e.g. Engelbach 1932) credit Lorain with first describing pituitary infantilism in 1871. An examination of Lorain's Prefatory Letter to the thesis of Faneau de La Cour (1871) discloses the fact that while infantilism (Lorain type) and conditions resembling persistent juvenility are beautifully described, no mention of the pituitary gland is made. Lorain describes these conditions as occurring in the phthisical.

Although many authentic accounts of gigantism were given from the time of Saucerotte (1772), the classical description of acromegaly is accredited to Pierre Marie who in 1886 described it and later together with Marinesco (1891) correlated it with pituitary tumor. To Minkowski, however, should go the credit for first calling attention to the constancy of pituitary enlargement in the acromegalic patient since in 1887 he wrote "It is noteworthy that in all cases so far dissected and really studied there is to be found together with a greater or lesser hypertrophy of the various internal organs an especially striking enlargement of the hypophysis cerebri." In 1900 Babinski gave the first description of dystrophia adiposo-genitalis but this was described as a clinical entity in a fourteen year old boy by Frohlich in 1901 since which time the condition in adolescence has been termed Frohlich's syndrome.

Thus, although towards the close of the 19th century the pituitary gland was definitely correlated with body length and body weight, little else was known concerning its function. Strides had already been made in the proper direction, however, when Horsley (1886) hypophysectomized two dogs without killing the animals. The controversy which followed through the experiments of Paulesco (1908); Reford and Cushing (1909); and Crowe, Cushing, and Homans (1910) who claimed the hypophysis essential to life has finally been overcome. This has been accomplished through the numerous investigations of Handelsmann and Horsley (1911), Aschner (1912), Benedict and Homans (1912), Sweet and Allen (1913), Camus and Roussy (1913), Brown (1923), Dandy and Reichert (1925), and Philip Smith (1930) all of whom have confirmed Horsley's original work. In addition, out of the maze of these and innumerable other investigations has grown the fact that although the pituitary gland is no longer indispensable to life, it possesses

so many important functions that it may almost be considered the very mainspring of one's existence. Among these many functions growth stimulation undoubtedly stands out, at least, as one of the important ones, but the new era of growth studies which began with the demonstration of the growth hormone by Evans and Long (1921) is still in its infancy. It will be the purpose of this thesis to add just another link to the long chain of investigations along lines of growth.

In order to successfully follow and fully appreciate the more recent studies concerning the growth hormone, it appears advisable to review the salient features of the morphology and development of the pituitary gland.

EMBRYOLOGIC AND PHYLOGENETIC CONSIDERATIONS OF THE PITUITARY GLAND

Although the tunicata (ascidians) possess a subganglionic organ which has been homologized with the pituitary gland of higher forms (Julin 1881), because of histological differences, this homology is now questionable. However, a pituitary gland is found in all true vertebrates and generally speaking its embryological development is similar in all classes. This statement is based upon the mass of evidence which has accumulated through the efforts of numerous investigators. Although a consideration of all this evidence is obviously beyond the scope of this work, it may be reviewed by referring to the works of Haller (1898, 1909, 1910, 1911), who worked with cyclostomes (petromyzon), amphibia (anura) and fish (Salmo irideus and Salmo fario); Kupffer (1903) who studied the cyclostomes (amocoetes and Bdellostoma stouti), fish (Acipenser sturio), amphibian (Rana fusca), reptile (Lacerta vivipara), and the chick (Gallus domestica); Gentes (1903, 1907) who investigated the cyclostome (petromyzon);

Sterzi (1904) who also worked with the cyclostomes (ammocoetes and petromyzon); Stendell (1913, 1914) who studied the dog fish (*Acanthia vulgaris*), the cyclostome (petromyzon), and rodents (*Mus decumanus*); Goette (1874) who worked with amphibians (anura); Rathke (1838, 1839, 1848, 1861) who investigated the reptile and mammal; Herring (1908) who studied the cat (*Felis domestica*); Wilney (1911, 1913), who worked with the crocodile (*Alligator mississippiensis*), opossum (*Didelphys virginianum*) and the baboon (*Cynocephalus babuin*); and Atwell (1926) who studied the development in the human.

As a result of the foregoing and other works too numerous to be mentioned, it may be concluded that, in general, the pituitary complex arises from two distinct structures; namely, the floor of the interbrain (diencephalon) which furnishes the posterior lobe and the roof of the embryonic mouth cavity which is responsible for the rest of the gland (pars buccalis). The latter contributes by sending an evagination towards the diencephalic floor. This evagination which in the human begins in the 3 mm. embryo (Waterston 1926) arises from the ectodermal mouth cavity and in lower vertebrates maintains a connection with the olfactory groove, thereby recapitulating the condition as it exists in prevertebrates (tunicates, amphioxus).

In addition to its ectodermal origin there are those who claim (Kupffer 1903) that entoderm also contributes to the formation of the anterior lobe. Whether or not this is so is still a moot point although Atwell (1926) stresses the difficulty of distinguishing ectoderm from entoderm at the point of evagination at such an early stage. This evagination of the pharynx (foregut) which is termed "Rathke's pouch" in honor of its discoverer (Rathke 1838) occurs normally at a level corresponding to the diencephalo-telencephalic junction.

As the process of evagination goes on, the floor of the pouch becomes more and more removed from the pharynx and its wide mouth becomes converted into a tubular structure which ultimately is replaced by a solid cord. In this way a vesicle is produced which is completely separated from the pharynx and comes to lie adjacent to the floor of the diencephalon. Remnants of the original pharyngeal connection remain as permanent structures in some forms (Stendell 1914) (myxinoids and selachians) where the cartilaginous floor of the skull is traversed by a canal which extends to the mucous membrane of the mouth. This may also explain the "pharyngeal roof hypophysis" ("pharyngeal hypophysis") which has been described in the human by Pende (1911) in which case a glandular portion of the hypophysis is found in the pharyngeal roof. This may be part of Rathke's pouch which has failed to traverse the entire skull floor. Under normal conditions where the floor of the skull is complete, the glandular hypophysis is completely severed from its original pharyngeal connection. In its formation, however, the skull bones surround the hypophysis, thereby furnishing the sella turcica.

The usual vesicular evagination may be replaced in other forms by a solid outgrowth from the pharyngeal wall. According to Stendell (1914) this epithelial bud occurs in cyclostomes (myxinoids) arising from the pharyngeal canal; and in many teleosts and amphibians in whom it springs from the mouth cavity.

Whether the pharyngeal offshoot is originally solid or vesicular by the time it reaches the infundibulum (diencephalic floor), it possesses a cavity which represents either the original vesicular lumen or, as in the case of the solid contribution, one formed during the process of development. This space, known as the hypophyseal cavity, divides the glandular

hypophysis into a pars distalis, the forerunner of the true anterior lobe and the pars juxta neuralis or middle lobe.

The anterior and middle lobes now differentiate to form a complex of epithelial tubules. Connective tissue and blood vessels simultaneously penetrate the intertubular spaces. During this process, the parenchyma of the middle lobe, for the most part becomes more solid due to the lesser amount of vascular proliferation. This leads to the structural differentiation between the middle and anterior lobes.

While these changes are occurring in the anterior and middle lobes, the diencephalic floor begins to contribute its share to the hypophyseal complex. In the human this begins in the 8 mm. embryo as a slight evagination from the neural tube which is directed toward the glandular hypophysis (Waterston 1926). The type of evagination, however, varies with different species. In selachians it sends tubular processes into the intermediate lobe, while in teleosts the tubules are replaced by solid fasciculi. Generally, however, the infundibulum merely thickens and becomes a markedly vascular and sponge-like structure, the neural lobe which, according to Stendell (1914) is capable of absorbing the secretion of the middle lobe. As the neural or posterior lobe passes ventrally its tubular surface is surrounded by lateral proliferations from the buccal contribution. This newly derived portion of the pars buccalis then becomes the pars tuberalis of the hypophysis (Atwell 1926).

Hence, the neural (posterior) lobe comes to lie adjacent to the brain while the main or anterior lobe is separated from the posterior lobe by the intervening middle lobe and hypophyseal lumen. The lumen in most animals remains quite distinct. In man, however, it becomes smaller and smaller until the age of sixteen years when it becomes practically obliterated

(Bucy 1932). Thereafter it is represented by a trabeculated space filled with colloid particles (Guizzetti 1927 - quoted from Bucy 1932).

Finally the glandular tubules of the anterior lobe lose most of their lumens and become epithelial cords. These cords which anastomose freely have their intervening spaces filled by a rich network of blood vessels which receive their secretion. It is this secretion which, in part, concerns itself with the growth processes of the body (Evans and Simpson 1927; 1931; Brouha et Simonet 1930).

THE GROWTH FUNCTION OF THE PITUITARY GLAND

Although the growth function of the pituitary gland was already conjectured by Minkowski in 1887, this was only experimentally proved within the last twenty-five years. The story of the numerous studies which culminated in the crystallization of an originally nebulous concept to the point where the actual elements responsible for growth have been identified is indeed interesting. As Cushing (1932) states "all this seems simple in the telling. Results get recorded, not the slow and painful process beset with discouragements by which they are attained."

It was Hahn (1912) who first noted the relatively and absolutely enlarged pituitary glands in the giant larvae of *Rana esculenta*. This observation was followed by the experiments of Gudernatsch (1912, 1913, 1914), Evans and Smith (1916) and Allen (1916) who confirmed the relationship of the pituitary gland to growth and development. Larson (1919) noted that if anterior lobe of the pituitary gland was injected into animals stunted by thyroidectomy, growth was hastened. If, however, animals were first hypophysectomized and thyroid subsequently injected no growth resulted. This definitely identified the growth effect of the pituitary gland with

the anterior lobe of this gland. Uhlenhuth (1920) in feeding pituitary gland to axolotls noted an increase in growth of the animals only if metamorphosis had already begun. In 1921 this same investigator (Uhlenhuth 1921) confirmed his own work in feeding experiments in which he again noted that only those salamanders which had metamorphosed before the feeding was begun, increased in size, while larval forms failed to respond. In view of these findings it is perhaps timely to mention that to Gudernatsch* (1930), it appears that merely feeding anterior lobe to the tadpole produces increased growth while injections of the same substance results in metamorphosis and growth. Hence, the factor responsible for metamorphosis seems to be destroyed in the amphibian gastro-intestinal tract.

The foregoing amphibian feeding experiments definitely attribute the growth function of the pituitary gland to the anterior lobe. That pars intermedia or posterior lobe take no part in the growth process seems to be indicated from a survey of the literature from which it is noted that attempts to obtain growth with these portions of the pituitary gland led only

*Footnote: Since reference is made to this survey by Gudernatsch (Handbuch der Inneren Sekretion - ed. by Max Hirsch), it becomes necessary to correct a misquotation in this monograph. Gudernatsch (vol. 2 section 8, p. 1606) quotes Uhlenhuth with explaining increased growth upon a basis of increased cell division - quoting "Er (Uhlenhuth) fuhr die Forderung auf eine direkte Beeinflussung der Zellteilung Zuruck, da vorderlappenextrakt auch die Teiligungsgeschwindekeit von Protozoen beeinflusse." In the original article (see Uhlenhuth 1920; 1921), Uhlenhuth not only refrains from such statement but actually quotes literature to the contrary. At the present time, however, it

to failure. The same conclusion is reached from the numerous attempts to increase growth with other endocrine glands. In each case the factor of specificity appears lacking.

In 1910 Aschner, after removing the entire hypophysis of the dog without injury to the tuber cinereum, noted inhibition of growth, infantilism of the skeleton including failure of epiphyseal closure, infantile genitalia, persistence of deciduous teeth, the appearance of lanugo-like hair, fat increase and trophic disturbances. Removal of the posterior lobe alone led to no skeletal defects although trophic disturbances did occur. Suffice it to say that since this time numerous attempts to remove the anterior lobe of the pituitary gland have been made. These attempts have finally been crowned by the success of Philip E. Smith (1930) who devised the ventral parapharyngeal approach to the pituitary gland in the rat. By this method he was able to remove the entire gland or only the anterior lobe and thus to study pure deficiency syndromes. Removal of the anterior lobe in these experiments led to inhibition of skeletal growth, a diminution of sex activity in which the graafian follicles failed to grow in the female, and spermatogenesis disappeared in the male, with atrophy of the adrenal cortex, thyroid and gonads.

The exact substance responsible for the growth stimulating function of the pituitary gland, however, only came to light in 1921 when Evans and Long succeeded in producing such a growth stimulating extract by the

Footnote continued from page 9: seems to be established that the potentiality of a cell to increase in size is fixed by the biologic limit of that cell so that in excessive growth the probability is that cells actually do divide. Studies by Putnam, Benedict and Teel on acromegaly substantiate this view.

use of weak alkaline aqueous solutions of fresh anterior lobe. With this substance they have been able to produce gigantic rats. Since this time, refinements in technique by Putnam, Teel and Benedict (1928) and Van Dyke and Lawrence (1930) have yielded preparations which are bacteriologically sterile and otherwise so harmless that their use on the human has been followed by no untoward effects (Engelbach 1932; Rubinstein 1934). In the rat, however, the extract produces growth response only when injected since Smith (1927) has shown that merely feeding pituitary substance, fails to repair the defects produced by hypophysectomy.

The exact source of the growth hormone may be surmised only from a survey of the histological elements making up the anterior lobe.

HISTOLOGICAL CONSIDERATIONS OF THE ANTERIOR LOBE OF THE PITUITARY GLAND

Microscopically, two distinct cell types are recognizable in the anterior lobe of the pituitary gland, chromophobes and chromophiles. These were so named by their discoverers (Flesch 1884; Lothringer 1886; Dostdiewsky 1885-1886) because of their different staining qualities. While the chromophobes fail to stain deeply, the chromophiles have a great affinity for dyes and have been further subdivided by Schoneman (1892) into acidophiles (eosinophiles) and basophiles (cyanophiles) because of their differently staining granules. Recently Bailey and Davidoff (1925) have shown the terms "acidophilic" and "basophilic" to be incorrect and have, therefore, substituted the nomenclature "cells containing alpha granules" and "cells containing beta particles" respectively.

Collin (1928) studying these different cells anatomically believes the chromophobes (Hauptzelle) to be the mother cell of the two granular

types. The process as described by this investigator allows the primitive agranular cell to acquire large eosinophilic (alpha) particles which may in turn mature into the finely granular basophilic (beta granular) cell. The ripe granular cell then either extrudes its cytoplasm retaining only its cell membrane and nucleus or it may completely degenerate. Those cells which do not degenerate, after extrusion of their cytoplasm, become refilled with an agranular substance which may again mature into the granular types and thus repeat the process. Since Severinghaus (1933) claims to have noted differences in the Golgi apparatus of the eosinophilic and basophilic cells which retain a specific shape even when traced back to the mother cell, it is questionable whether a particular chromophobe is potentially capable of producing both forms.*

Both investigators, however, agree that the chromophobe represents an immature type of cell. More and more evidence is accumulating to support this view.

From the experimental studies of Rasmussen (1921, 1922, 1929), Engle and Severinghaus (1932), Smith, Severinghaus and Leonard (1933) and the clinical observations of Cushing (1932a, 1932) it has become possible to associate the basophilic cells with the sexual function.

*Footnote: According to Severinghaus those cells which are destined to become acidophiles contain a netlike Golgi apparatus which caps the nucleus, while those destined to become basophiles contain ring-like structures which enclose a denser cytoplasm. The mature granular cells maintain this difference in Golgi apparatus.

On the other hand, in pregnancy where the fetus increases its size many times during gestation, the acidophilic cells have been shown to increase in number (Erdheim and Stumme 1909). Although Rasmussen (1929) failed to notice a correlation between body length and the number of alpha granular cells, cases of acromegaly studied by Erdheim (1926) disclosed the association of this condition with acidophilic adenomata. Similar studies by Bailey and Cushing (1928) have confirmed this finding, and in addition, show that the dyspituitarism which does exist is in proportion to the tumors present.

In 1930 Smith and MacDowell studied the endocrine system in naturally dwarfed mice and found that their glands presented the same deficiencies noted in animals artificially dwarfed through hypophysectomy. In addition, it was observed that the anterior lobe of the pituitary gland was free from acidophilic cells. Treatment with anterior pituitary gland restored the deficiency pictures of all other glands to normal. The absence of acidophilic cells in the anterior lobe, however, remained unchanged. For these reasons the eosinophilic cells of the anterior lobe are believed to be the source of the growth stimulating hormone of the pituitary gland.

THE PROBLEM

Since it has been demonstrated that the growth hormone properly extracted and administered, produces increase in body size, the question arose as to whether the brains of such artificially enlarged animals would become proportionately enlarged.

This problem appears particularly interesting since Donaldson (1925) reported that in the human, brains of large men (5'10") are 6% heavier

than those of small men (5'2"), and that this same difference (6%) occurs between corresponding groups of women. He also showed that the brains of males are usually 12% heavier than those of females belonging to corresponding groups. In the human, therefore, the brain of a heavy male may differ from that of a light female by as much as 18%. Furthermore, Sugita (1918) had previously shown that the Norway rat, which is heavier than the albino rat, possesses a brain which is 15%-17% heavier than that of the albino. Finally, Hatai (1908) after an analysis of all his laboratory data, concluded that brain weight is a function of body weight and expressed this relationship in a mathematical equation which will be considered later. Hence, several questions arise concerning the brains of animals subjected to growth hormone. First, does the brain weight increase in proportion to body weight? If it does not show a proportional increase, does it become larger at all? Finally, can the mathematical relationship which normally exists between brain weight and body weight be altered?

Obviously, the solution of these problems resides in the enhancement of body growth beyond normal and a study of the comparative effects of such treatment upon the brains of the animals.

THE CHOICE OF AN EXPERIMENTAL ANIMAL

For the following reasons the white rat (*Mus norvegicus* - var. *albus*) was chosen as the animal to be used in the following experiments.

1. It is easily bred and controls are easily maintained.
2. Its biological position (*Mus norvegicus* - var. *albus*) has been thoroughly established (Hatai 1907) and its mammalian physiology

permits of a closer correlation with man than would a lower species.

3. Its normal growth curve has been studied and plotted (Donaldson 1924) so that deviation of the strain used from the normal may be better appreciated.
4. Its individual organs have been thoroughly studied and normal weights and measurements for these established (Donaldson 1924).
5. Mathematical formulae have been computed for most of its measurements (Hatai 1909; 1910) at given ages so that deviations may be accurately determined.
6. Its brain has been examined and, although relatively simple (lissencephalic), has been found to possess all the fundamental features of man's brain (Tilney 1933).
7. The growth curves of its body and brain have been shown to possess all the phases exhibited by those of the human; even the sexual differences of the two species coincide with each other (Donaldson 1906; 1908). This undoubtedly enhances the significance of results obtained.

For these reasons the white rat (*Mus norvegicus* - var. *albus*) has been used as the animal of choice for the experiments which follow.

THE GROUPING OF EXPERIMENTAL ANIMALS

For these experiments seventeen litters of white rats (*Mus norvegicus*-var. *albus*) were used. These totalled seventy-four animals six to eight months of age, who had already reached the plateau of their normal growth curve. Younger animals were avoided because previous experiments demon-

strated that the growth hormone fails to markedly influence the normal growth process during the early growth period. The animals were divided according to sex and weighed. The lightest males or females of each litter were used as test animals while the two heaviest were used as controls. Thus, only litter mate brothers or sisters were used as controls. The controls of each group were further subdivided so that the heaviest remained uninjected while the lighter of the two received meat extract injections. The grouping as thus described may be noted in table I.*

THE PREPARATION OF THE GROWTH HORMONE

The growth hormone used in these experiments was at first supplied by a commercial laboratory, but this proved unsatisfactory from the growth standpoint so that after the first nine weeks, an extract prepared in this laboratory by a modification of the Putnam, Benedict and Teel (1928) method was substituted. The procedure as carried out in its preparation was as follows:

Fresh beef pituitary glands were obtained from the abbatoir and within an hour the anterior lobes were shelled free from the rest of the gland. These were weighed and ground with sterile sand to a fine paste and to each 100 gm. of anterior lobe were added 400 cc. of $n/20$ NaOH. This was stirred at frequent intervals and then allowed to stand in the refrigerator for 24 hours. The mixture was then neutralized using phenolphthalein as an indicator with $n/5$ acetic acid and centrifuged. The gland residue was discarded and the supernatant liquid was heated in a water bath to 37° C. The proteins of the supernatant fluid were then precipitated by

*Footnote: Thirteen additional animals were used for water and solid content determinations--see page 30

the addition of 20 gms. of sodium sulphate for each 100 cc. of fluid. The mixture was immediately centrifuged and the supernatant fluid discarded. To the precipitate was added sufficient $n/100$ NaOH to make 2 cc. of the final product represent 1 gm. of the fresh anterior lobe.

LABORATORY PROCEDURE

At the beginning of the experiments and each week thereafter all animals were weighed to a tenth of a gram and these weights were recorded as shown in tables II-VII. Linear measurements were not obtained at the outset because exactness could only be obtained by anesthetizing the animals. Since, anesthesia might have altered the growth function of rat for the time being, this procedure was deemed inadvisable. Furthermore, the rats used compared favorably with the Wistar Institute strain from which they were originally obtained. Since it has been shown for this colony (Donaldson 1924) that body length is a function of body weight, comparisons in linear measurements could be made indirectly.

All animals were kept in similar surroundings and were fed the standard rat diet #1 of Evans and Bishop (1922) to which carrots and lettuce were added once weekly. Water was constantly kept before the animals.

The test rats received daily (except Sunday) intra-peritoneal injections of 2 cc. of the growth hormone while a similarly prepared meat extract was injected into one set of controls. The other of the two sets of controls remained uninjected.

At the end of the experiment, the animals were weighed and then sacrificed by anesthetization with ether and bleeding through the common carotid and jugular vessels. This procedure was found advantageous since

it minimized the amount of blood in the brain which ordinarily remains stagnant when other modes of sacrifice are utilized.

The animals were then measured. This was accomplished by laying each animal flat on its back and extending the head until the dorsum of the snout touched the table. Body length measurement was then taken with calipers between the tip of the snout and the anus, and tail length measurement determined between the anus and tip of the tail.

The skull was then opened by removing the calvarium and the brain dissected out with the olfactory bulbs intact. All other cranial nerves were clipped close to their points of emergence from the brain stem. The brain was then severed from the spinal cord just above the level of the first cervical spinal nerve and immediately placed in a weighing bottle and its weight determined. The pituitary gland was then removed from the sella turcica and added to the weighing bottle containing the brain and the whole reweighed, thus determining the pituitary weight. Then by a simple process of water displacement, previously described (Rubinstein 1932), the volume of the brain was determined.

METHOD OF EVALUATING RESULTS

All observations made in these studies were recorded separately for each group and their significance tested by treating them on a statistical basis. The statistical method used was that usually employed as described by Pearl (1930). This consisted in obtaining the arithmetic mean, deviation from the mean for each observation, squaring each deviation, totalling these squares and then applying the formula

$$\sqrt{\frac{\sum dx^2}{n-1}}$$

where the numerator represents the sum of the deviations squared, and the denominator represents one less than the total number of observations (for small series).

The result thus obtained represents the standard deviation which is denoted by the Greek letter σ .

In these computations $2/3 \sigma$ was used as the probable error of each observation. This simple formula was substituted for the more exact but rather intricate formula of Bessel where

$$\text{P. E. of a single observation} = .6745 \sigma$$

because computation based upon the relatively few animals used in these experiments at best merely leads to an approximation of the true error. Since $2/3$ is a fairly close approximation of .6745, it was substituted for the latter.

The probable error of the arithmetic mean was then obtained by the formula.

$$\frac{\text{P. E. of single observation}}{\sqrt{n}}$$

Comparisons of observations were then made between the "mean \pm P. E. of the mean" of the test animals and the uninjected controls and between the two sets of controls. This was done by the method as represented by the formula:

$$\frac{M_1 - M_2}{\sqrt{(P. E._{m1})^2 + (P. E._{m2})^2}}$$

where M_1 and M_2 represent the means of the respective groups and the denominator represents the square root of the sum of the squares of the respective probable errors.

This led to the "critical ratio" which had to approximate at least "3" before the difference noted between the two sets of animals was considered statistically significant.

A CONSIDERATION OF THE INITIAL BODY WEIGHTS

Before examining the final body weights and growth curves of the animals, it may be of interest to see how the weights of the different groups of animals compared with each other before experimentation. This will permit a greater appreciation and a more accurate evaluation of comparisons between the groups at the end of the experiments. For this purpose table VIII has been constructed.

From this table it may be noted that at the onset of experimentation, the test animals represented the lightest (in weight) group, while the uninjected controls made up the heaviest groups. The controls injected with meat extract represented a group which as far as weight was concerned, occupied a position between the test group and uninjected controls. This same arrangement has been maintained throughout the work so that all "tables" are constructed similarly. The third column of table VIII shows the average deviations in body weights of the male and female test animals, and meat injected animals from their uninjected controls. Column 4 of this same table shows that when these deviations are considered with their probable errors, that they yield critical ratios of 6.56 and 5.35 for the male and female test animals respectively, showing that these animals are significantly lighter than their controls at this time. The critical ratios of 2.68 (almost 3) and 3.64 respectively for the male and female meat injected controls, likewise, show that these sets of controls

were significantly lighter than the uninjected animals at the onset of these experiments.

FINAL BODY WEIGHTS

From table IX it may be seen that at the end of the experiment, the test males average 43.1 gms. heavier than their uninjected controls and that the test females average 75.7 gms. heavier than their uninjected controls. It is interesting to note further that the relationship between the two sets of controls for both sexes was practically the same as at the beginning of the experiment in that the male and female meat injected controls were 12.9 gms. and 11.5 gms. lighter than the respective uninjected controls. These figures agree almost exactly with corresponding figures at the onset of the experiments. A consideration of the critical ratios as shown in this table again discloses the significance of these differences. The striking fact noted when this table is compared with table VIII is that while the test animals showed a change from a significantly lesser weight to a significantly heavier weight, the weight ratios of the two sets of controls for both sexes remained practically unaltered. This may be best appreciated from table X which discloses the average "body weight increases" for all groups of animals.

AVERAGE BODY WEIGHT INCREASES FOR ALL GROUPS

When table X is considered, it is at once discernible that the male and female test animals gained 73.9 gms. and 94.6 gms. over their respective uninjected controls. Column 2 of this table shows that the aver-

age gain in grams for the two sets of controls was practically identical. Consideration of the critical ratios (column 4) discloses the important facts that while the deviations of the test animals from their controls were highly significant, any differences noted between the two sets of controls were negligible.

These differences in growth response may best be represented by graphs constructed on the basis of weekly weight changes of all animals shown in tables II-VII.

GROWTH CURVES (GRAPHS OF WEIGHT CHANGES)

Figs. 1 and 2 represent the average weight changes of all the males and females throughout the experiment. In both sexes at the end of the experiment the test animals, which were the lightest to begin with, exceeded by a fair margin the weights of the two sets of controls. The weight curves of the two sets of controls seem to parallel each other throughout the twenty-two weeks. Two phenomena present themselves when the growth curves of the test animals are examined. It appears that these animals did not gain as rapidly during the first nine weeks. This is more striking in the females than the males. Then again, it may be noted that the growth is not a steady climb but interrupted here and there with plateaus or actual recessions. These phenomena are not only noted in the groups taken as a whole (figs. 1 and 2) but also in individual animals (figs. 3, 4 and 5). The weak growth response during the first nine weeks is attributed to the fact that the extract used during this period was received from an outside laboratory so that it may have lost most of its potency by the time it reached this laboratory. The interruptions in the ascent of the curves are attributed to a diminution in growth stimulating

power of the hormone produced in this laboratory. These untoward phenomena have been shown to be due to inadequate refrigeration and exposure of the extract to air (Rubinstein 1933, 1934).

The outstanding impression that one gains from all the graphs presented is that the animals which received the growth hormone underwent body-weight increases over and above normal as judged by their controls.

AVERAGE FINAL BODY AND TAIL LENGTHS

Since it has been shown that a definite amount (8%) of this gain in body weight is due to the accumulation of water (Downs and Geiling 1929), it becomes important to note that true growth also occurs as judged from the increase in body lengths and tail lengths of the test animals. A comparison of the different groups of animals may be obtained from table XI from which it is seen that the growth hormone actually increases the length of the animal. This tendency is greater in the female than in the male and in this respect coincides with body weight responses of the two sexes.

While, as previously mentioned, actual measurements of body and tail lengths were not obtained at the beginning of the experiment, the work of Donaldson (1924) which establishes a definite ratio between body weight and body length and between body length and tail length supports the statement that at the outset of these experiments, the body lengths and tail lengths of the test animals were definitely less than those of the controls. This statement is based upon the fact that at the beginning of the experiments, the test animals were always lighter than either of the two sets of controls (table VIII). From table XI it may be noted that the test animals actually exceeded the controls in body and tail lengths. The significant fact here is that every animal which gained in body weight also gained in

total length (Rubinstein and Kolodner 1934). Incidentally, it may be noted if one considers the critical ratios in table XI that the meat extract significantly suppresses tail growth in the female.

X-RAY EVIDENCE OF GROWTH

An examination of figures 6-11 which portray the roentgenographs of three test animals and their litter mate controls demonstrates the larger size of the animals treated with the growth hormone. These illustrations represent those animals whose weekly weight changes are depicted in graphs 3-5 and show that the skeletons of the test animals are larger in all dimensions than those of their controls.

THE RESPONSE OF THE VISCERA TO THE GROWTH HORMONE

Although the viscera of these animals were not subjected to critical measurements, those of the test animals were obviously larger than those of their controls. In this respect these observations agree with those of Putnam, Benedict and Teel (1929a) who also noted a generalized splanchnomegaly in the dog treated with growth hormone. On the other hand, the response of the brain to the growth hormone differed materially from that of the rest of the body as shown by the following.

FINAL MEAN BRAIN WEIGHTS

An examination of table XII discloses the fact that the brain weights of the test animals at the time of sacrifice did not differ significantly from those of their controls. It may be further noted

that the brain weights of the uninjected controls were heavier than those of the test animals. Since, generally speaking, the heavier an animal the heavier its brain (Donaldson 1924; Hatai 1908), this observation agrees with their initial body weights and, hence, appears to correspond to the brain weights of these two groups if all animals would have been allowed to grow normally. The fact that the final brain weights exhibit this phenomenon favors the assumption that they did not keep pace with the general body weight increase as exhibited by the test animals.

In addition, this table further shows that the final brain weights of the female meat injected controls were lighter than those of the test animals of the same sex. This, of course, is not in agreement with their initial body weights since to begin with, this set of controls was heavier than the test animals and if all animals had grown normally their brains should really be heavier than those of the test animals.

However, since any differences which do exist, if judged by their small critical ratios, are insignificant, one may safely conclude that the brains of all groups, so far as final weight is concerned, are essentially similar.

THE MEAN BRAIN WEIGHT-BODY WEIGHT RATIO

Since the brain weight normally increases to a relatively lesser extent than the body as the weight of the body becomes heavier, as has been advocated by Hatai (1908), Donaldson (1924) and others, a consideration of the brain weight-body weight ratios of all groups of animals should show a relatively smaller ratio for the larger animals. However, if growth were similar in all groups, proportional changes should occur in all

groups and no significant difference should exist between the groups at any given time.

Calculations have been made according to the formula $\left(\frac{\text{brain weight}}{\text{body weight}} \%\right)$ and their results have been tabulating in table XIII. It may be seen from this table that the brain weight-body weight ratios of the test animals are significantly smaller than those of the controls. A comparison of the same ratio between the two sets of controls fails to show this difference. Since the test animals at the end of the experiments were significantly heavier than their controls (table IX), the smaller brain weight-body weight ratios of these heavier animals must be due to their relatively smaller brains. In addition, although the test males possessed the smallest ratios, the test females showed the greatest deviation (-.2201 gms.). Obviously as the body grows larger and larger, the rate of growth of the brain becomes less and less so that an extremely large body would have a smaller brain weight-body weight ratio than a smaller body. This fact coincides with the small ratio of the test males since these animals were the heaviest of all at the time of sacrifice. However, since the brain weight-body weight ratio of the test females showed the greatest deviation from that of their controls one may conclude that their body weights were increased to a greater degree than were the body weights of the males. This is in agreement with the data presented in table X where gains in body weight are tabulated.

THE MEAN BRAIN WEIGHT-BODY LENGTH RATIO

Added indirect evidence that the brain weights of all groups remained essentially unaltered as a result of this experimentation is af-

forded from a consideration of table XIV. This table which considers brain weight-body length ratio for all groups was computed according to the formula $\left(\frac{\text{brain weight}}{\text{body length}}\right)$ and takes its significance from the fact that normally brain weight increases with an increase in body length. The close agreement of the two sets of controls shows the accuracy of this ratio in normal animals.

One may reverse the argument and, instead of using this table as a proof that the brain weights of the test animals remained unaltered, disclose thereby the fact that the body length of the test animals did increase over that of their controls. In addition, by a comparison of critical ratios as presented in tables XIII and XIV, it may be surmised that the actual gain in body weight is definitely greater than the gain in body length. This is again in agreement with the work of Downs and Geiling (1929) who showed that some of the increased body weight was really due to water accumulation rather than tissue increase.

MEAN BRAIN WEIGHT-TAIL LENGTH RATIO

Like body length, tail length is also increased by the administration of growth hormone (Rubinstein and Kolodner 1934). As a matter of fact, the increase noted in this caudal appendage is so nearly like that of the body that this fact has already been brought out to show that the rats do not grow absolutely normally*(Rubinstein 1934b). Since, however, such growth is evident, the brain weight-tail length ratios have been computed

*Footnote: It must be recalled that as rats grow normally their tails become relatively smaller.

according to the formula ($\frac{\text{brain weight}}{\text{tail length}}$) and the results tabulated in table XV.

From this table, it is evident that while the ratios of the two controls do not differ significantly, those of the test animals show a definite deviation from the normal. This may be interpreted as signifying a definite increase in tail length but unaltered brain weight.

MEAN BRAIN VOLUMES

It is obvious that a body may become larger i.e. grow and yet, not actually become heavier. Since those (test) animals which had become heavier in body weight and larger in body proportions than their controls possessed brains which had not increased in weight over those of their controls, it is interesting to note whether any volumetric increase of the brains occurred. This could easily take place if the specific gravity of the brains were diminished. Also, since brain size and skull size are proportional (Davis, J. B. 1868) and, since grossly, the skulls of the test animals become larger than the controls', it would appear possible that the brains of the test animals might take on water and thus swell enough to maintain their original proportional relations. Hence, volumetric determinations are quite relevant before conclusions may be drawn concerning true brain growth.

As previously mentioned, the volume of each brain was determined by the water displacement method (Rubinstein 1932) and results computed as explained and their means compared in table XVI. This table shows that the brains underwent no significant volumetric change.

MEAN BRAIN SPECIFIC GRAVITIES

Since brain weights and brain volumes were statistically the same in all groups, it appears that specific gravities should likewise be quite similar. That this is borne out may be seen from the results tabulated in table XVII. It may be noted here that none of the critical ratios equals 3, although that for the meat injected female controls does approach this figure (actually 2.17). This seems to indicate that there is a definite trend towards an increase in brain specific gravity for this group of animals.

While the specific gravities of the brains of our control rats (1.052 for males and 1.057 for females) differ noticeably from the figures quoted by Smith (1930) who concludes that the density of the rat brain coincides with the human's, they are supported by the earlier work of Reichert (1906). The latter concluded that the brain specific gravity for the rat varied from 1.050 to 1.056 while that for the human varied between 1.032 and 1.046. Since the cerebral cortex has a somewhat lower specific gravity than the white matter (Kappers 1926), any appreciable alteration in their relative quantities would manifest itself by a significant change in specific gravity of the brain. It appears, however, that the figures for our animals, whether they agree or disagree with those of an outside strain of rats, do agree for all groups themselves. It is, therefore, concluded on the basis of these specific gravity studies that no significant alteration in cortex or white matter occurred in the brains of the test animals.

THE WATER AND SOLID CONTENTS OF THE BRAIN

In 1916, Donaldson (1916, 1916a, 1916b) showed that as an animal (rat) becomes older, myelinization increases and, paralleling this increase in myelinization, there is a decrease in water content of the brain. Since all indirect methods and calculations in the experiments herewith submitted point toward the fact that the brain remains essentially unaltered as a result of the growth hormone, it appeared advisable to analyze the water and solid contents of the brains. For this purpose thirteen animals were chosen and divided into three groups so that the lightest (in weight) five received the growth hormone while the heavier eight were used either as the uninjected or meat injected controls as previously explained. The same extracts were used and similarly administered for twenty-two weeks at the end of which time the animals were thirteen months old. The brains were then removed by the method already described and these were immediately weighed in a stoppered bottle and placed in a dessicator at 90° C. where they were kept until their weights were constant.

The results of such a study showed that while the test animals gained appreciably in body weight over their controls, their brain weights were lighter and coincided with their lighter initial body weights. In addition, the percentage of water as determined by weighing after dessication was 77+% for all groups. The solid matter of the brains were, therefore, 23-% for all groups.

According to Donaldson (1924) the albino rat of one year has a brain water content of 77.5%. Since, as mentioned above, the water content of the brain gradually diminishes with age, somewhat smaller percentages of water in the brains of our thirteen month old rats (77.01%-77.36%) agrees very closely with Donaldson's normals.

On the basis of these experiments it was concluded that

1. "The growth hormone fails to increase the size of the brain in proportion to the body.
2. The water and solid contents of the brains of animals treated with growth hormone remain within normal limits, as judged by their controls." (Rubinstein and Fox 193-).

BRAIN WEIGHT-BODY WEIGHT RELATIONS

It is evident from the foregoing that the general body dimensions have been augmented and brain structure essentially unaltered by the growth hormone. It is obvious, therefore, that brain weight-body weight relations in the test animals have been definitely changed. The observations upon which this conclusion was originally based (Rubinstein 1932) have been extended in the present work as shown in table XIV which amply confirms the previous findings. For this reason it appears advisable to review the literature on brain weight-body weight relations and see how well these relationships are established and to note how the present experiments have influenced them.

In the past the size of the brain has been considered as closely correlated to three properties of the individual. These are:

1. the complexity of the central nervous system as judged by the greater cephalization as the phylogenetic scale is ascended;
2. the size of the body, including weight, stature, muscular and skeletal development; and
3. the intellect - which is used here to denote the synthesizing and integrating power of the individual as contrasted to mere sensory perception.

An analysis of the literature discloses the fact that while the degree of cephalization and body size are definitely linked with the size of the brain, differences of intelligence within a given species, have little if any relation to brain weight.

Although in the work with the growth hormone, intellectual differences of the animals were not studied and should not be discussed at this time, this phase of the subject, will for the sake of completeness, be appended (see Appendix I) as part of this survey.

THE RELATION OF BODY SIZE TO BRAIN WEIGHT

The work of Donaldson (1895; 1908; 1924), Lapicque (1907), Hatai (1908) and Sugita (1918) has firmly established the close relationship which exists between body size and brain weight. In contrast to the low correlation coefficient ($0 \pm .6$) which was established between intelligence and brain weight, Pearl (1905) found the coefficient of correlation between brain weight and body weight to be $.1671 \pm .0343$ and $.2260 \pm .0412$ for the male and female Bavarian brains respectively. While these figures are relatively low in comparison to the maximum coefficient of 1., yet these represent the result on weights taken post mortem, upon patients many of whom were undoubtedly emaciated. However, when studied in the white rat where brain weights and body weights were obtained under the best of laboratory conditions, the coefficient of correlation as determined by Donaldson (1908) is as high as $.7639 \pm .0108$.

One of the earliest attempts to correlate the brain with body size occurred when Brandt (1867) compared animals of similar intelligence but of different size with each other and concluded that their brain volumes were proportional to their body surfaces. The first attempt to consider this relationship on a scientific basis was made by Snell (1891) who applied to this field the geometrical fact that two similarly shaped bodies of unequal sizes but of equal densities, have surfaces which are related to each other as the (.66) power of their volumes or weights.

The mathematical basis for this principle has been dealt with elsewhere (Rubinstein 1934e) and may be denoted by

$$\frac{S_1}{S_2} = \frac{V_1^{2/3}}{V_2^{2/3}}$$

where S_1 and S_2 represent the respective surfaces and V_1 and V_2 the respective volumes of the two objects. Hence, if Brandt was correct in claiming the brain proportional to body surface, and if body volume is proportional to body weight, this formula may be replaced by

$$\frac{E_1}{E_2} = \frac{P_1^{2/3}}{P_2^{2/3}}$$

where E_1 and E_2 represent the respective brain weights (or volumes) and $P_1^{2/3}$ and $P_2^{2/3}$ represent the respective body weights to the $2/3$ power.

Accepting this formula, Dubois (1898) substituted x for $2/3$ in an attempt to determine empirically the true value of the power to which body weight (P) had to be raised. This was done by converting the equation

$$\frac{E_1}{E_2} = \frac{P_1^x}{P_2^x} \quad \text{or} \quad \frac{E_1}{E_2} = \left(\frac{P_1}{P_2}\right)^x$$

to its logarithmic form

$$\log \frac{E_1}{E_2} = x \log \frac{P_1}{P_2} \quad \text{or}$$

$$\log E_1 - \log E_2 = x (\log P_1 - \log P_2)$$

and solving for

$$x = \frac{\log E_1 - \log E_2}{\log P_1 - \log P_2}$$

Substituting the brain weights and body weights collected by Weber (1896), Dubois thus found x to be .56 instead of .66 for different species of mammals. Since this time other studies among other mammals (Lapicque 1898), birds (Lapicque and Girard 1905) and lower vertebrates (Dubois 1913)

have confirmed and thus established the value of this exponent for brain weight body weight relations between animals of different species to be .56.

When, however, comparisons were made between different sized animals of the same species (e.g. 2 dogs etc.), the exponent was shown to be much lower, ranging between .22 and .28 (Lapicque 1907; 1908; Dubois 1898). The lower values .22 to .24 were constantly found in the domesticated species and is believed to be the result of domestication (Klatt 1921). This lower exponent for the domesticated animals is in keeping with the observations of Sugita (1918) and Donaldson (1924) who found smaller brain weights for the domesticated rat and was explained by Kappers (1929) as due to the deteriorating influence of domestication upon the brain.

Because of this wide difference between the brain weight-body weight relation exponents of animals of different species (.56) and animals of the same species (.22--.28), the former has been named the interspecial--or phylogenetic exponent while the latter (.22--.28) has been called the intraspecial--or ontogenetic exponent.

It is now interesting to apply the foregoing to the data on brain and body weights as shown in tables IX and XII in an attempt to see whether this relation exponent has been altered in the test rats.

Since .22 represents the lowest intraspecial exponent for domesticated animals, this figure was accepted for the uninjected controls.

Then letting

E_1 = the brain weight of the uninjected control males

E_2 = the brain weight of meat injected control males

P_1 = the body weight of uninjected control males

P_2 = the body weight of meat injected control males

the ontogenetic exponent may be determined for the meat injected animals.

Letting the exponent of P₁ (i.e. x₁) = .22 in the formula

$$\frac{E_1}{E_2} = \frac{P_1^{.22}}{P_2^{x_2}} \quad \text{and solving for } x_2 \text{ thus:}$$

$$\log E_1 - \log E_2 = .22 \log P_1 - x_2 \log P_2$$

$$x_2 \log P_2 = .22 \log P_1 - \log E_1 + \log E_2$$

$$x_2 = \frac{.22 \log P_1 - \log E_1 + \log E_2}{\log P_2}$$

Applying the last equation successively to all the other groups by allowing the "sub-two" letters to represent the brain and body weights of the group to be determined, it was found that for the:

meat injected males, the exponent = .217

meat injected females, the exponent = .218

hormone injected males, the exponent = .210

hormone injected females, the exponent = .208

Hence, although the meat injected controls possess relation exponents which approximate that of the uninjected controls (.22), the test animals show exponents definitely lower (.21). Since the probable errors of these differences have not been calculated, the exact statistical significance of the lower ontogenetic exponents in the test animals can not be fully evaluated. However, since we know that the body weights of these (test) animals have increased and their brain weights have not, it appears that there is a definite trend towards the lowering of this exponent in the artificially enlarged (test) animals. One may thus conclude that increase in body size due to artificial stimulation is a factor

which will lower the exponent in brain weight-body weight relations. It seems logical to conclude, therefore, that the lowered exponent in domesticated animals is not only the result of a deteriorating influence upon the nervous system (Kappers 1929) but is also influenced by the added corpulence which ensues upon domestication of wild animals. If civilization can be considered a form of domestication this fact is substantiated by the bulkier bones possessed by civilized races when compared to the savage (Hanger 1921).

It is true that many lower animals, as the rat for example, possess heavier bodies and heavier brains when in the wild state (Donaldson 1923) than they do in captivity but here we are dealing with animals who are not only influenced by domestication but whose free activities and muscular development are hindered by the limitations set by cages. If one compares the growth curves of the domesticated albino rat with its wild relatives (*Mus norvegicus*), as has been done by King (1923), the effect of domestication is immediately noticed not only upon the final body weight but upon the entire curve. In the rat, it is true that domestication leads to a lowering of final body weight--but the domesticated rat shows a more rapid early growth period so that up to about two years of age it is heavier than the wild animal. These calculations are made on domesticated rats less than 15 months of age so that for this age, they are heavier than the wild rat.

THEORETICAL BRAIN WEIGHT

Since it has been shown that normally growing animals of the same species possess brain weights which are relative to their body weights, it is interesting to compare the observed brain weights with the theoretical. It has been shown (tables IX and X) that although the body weights of the test animals were significantly enlarged, their brains as judged from gravimetric, volumetric and analytical studies failed to differ from the normals. It is interesting, therefore, to compare the observed brain weights with those which theoretically should serve for these artificially enlarged animals if they had grown normally.

That such theoretical brain weights may be calculated for the rat has been shown by Hatai (1908) who did so after an extensive study of the rat colony at the University of Chicago. This study resulted in the formulation of a mathematical equation which has since been extensively applied to this field.

The Hatai formula is of fundamental importance in brain weight-body weight studies (in the rat) because unlike "brain weight-body weight ratios" or "exponents of relation" it expresses brain-body weight relations not only at a given time, but for any point on the growth curve.

This was accomplished by assuming

$$y = f(x).$$

where y = brain weight and x = body weight.

By inspecting the growth curves of brain and body weights plotted upon one another it was seen that the rate of growth of the brain decreased as the body weight increased. In other words the brain grew more rapidly while the animal was young than during successive later periods. Hence,

denoting rate of brain growth by dy and rate of body growth by dx , the growth rate ratio of the two was expressed by

$$(1) \quad \frac{dy}{dx} \propto \frac{1}{x}$$

and was put into an equation by using the constant k , thus

$$(2) \quad \frac{dy}{dx} = k \frac{1}{x}$$

From this growth rate equation it is seen that when x is small

$$\frac{dy}{dx} \text{ is large --i.e. for very small body weights,}$$

brain growth is very rapid. Conversely, when x becomes very large, $\frac{dy}{dx}$ becomes very small so that for large body weights, the rate of brain growth is very small. From equation (2), it is obvious that

$$(3) \quad dy = k \frac{1}{x} dx \text{ so that } y \text{ may be evaluated by}$$

$$\int dy = k \int \frac{1}{x} dx,$$

whence

$$(4) \quad y = k \log x + C$$

Placing equation (4) in its exponential form

$$\log x = \frac{y-C}{k}$$

so that

$$(5) \quad x = e^{\frac{y-C}{k}}$$

shows that as y becomes very large, x does likewise, which signifies that large brains are associated with large bodies.

The two constants (k and C) of equation (4) were determined by the method of least squares and after consideration was made for the conversion of the natural logarithm to the common logarithm, the formula became:

$$(6) \quad y = .569 \log x + .554$$

It was found however that when body weight was small, formula (6) led to too large a value for brain weight. This could have been surmised from the discussion of the growth rate equation (2) at which time it was mentioned that as $x \rightarrow 0$, $\frac{dy}{dx} \rightarrow \infty$. In order to overcome this from the practical standpoint another constant empirically determined had to be introduced into equation (6) so that in its final form brain weight

$$(7) \quad y = .569 \log (x - 8.7) + .554.$$

By means of this formula (7), the theoretically correct brain weights for all the animals were computed.* These theoretical weights were compared to the actual weights as determined by weighing and the differences noted.

From table XVIII it may be seen that the mean theoretical brain weight of the male test animals was .0757 grams heavier than their mean actual weights; and the corresponding comparison for the female test animals showed .0445 grams in favor of the theoretical brain weights. On the other hand, the calculated brain weights of the male and female uninjected controls were less than the respective actual weights. The facts

*Footnote: Since the brain weight of the male rat is about 1.5% heavier than that of a female rat of corresponding weight, values obtained for y are increased by .75% for males and decreased by .75% for females.

show that while the artificially enlarged test animals had brains which were lighter (in weight) than the theoretical normal, the control animals possessed brains which, if anything, were heavier than the theoretical. In the case of the meat injected controls, the mean theoretical brain weight of the male animals was only .0167 grams heavier than the observed average weight. This same computation carried out for the meat injected females showed the mean theoretical weight to be less (by .0138 gms.) than the observed mean. In this respect, the female meat injected controls agree with the uninjected male and female controls.

When these theoretical deviations from the observed brain weights are compared with each other (table XVIII) it is seen that the male and female test animals differ from their controls by +.0778 gms. and +.0765 gms. respectively while similar comparisons between the two sets of controls show differences of only +.0188 and +.0181 grams for the respective sexes. How significant these differences are may be gathered from a consideration of the critical ratios which show that the differences noted for the test animals are quite significant (critical ratio = 3.63 and 3.46 for males and females respectively), while those differences existing between the two sets of controls are not beyond the confines of random sampling.

This statistical analysis of the foregoing set of observations and calculations indicates that the artificially enlarged animals possessed brains which were significantly smaller than those which are theoretically normal for such animals. The differences as shown in table XVIII are the more reliable since no significant differences were noted between the controls.

Although such statistical computations were not carried out for all the organs of the body, it was previously mentioned, that in agreement

with the observations of others (Putnam, Benedict and Reel), the test animals did present a generalized splanchnomegaly.* Hence, if this were the whole story, one might conclude by saying that with the exception of the brain all organs join in the gigantism which results from hyper-eosinophilic pituitarism. However, if we consider the pituitary gland as a part of the brain it may be said that the brain itself is not completely immune to this influence as will be shown by the following data.

THE EFFECT OF THE GROWTH HORMONE UPON THE PITUITARY GLAND

In the course of these studies it was noted that the pituitary glands of the artificially enlarged (test) animals showed a distinct reactive difference depending upon the sex of the animal (Rubinstein (a)). This difference was so striking and interesting that the data obtained were subjected to the statistical methods previously described in order to test their significance.

It has been definitely shown by now (tables VIII and IX) that the test animals had become significantly heavier than their controls. From these tabulations it was noted that the differences which initially existed between the two sets of controls remained unaltered throughout the experiment. On the other hand, when the test animals were compared with the controls, it is to be recalled that the differences between these groups actually changed from an initial minus--to a final plus-difference in favor of the

*Footnote: The recent work of Collip, Selye and Thomson (1933) seems to indicate that the liver does not increase in size.

test animals. The unchanged differences and critical ratios of the control groups suggest a parallelism in the slopes of the growth curves for these groups, indeed, when these curves were plotted out (figs. 1-5) such was found to be the case. On the other hand, the change in sign of the "deviation from the control" from a minus to a plus for the test animals shows how much larger the slopes of their growth curves had become. This deduction likewise is borne out by figs. 1-5. The significance of this difference may be more immediately appreciated from the critical ratios of table IX. In addition to weight increase, as previously shown (table XI) total lengths of the test animals were also definitely increased beyond those of their controls.

With these facts in mind; namely, that general body size was increased in both sexes, more so in the female, however, than in the male by the administration of the growth hormone, we may now examine the data as shown in table XIX.

THE MEAN FINAL PITUITARY WEIGHTS OF ALL GROUPS

A study of the final pituitary weights as tabulated in table XIX shows that these averaged .0033 gms. heavier in the male test animals than in the uninjected controls. The difference between the two control groups was insignificant as shown by the small critical ratio of .23. In the females, on the other hand, the test animals possessed pituitary glands averaged .0003 gms. below those of the uninjected controls. This difference as shown by the small critical ratio (.43) is insignificant.

However, when the differences of the pituitary glands are considered between the two sets of female controls it may be noted that the difference

is .0021 gms. in favor of the uninjected controls. This difference divided by its probable error of -.00073 leads to the significant ratio of 2.88 (almost 3) and, therefore, approaches the limit which was set as the criterion for significant results.

Briefly stated, then, the above denotes a significant weight increase in the pituitary glands of the male test animals and a significant weight decrease in the pituitaries of the female meat-injected controls. The evaluation of these findings will be attempted below.

THE NORMAL PITUITARY GLAND OF THE RAT

The pituitary gland of the albino rat for the first 40 or 50 days of life is of the same weight (in relation body weight) in the two sexes. Thereafter, the hypophysis of the female becomes progressively heavier than that of the male so that the difference becomes more and more marked until the plateau of the body growth curve is reached. At this time the pituitary gland of the female is 4 or 5 mgm. heavier than that of the male (Donaldson 1924). That the animals of this series compare favorably with these accepted normals may be seen from table XIX from which it may be noted that the hypophysis of the female averaged 5.4 mgms. more than that of the male.

Whatever may be the cause for this relatively normally heavy pituitary gland in the female albino rat, it can not be a sex difference since no such difference exists in the wild Norway rat (*Mus norvegicus*). Furthermore, it can not be associated purely with albinism since this sex difference does not exist in the albino rabbit or albino guinea pig.

Hence, at the present time this phenomenon can not be explained, although,--since Donaldson holds the "very heavy hypophysis in the female"

to be the only outstanding characteristic of the albino rat as an albino-- it may be a mutation.

DISCUSSION

Although the test animals were initially significantly smaller (in weight and length) than the control groups, at the end of the experiment they were significantly heavier and showed an average body weight increase which was much in excess of that of the controls. These changes were unmistakably reflected in the growth curves of these animals (figs. 1-5) and in their final body lengths.

In addition Roentgen ray studies showed that the dimensional increase of the test animals was quite generalized. An examination of the viscera disclosed a general splanchnomegaly but this was not critically studied.

Final brain weight studies, however, disclosed the fact that the brains of the artificially enlarged test animals did not gain in weight to a degree consistent with what would be considered normal if these animals were growing without stimulation.

In an earlier communication (Rubinstein 1932a), it was concluded on the basis of experimentation "that the brain is less responsive to the growth hormone than the body as a whole." This statement, however, did not preclude the possibility that the brain did enter into the growth process but to a proportionately lesser degree than the rest of the body. However, on the basis of brain weight-body weight ratios, brain weight-body length ratios, water and solid contents and a study of the volumes of the brains, it may now be stated that the conservatism exhibited by the

brains of animals treated with growth hormone is not only relative but absolute. In other words, one may say that the brains of such animals fail to grow at all in excess of that which is considered normal.

Obviously, the enlargement of body without corresponding enlargement of the brain leads to an alteration of the normal brain weight-body weight relations. This alteration is reflected both in the ontogenetic (relation) exponent (p.56) and in the theoretical brain weight. In the former case where the DuBois formula ($E_1:E_2: :P_1^{x_1}:P_2^{x_2}$) was applied allowing .22 to represent the relation exponent of the control, it was found that this exponent dropped to approximately .21 for the enlarged animals. Although Kappers (1929) considers the smaller ontogenetic (relation) exponents which are consistently found in domesticated animals normally to represent the deteriorating influence of domestication upon the brain, on the basis of these experiments it must be concluded that ^{experimentally} increased size of the body generally is another factor in lowering this exponent. In the general text it was brought out that domesticated rats do possess heavier body weights at the age at which these brains were examined (13 months). Domesticated (civilized) man likewise possesses heavier body weights (as judged by bone volume) than savages. However, many animals, including the white rat after the age of two years, are heavier in the wild state than when caged. Hence, any lowering of the relation exponent in these tamed animals must be due to a relatively greater diminution in brain bulk than body weight so that Kapper's explanation for this lowered exponent; namely, an actual deteriorating effect upon the brain itself--must still maintain. Therefore, both factors may play a part in altering the exponent.

One is tempted to question what change domestication brings about in addition to increased body weight--where this does occur, to cause such a lowering of the relation exponent. In order to explain this some investigators including Kappers, claim that the pragmatic faculties which are so highly developed in the wild state where each need in life must be supplied by practical resources such as combat, are diminished through domestication. In the captured state, especially where the animals are caged the immediate life-sustaining needs are supplied without the necessity for prowling, preying or combat. If this explanation be accepted, it means that mental activity as gaged by practical resourcefulness is reflected in brain size. Furthermore, it would mean that the brain of civilized (domesticated) man living in communities where his savagery is minimized would be relatively smaller than that of the savage. This, of course, is not so.

It may be argued that any retrogression in civilized man's brain incident to a diminution in pragmatic enterprise is compensated for by the increased cognitive and conative faculties brought about by civilization and education. But here again we find no significant difference in the form or weight of the brains of the intelligentsia as compared to less talented individuals when any existing differences are considered from a statistical view point (see Appendix I). It is true that the brain of the primitive Australian is relatively smaller than that of the more enlightened European but, in spite of this it appears that within individual races the functional state in brain activity plays but a minor role, if any, in determining brain size. The differences noted in the brains of the two races herein compared are undoubtedly pure racial differences which have been

determined by the same factors which have led to the other distinctive features of the two races. As mentioned in Appendix I, any apparent largeness of the brain in those given to mental preoccupation may be more the result of better cerebral nutrition than mere structure.

So far as the immediate relationship between brain weight and body weight is concerned, it may be said that although brain weight is relatively increased as the phylogenetic scale is ascended so that a small mammal may possess a heavier brain than a larger animal of a lower phylum, within a given species brain weight and body weight are highly related. This normally high relationship has been found to be so constant that in the past it has been taken for granted that the size of the brain depends upon the size of the body. However, it must be realized that this high correlation in the normal body does not necessarily imply that one is the result of the other. It has been amply demonstrated that under the experimental conditions cited the brain remains unaltered in spite of the fact that the body continues to grow.

This statement is supported by a consideration of the results when the Hatai formula was applied to these data whence it was seen that the normal rat possessed a theoretical brain weight which coincided with that (brain weight) observed, while in the test rat the theoretical brain weight was much above that observed. In other words, the observed brain weights for the test animals seemed to correspond to those weights which should have served if the animals had grown normally.

Hence, under these conditions the hypothesis which holds that brain weight is dependent upon body weight does not maintain. As a matter of speculation, it may be said, that perhaps even in the normal the high relationship which does prevail is determined by some other common factor,

that "biologic formula" which at the same time determines the normal progressive development of all the anatomical and functional increments into a psychobiologic unit.

Finally, in the light of this work, it seems possible to clarify a very important observation which until now has never been satisfactorily explained. It has often been noted that the pathological human giant is quite sluggish as judged by his activities. It has been repeatedly stated that under normal circumstances, the brain size is directly correlated to body size which in turn is definitely correlated to body surface. These facts were already known to Brandt (1867) who, therefore, held that brain weight was directly dependent upon metabolic processes which being greater in larger bodies than in smaller ones required heavier brains for the proper functioning of these larger bodies. It has been shown since then, however, that within a given species the larger surface areas and larger muscles of normally large bodies contain more sensory and motor nerve endings (Donaldson 1895; Lericq and Giroud 1923) than smaller bodies with their correspondingly smaller surfaces and muscles. In the light of these observations and the experiments herein cited it appears advisable to consider brain weight neither dependent upon body weight nor upon body surface since these relations are probably merely coincidental and maintain only normally. As a matter of fact, it is not even safe to conclude that brain weight depends upon peripheral innervation which in contrast to other features of the organism remains fixed. It is probable that they are all determined by that unknown biologic formula which regulates this relationship. If this concept is accepted it becomes clear why the brains of the test animals were not increased in size since nothing was done in these artificially giganticized rats which would either increase the fixed number of nerve endings or in any other way alter the fixed genotypic characters.

Furthermore, since the degree of responsiveness on the part of individuals depends, in a measure upon the perception or awareness of environmental change, it seems obvious that where receptors are more widely separated (as in the case of artificially increased surface area with consequent separation of peripheral receptors) stimuli must be broader in their scope to evoke the same response as they would in the normal. In other words, other things being equal, what would just be an adequate stimulus for the normally sized individual with normally spaced receptors would be inadequate for the abnormal giant. Similarly, what would be considered a larger stimulus to the normal person would be perceived as a correspondingly smaller stimulus to the giant. Hence, the pathological giant exhibits a sluggishness which for him represents the reaction to relatively smaller stimuli.

As pertains to pituitary response, it is of striking interest that the normally smaller pituitary gland of the male, the sex which responds less to added growth hormone, reacts under test conditions by becoming heavier. On the other hand, the naturally heavier pituitary gland of the normal female, the sex which is more responsive to growth hormone, fails to increase in size. What can this mean? Is it possible that the male albino rat which is normally growing at a rapid rate as a result of a maximum growth efficiency of the pituitary gland can only obtain super-growth if his pituitary gland is enlarged? On the other hand, may it not be that the pituitary gland of the female albino is normally more sluggish from the growth standpoint than that of the male? If this be true, then the lack of enlargement in the test female's pituitary gland may be explained by a functional excitation of an already overabundantly present but, from the growth standpoint, hypoactive structure. Although the

above suggestions are merely speculative, not having been proved at this time, it may be definitely stated that the growth hormone tends to restore the predomesticated condition so far as the weight of the pituitary glands is concerned.

Where the female pituitary gland appears significantly deviated from the normal as noted when the meat injected control was compared with the uninjected control, the alteration, if it is an alteration, may not be as significant as it first appears. This statement is based on the fact that as shown in table IX, the significantly smaller female meat injected control may be expected to possess a significantly smaller hypophysis, since normally, pituitary and body weights show a high degree of correlation.

SUMMARY AND CONCLUSIONS

Generally speaking, although man has interested himself in growth from time immemorial, the factor responsible for growth was only isolated and used as a tool in the laboratory and clinic during the past thirteen years. Since generalized gigantism had been obtained in laboratory animals with the growth hormone and since normally brain weight varies as body weight, it became interesting to see whether experimental gigantism would maintain the same brain weight-body weight relations as observed in normally large individuals.

Accordingly seventy-four white rats (*Mus norvegicus*-var. *albus*) were divided into 3 groups and studied. To one group was given intraperitoneal injections of growth hormone, to another group, intraperitoneal injections of meat extract, and the third group remained uninjected. The two latter groups were considered controls. After twenty-two weeks of injections (growth during the first nine weeks was only slightly above the normal)

the animals were sacrificed and studied as described in the general text and the data obtained were submitted to statistical analysis.

From a review of the works of others, an analysis of the experiments carried out and a consideration of all the data available it seems safe to conclude that the growth hormone produces generalized body growth. It fails to influence in any way the structural make-up of the central nervous system as judged by studies of the weight, volume, specific gravity, water and solid contents of the brain. The growth hormone, therefore, affects the normal brain weight-body weight relations by decreasing the "brain weight-body weight ratio," by lowering the "exponent of relation" and by leading to a significant deviation from the body-brain growth curves as established by Hatai for the normal. It tends to increase the size of the male pituitary gland but fails to affect the normally large pituitary gland as found in the female white rat. In this it tends to restore the size of the pituitary gland of the white rat to that which is normal for the wild Norway rat.

The most important concept that one may acquire from a study such as this is that while within normal limits the brain is highly correlated to body size, this correlation does not hold under the experimental conditions cited. It probably represents just further evidence of that fine adjustment in that great series of events which we have come to look upon as being normal. Behind it all, there still remains that mysterious formulation of nature which tends to maintain a constancy in the face of everchanging environmental forces. Every so often, perhaps, through some genetic process as yet incomprehensible a change which strikes at the very fundamentals of the biologic make-up of an organism

may occur, but this is not often. From these experiments one may conclude that the endocrine system merely influences but does not strike at the very root of the organism as a psychobiologic unit. What the controlling mechanism is still remains a mystery. We speak glibly of it as the constitution, predisposition, inheritance, prevailing trend or genetic force but after all what are these? What determines them? What governs them? So we could go on asking question after question but ultimately have to admit that as we forge ahead toward that ever-receding goal each stepping stone of research only adds to the light which never completely enlightens.

TABLES

I to XIX

I Males - 31 animals subdivided into:

a. test animals	11 animals
b. uninjected controls	10 animals
c. meat injected controls	10 animals

II Females - 43 animals subdivided into:

a. test animals	16 animals
b. uninjected controls	12 animals
c. meat injected controls	15 animals

Table I—The grouping of the animals used.

RAT No.	WEEKS →																						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
2G5	252.6	252.0	258.8	264.5	266.5	251.1	253.0	262.5	283.0	297.7	309.0	300.5	302.0	295.5	304.0	312.0	315.5	331.5	326.0	330.0	335.0	345.0	346.2
9B2	258.0	260.8	272.8	275.0	279.5	283.0	277.2	280.0	308.3	326.0	329.0	332.0	332.5	335.2	335.0	339.5	339.5	350.0	341.0	349.0	355.0	359.0	355.8
9G4	257.8	252.5	265.4	275.2	284.2	284.0	286.7	280.4	280.0	288.5	307.2	312.5	318.0	326.5	327.0	334.0	346.6	365.0	358.0	360.0	371.5	382.3	385.6
10G3	237.0	242.2	238.8	243.0	254.3	254.5	256.5	257.3	257.7	262.5	267.7	283.0	292.4	296.5	295.0	298.0	312.5	326.7	330.0	346.0	345.6	346.2	350.8
19G4	279.3	275.7	297.3	300.0	300.0	315.5	323.7	325.2	319.0	340.0	357.0	341.5	350.0	358.7	357.5	360.0	350.5	346.6	353.4	358.0	365.0	370.0	374.8
19G5	263.0	242.8	279.5	276.0	271.5	277.0	287.3	293.0	308.0	303.7	314.0	314.3	325.6	332.0	336.0	345.4	306.0	294.5	312.8	318.5	325.6	330.0	335.6
23G1	252.2	253.9	264.0	278.0	285.3	278.5	281.0	280.0	299.5	303.0	312.0	329.0	339.0	340.5	342.0	354.5	370.5	384.0	398.0	406.2	415.8	412.5	—
23G5	233.5	236.0	246.8	249.0	253.0	244.0	240.6	247.0	252.7	260.0	268.0	279.2	283.3	275.5	281.0	274.6	288.5	320.0	332.6	340.7	350.2	350.1	—
24G3	233.3	233.9	247.6	257.1	268.3	260.8	270.0	254.5	265.5	277.0	298.5	295.0	291.8	301.5	297.0	300.0	325.5	342.0	351.0	359.2	365.2	370.2	365.7
28G1	258.2	245.0	258.6	260.0	268.0	251.1	265.0	260.8	250.7	268.0	270.0	283.5	284.4	293.6	294.0	309.5	332.2	339.0	350.7	358.6	360.1	362.3	365.9
28G4	221.5	223.2	235.0	244.0	266.0	238.2	247.5	247.5	251.0	260.0	264.7	274.5	284.5	285.8	299.0	304.0	318.2	330.0	342.1	351.0	355.0	360.0	362.6
TOTALS	2726.4	2718.0	2864.6	2915.8	3000.6	2948.2	2988.5	2988.7	3075.4	3176.4	3421.1	3345.0	3398.5	3441.3	3447.5	3541.5	3609.5	3706.1	3796.1	3871.0	3944.0	3987.6	3248.0
MEANS	247.8	246.2	260.4	265.7	272.7	268.2	271.7	271.7	274.6	248.5	311.9	305.0	308.4	312.8	313.4	321.9	322.2	336.9	345.1	351.9	358.5	362.5	360.9

Table II Weekly weight changes of eleven male rats injected with the growth hormone.

RAT No.	WEEKS →																						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
2C2	270.8	273.5	276.7	293.3	300.0	293.0	297.0	292.8	312.5	315.0	327.0	326.0	330.0	344.0	343.0	345.3	323.0	339.0	331.0	328.0	319.0	321.0	321.6
2C6	288.5	283.5	294.8	307.3	314.0	312.0	313.0	310.0	316.8	324.5	325.1	323.0	328.0	333.5	342.5	349.0	345.0	321.1	319.5	317.5	311.5	312.0	312.8
9C3	285.5	283.5	298.2	307.1	307.0	315.0	314.6	315.2	320.8	328.4	337.0	337.5	342.0	343.0	344.0	338.0	338.8	341.0	341.2	341.0	330.0	340.0	342.0
10C2	282.5	283.1	293.2	296.5	301.0	309.2	318.0	315.1	310.0	320.0	320.0	330.0	333.0	335.0	333.4	334.3	330.0	330.0	323.5	323.0	325.6	300.0	280.6
19C2	298.0	294.5	315.4	322.0	318.5	328.9	326.3	330.0	339.5	349.0	352.8	352.0	357.8	362.0	372.5	375.0	369.0	385.5	387.2	372.5	374.5	367.5	365.2
19C3	294.0	292.6	314.0	314.2	314.6	320.3	324.0	325.0	334.2	344.0	342.5	339.5	338.5	336.0	338.2	340.5	333.5	335.0	338.2	336.5	332.1	336.1	334.0
23C4	266.2	276.8	280.7	282.6	283.5	290.4	292.5	299.2	294.3	283.0	280.0	288.0	274.5	282.0	280.8	281.8	280.0	290.0	285.0	292.0	297.0	300.3	—
24C4	268.7	269.8	278.8	291.4	292.0	301.0	303.7	297.0	300.5	297.0	313.3	323.5	316.2	318.0	325.0	324.0	316.0	309.4	311.2	298.0	302.3	306.8	307.9
24C5	255.0	259.0	265.5	278.7	280.8	288.3	287.5	287.8	298.8	305.0	308.0	307.3	296.4	310.8	314.5	314.3	325.0	324.0	330.0	336.1	335.7	332.3	335.6
28C2	277.9	283.0	290.2	296.7	304.3	294.4	303.5	315.2	312.5	321.5	321.0	325.0	335.5	331.2	334.5	332.6	335.0	337.5	338.1	345.3	342.3	340.0	342.1
TOTALS	2787.1	2799.3	2912.5	2990.3	3015.7	3052.5	3080.1	3087.3	3134.9	3187.4	3232.7	3251.8	3251.4	3263.5	3272.9	3274.8	3266.3	3312.5	3304.9	3284.9	3267.0	3257.0	2941.8
MEANS	278.7	279.9	291.7	299.0	301.6	305.2	308.0	308.7	314.0	318.7	323.3	325.2	325.2	326.3	327.3	327.5	326.5	331.2	330.5	328.5	326.7	325.7	326.9

Table III Weekly weight changes of ten male rats used as uninjected controls.

RAT No. ↓	WEEKS - >																						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
8M1	266.4	263.0	265.6	271.4	284.0	277.2	276.5	272.0	284.8	286.5	295.5	295.5	292.0	291.0	291.2	294.0	292.5	292.5	293.5	290.0	289.0	275.5	278.9
9M1	270.5	270.5	284.0	286.0	287.6	296.3	291.7	297.5	302.0	312.5	311.0	312.0	317.0	314.0	315.3	313.0	316.5	316.5	321.0	325.0	322.5	320.0	328.1
10M1	278.5	270.4	282.9	284.1	288.0	296.1	297.0	299.7	300.1	310.0	313.0	321.6	323.5	330.0	333.6	325.0	332.0	327.3	329.5	332.0	335.8	343.6	337.0
19M1	293.5	292.5	311.9	313.0	308.6	309.3	322.0	328.5	338.8	368.5	364.5	355.0	360.3	361.4	358.2	377.6	346.0	344.0	346.0	350.0	349.0	346.0	347.8
19M6	286.5	278.1	261.4	284.5	285.4	300.5	300.2	304.0	306.0	315.0	317.5	312.0	310.0	309.0	306.0	306.0	308.0	307.0	306.0	312.0	319.2	315.0	314.9
23M2	254.0	253.0	257.7	263.6	269.5	277.0	274.0	286.7	280.7	274.0	272.0	288.4	285.5	286.0	286.0	282.0	282.5	291.5	293.6	298.0	297.9	300.0	—
23M3	257.0	260.0	261.4	264.3	270.5	275.5	271.5	286.0	281.3	286.7	286.0	294.5	294.0	293.2	289.0	278.5	282.0	291.0	290.0	299.0	298.6	299.8	—
24M1	250.2	244.4	256.0	270.0	266.2	276.0	272.0	268.0	275.4	280.0	280.7	279.3	278.4	288.5	285.0	279.3	288.0	282.0	286.0	280.0	285.2	281.3	280.1
24M6	251.5	255.3	264.7	272.2	279.4	280.4	280.4	277.2	287.7	297.0	298.7	305.2	297.2	309.0	311.0	313.5	321.0	326.0	328.0	324.0	330.0	333.1	329.0
28M3	252.8	252.0	258.0	259.0	273.0	268.5	274.5	282.5	276.6	284.0	278.8	283.5	284.5	281.2	281.3	282.5	282.5	282.5	285.1	292.0	291.6	293.0	290.8
TOTALS	2660.9	2649.5	2702.4	2769.1	2812.2	2866.8	2864.4	2901.1	2935.4	3014.2	3077.7	3062.0	3042.4	3063.3	3056.6	3051.4	3046.0	3060.3	3078.7	3077.0	3088.8	3107.3	2806.6
MEANS	266.7	264.9	270.7	276.9	281.2	286.7	286.4	290.1	293.5	301.4	307.8	306.2	304.2	306.3	305.7	305.1	304.6	306.0	307.9	307.7	308.9	310.7	313.3

Table IV Weekly weight changes of ten male rats used as meat injected controls.

Rat No.	WEEKS →																						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
1G1	174.4	185.0	198.5	201.0	208.0	204.7	204.1	200.0	194.7	198.6	227.2	233.0	243.5	248.8	260.5	237.8	233.0	249.0	252.5	257.0	273.4	290.0	295.1
5G3	185.5	192.5	198.0	187.5	193.0	192.5	199.0	198.0	200.0	203.2	221.2	233.1	245.0	248.3	267.5	283.6	295.0	311.7	313.2	330.0	342.0	352.0	—
5G4	163.8	168.5	176.8	175.4	185.2	180.4	184.6	181.0	174.0	178.8	215.5	208.0	205.0	210.0	217.5	220.0	234.2	248.5	250.3	256.5	260.3	—	—
7G3	184.5	179.3	199.7	223.7	223.5	204.3	198.3	194.0	189.0	213.1	240.0	236.0	238.2	235.2	238.6	232.5	232.5	245.0	251.0	256.0	260.8	263.5	269.7
7G6	179.5	177.0	195.2	212.1	211.8	200.0	201.0	200.0	183.8	199.6	234.0	236.0	234.7	236.2	238.0	243.6	246.0	266.0	282.0	288.0	295.7	300.0	308.8
12G2	172.2	184.0	194.5	196.3	198.1	201.5	211.0	206.5	204.0	184.0	214.5	230.0	242.0	244.5	254.0	267.8	269.5	273.7	280.3	—	—	—	—
13G1	158.3	162.0	165.7	175.0	185.0	182.9	188.0	190.5	184.8	183.0	195.6	216.0	224.5	228.5	244.0	240.0	272.3	292.0	300.2	—	—	—	—
13G2	146.0	201.3	210.5	215.1	221.2	220.5	228.0	230.5	219.0	224.0	241.5	258.4	276.3	270.0	272.5	286.6	298.0	313.0	319.3	—	—	—	—
26G3	192.2	196.0	202.2	211.8	214.2	203.9	209.6	207.0	212.5	217.0	228.5	241.0	252.5	249.3	259.0	265.2	265.8	255.6	263.4	268.3	274.5	—	—
32G2	183.7	192.4	198.0	197.2	213.5	204.5	213.2	207.5	205.5	219.5	224.0	224.0	228.4	238.5	247.2	248.0	248.0	255.0	261.0	269.8	—	—	—
32G5	197.2	204.0	216.6	214.0	227.0	222.4	226.4	225.2	222.6	227.5	242.0	250.5	257.7	264.4	271.0	276.0	276.0	293.0	301.2	308.5	—	—	—
33G4	192.6	196.2	198.0	189.5	184.5	185.4	187.5	191.6	197.6	197.3	204.5	214.8	221.4	230.2	242.5	251.3	244.5	255.5	263.0	274.9	279.9	290.0	295.9
33G6	193.5	198.5	204.0	213.3	216.4	208.0	206.0	206.7	209.6	209.5	217.5	219.0	225.5	234.6	233.5	233.0	237.5	242.0	256.0	260.9	265.6	265.0	268.7
36G5	196.0	193.5	195.3	201.0	215.3	203.5	210.0	205.8	206.0	213.3	227.0	249.5	241.5	239.1	245.0	250.0	264.6	286.2	290.3	300.8	315.5	322.6	336.6
36G7	198.2	197.8	211.0	213.0	221.5	219.2	220.5	215.6	214.8	210.0	221.5	233.0	244.5	247.0	257.5	253.6	258.5	266.0	278.0	288.3	295.0	302.8	308.6
38G2	165.0	175.0	185.0	190.0	192.8	191.5	197.0	192.0	193.5	193.0	208.0	217.5	255.5	221.0	221.0	225.0	230.7	241.0	246.0	245.0	—	—	—
TOTALS	2932.6	3003.0	3154.0	3215.9	3307.0	3225.2	3276.1	3251.9	3311.4	3268.4	3387.5	3699.8	3760.2	3845.6	3962.3	4044.0	4106.1	4293.2	4407.7	3604.0	2862.7	2385.9	2083.4
MEANS	193.3	187.7	190.9	201.0	206.7	201.6	204.8	203.3	206.9	204.3	223.0	231.2	235.0	240.4	247.7	250.9	256.7	268.4	275.5	277.2	286.3	298.2	297.6

Table V Weekly weight changes of sixteen female rats injected with the growth hormone.

RAT NO.	WEEKS →																						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
1C3	178.5	184.0	183.7	185.3	180.4	184.0	184.0	184.0	186.0	190.5	190.7	190.0	191.4	196.6	197.3	188.5	198.0	194.3	188.3	184.0	182.5	185.5	190.6
1C4	196.0	196.4	202.8	200.2	199.0	216.8	213.0	206.7	203.7	211.5	216.3	215.5	214.8	217.0	221.0	217.8	218.3	216.0	222.0	220.0	220.0	223.0	220.4
5C2	208.4	208.4	209.5	208.8	213.0	214.0	216.5	217.5	213.0	221.8	229.0	235.0	235.0	236.0	239.2	241.0	234.0	233.0	234.0	237.0	231.5	236.0	—
7C4	196.0	184.8	206.5	222.2	222.5	222.8	222.0	218.5	204.0	225.0	236.4	233.7	230.0	225.5	222.5	219.5	221.0	218.0	229.5	226.5	218.0	220.3	—
12C1	221.5	209.0	217.0	218.1	218.7	220.0	222.5	226.0	227.0	212.0	220.5	226.0	232.0	230.0	232.5	233.5	234.0	236.5	233.1	234.2	—	—	—
13C4	211.2	211.0	212.3	213.2	210.5	212.2	215.5	213.5	214.0	222.5	220.0	217.7	219.2	215.0	219.0	223.0	230.0	228.0	230.0	232.0	—	—	—
26C1	196.8	202.5	202.2	206.5	209.5	206.6	206.3	210.0	211.5	171.0	166.8	174.0	159.5	159.3	164.5	163.0	163.5	168.0	171.0	170.5	188.5	—	—
32C4	191.8	192.0	200.0	208.5	216.5	203.0	208.0	208.3	208.5	215.0	220.5	217.5	212.8	219.0	217.5	226.0	222.0	217.0	216.0	223.0	—	—	—
33C2	220.5	226.5	226.0	232.2	232.0	234.5	233.0	235.0	255.0	249.2	247.8	250.8	250.0	263.0	257.5	246.0	247.0	246.5	245.0	250.0	248.6	246.8	247.6
33C5	199.0	204.8	207.3	218.7	215.3	211.8	208.0	212.5	222.0	221.6	222.7	223.8	224.0	231.3	230.0	213.0	197.0	194.2	200.1	207.0	209.3	212.2	214.9
36C3	213.0	213.0	221.5	228.3	232.0	222.0	221.8	217.9	222.8	232.5	224.6	233.2	231.5	236.0	233.0	227.0	227.0	223.7	228.0	240.0	236.5	238.3	234.2
38C3	185.3	183.5	188.3	183.8	186.4	186.5	184.8	196.0	190.0	189.7	187.5	191.0	211.6	199.0	192.0	200.0	196.2	199.0	201.0	208.7	—	—	—
TOTALS	2418.0	2415.9	2477.1	2525.8	2546.8	2534.2	2535.4	2545.9	2557.5	2588.3	2592.8	2608.2	2611.8	2627.7	2628.0	2544.3	2588.0	2574.2	2578.0	2632.9	1734.9	1561.8	1107.7
MEANS	201.5	201.3	206.4	210.5	212.2	211.2	211.3	212.2	213.1	214.1	216.1	217.4	217.2	218.9	219.0	216.5	215.7	214.9	216.5	219.4	216.8	223.1	221.5

Table VI Weekly weight changes of twelve female rats used as uninjected controls.

RAT No.	WEEKS -																						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
1M2	175.5	175.0	174.2	178.4	188.7	192.3	189.0	186.4	190.5	195.0	197.0	198.0	195.5	194.4	191.5	190.5	184.0	182.5	185.9	183.2	182.3	190.0	192.8
1M5	176.7	182.0	185.5	176.5	181.3	190.6	193.7	189.5	196.0	193.0	197.8	192.0	191.0	195.0	195.5	187.8	183.0	187.0	190.0	196.5	202.5	199.5	202.0
5M1	191.5	191.3	191.0	188.4	197.7	201.5	205.8	211.0	216.7	215.7	217.2	208.5	214.5	214.1	214.5	218.0	214.0	202.5	201.0	210.0	213.5	212.5	—
7M1	194.0	184.3	184.4	205.6	204.1	201.5	198.5	201.7	186.0	206.7	215.7	210.8	211.3	207.7	206.5	202.1	209.5	206.5	217.7	213.0	209.5	212.6	211.8
7M2	186.3	178.4	182.0	211.0	213.5	210.0	204.0	206.7	193.0	211.2	228.7	227.2	226.0	218.9	214.8	211.8	207.8	207.0	222.0	222.0	219.5	220.0	218.7
12M3	201.0	205.1	206.7	204.4	206.3	210.0	213.5	219.0	225.5	205.0	211.3	219.0	221.3	219.0	213.5	215.0	218.0	218.1	220.0	219.0	—	—	—
13M3	207.5	208.8	220.5	214.6	219.0	219.0	221.0	222.4	224.3	233.0	232.5	233.6	237.6	230.0	235.0	232.0	237.0	238.0	236.0	234.0	—	—	—
26M2	192.4	194.2	197.0	200.0	203.2	203.2	206.0	208.0	212.0	211.9	204.5	213.5	214.0	211.0	207.7	206.0	206.0	205.0	208.3	205.5	202.3	—	—
32M1	184.5	187.5	187.3	189.0	194.5	192.3	190.5	195.5	196.5	201.5	199.5	191.0	186.4	197.5	195.3	190.8	188.0	196.0	192.0	212.0	—	—	—
32M3	190.4	194.9	197.9	201.4	204.5	194.9	194.0	201.8	206.5	210.0	211.2	203.0	195.2	208.5	200.7	194.3	190.5	202.7	201.0	203.8	—	—	—
33M1	183.0	187.0	195.5	191.5	190.0	189.0	183.3	191.0	201.5	205.0	198.3	197.0	200.0	218.0	209.5	200.5	201.5	204.5	202.1	210.5	211.8	212.3	210.3
33M3	194.8	200.6	196.8	196.8	197.5	197.9	191.0	198.0	213.8	204.5	221.0	212.0	215.2	214.4	223.7	212.0	212.0	207.0	208.0	212.0	210.6	214.3	212.1
36M1	200.5	191.5	192.8	205.0	214.5	197.2	193.5	194.7	190.5	190.0	180.0	181.0	195.0	192.0	181.3	188.0	198.2	186.5	187.3	195.2	200.6	203.2	201.2
36M2	195.2	195.2	195.7	204.0	220.0	204.5	204.2	203.0	202.1	204.6	222.6	211.3	211.0	210.0	202.5	202.3	201.0	201.6	202.0	215.0	211.6	212.9	214.6
38M1	179.8	177.9	185.0	174.0	182.3	183.0	176.7	182.8	180.0	181.8	180.0	182.7	190.5	183.0	178.5	177.0	180.0	179.2	178.2	182.5	185.6	—	—
TOTALS	2853.1	2854.7	2878.7	2937.6	3037.1	2983.5	2967.2	3018.5	3028.9	3069.7	3117.5	3085.6	3102.5	3121.5	3181.5	3028.1	3021.5	3034.1	3051.5	3114.2	2251.8	1878.3	1664.5
MEANS	190.2	190.3	191.9	195.8	202.5	198.9	197.8	201.2	201.9	204.6	207.8	205.7	206.8	207.6	212.1	201.9	201.4	201.6	203.4	207.6	204.7	208.7	208.0

Table VII Weekly weight changes of fifteen female rats used as meat injected controls.

	Mean initial body wt. gms.	Deviation from control	Critical ratio
Males:			
Test animals	247.9±3.32	-30.8±4.7	6.56
Uninjected controls	278.7±3.30		
Meat injected controls	266.1±3.32	-12.6±4.7	2.68
Females:			
Test animals	183.3±2.20	-18.2±3.4	5.35
Uninjected controls	201.5±2.60		
Meat injected controls	190.2±1.58	-11.3±3.1	3.64

Table VIII--Showing initial body weights for all groups.

	Mean final body weight gms.	Deviation from uninjected control	Critical ratio
Males:			
Test animals	365.7±3.98	+43.1±5.92	7.3
Uninjected controls	322.6±4.43		
Meat injected controls	309.7±4.50	-12.9±6.31	2.1
<hr/>			
Females:			
Test animals	296.1±4.48	+75.7±5.48	13.8
Uninjected controls	220.4±3.18		
Meat injected controls	208.9±1.97	-11.5±3.74	3.1

Table IX--Showing the average final body weights for all groups.

	Mean gain in grams	Deviation from controls	Critical ratio
Males:			
Test animals	117.80±4.87	+73.9±6.40	11.53
Uninjected controls	43.90±4.10		
Meat injected controls	43.56±3.66	-.34±5.48	.062
Females:			
Test animals	113.5±4.49	+94.6±4.89	19.34
Uninjected controls	18.9±1.97		
Meat injected controls	18.7±1.33	-.20±2.38	.84

Table X--Showing the mean body weight increases for all groups.

	Mean final body length cm.	Deviation from control	Critical ratio	Mean final tail length cm.	Deviation from control	Critical ratio
Males:						
Test animals	23.1±.11	+1.3±.14	9.30	19.0±.13	+.3±.14	2.86
Uninjected controls	21.8±.08			18.7±.04		
Meat injected controls	21.6±.16	-.2±.18	1.11	18.6±.04	-.1±.06	1.66
Females:						
Test animals	20.9±.18	+1.4±.23	6.10	18.9±.05	+1.0±.11	9.10
Uninjected controls	19.5±.15			17.9±.10		
Meat injected controls	19.2±.05	-.3±.16	1.88	17.2±.04	-.7±.11	6.36

Table XI--Showing mean final body and tail lengths for all groups.

	Mean brain wt. gms.	Deviation compared to controls	Critical ratio
Males:			
Test animals	1.9455 \pm .0133	-.0546 \pm .0235	2.32
Uninjected controls	2.0001 \pm .0194		
Meat injected controls	1.9611 \pm .0092	-.0390 \pm .0215	1.81
Females:			
Test animals	1.8925 \pm .0207	-.0013 \pm .0255	.051
Uninjected controls	1.8938 \pm .0148		
Meat injected controls	1.8634 \pm .0146	-.0304 \pm .0208	1.46

Table XII--Showing the final mean brain weights of all groups.

	Mean brain wt.-body wt. ratio %	Deviation compared to control	Critical ratio
Males:			
Test animals	.5342 \pm .004	-.0885 \pm .0099	8.93
Uninjected controls	.6227 \pm .009		
Meat injected controls	.6354 \pm .010	+.0127 \pm .0135	.94
<hr/> Females:			
Test animals	.6432 \pm .009	-.2201 \pm .0135	16.30
Uninjected controls	.8633 \pm .010		
Meat injected controls	.8933 \pm .007	+.0300 \pm .0122	2.46

Table XIII--Showing the average brain weight-body weight ratios for all groups.

	Meat brain wt.-body length ratio	Deviation from control	Critical ratio
Males:			
Test animals	8.51 [±] .057	-.63 [±] .116	5.43
Uninjected controls	9.14 [±] .101		
Meat injected controls	9.08 [±] .067	-.06 [±] .121	.49
<hr/> Females:			
Test animals	9.03 [±] .097	-.69 [±] .135	5.14
Uninjected controls	9.72 [±] .093		
Meat injected controls	9.75 [±] .072	+.03 [±] .118	.25

Table XIV--Showing average brain weight-body length ratios for all groups.

	Mean brain wt.-tail length ratio	Deviation from control	Critical ratio
Males:			
Test animals	10.22 [±] .062	-.44 [±] .128	3.44
Uninjected controls	10.66 [±] .112		
Meat injected controls	10.56 [±] .059	-.10 [±] .126	.79
<hr/> Females:			
Test animals	9.97 [±] .114	-.60 [±] .131	4.58
Uninjected controls	10.57 [±] .064		
Meat injected controls	10.83 [±] .113	+.26 [±] .130	2.0

Table XV--Showing average brain weight-tail length ratio for all groups.

	Mean brain volume cc.	Deviation from control	Critical ratio
Males:			
Test animals	1.8680 [±] .0308	-.0341 [±] .0347	.98
Uninjected controls	1.9021 [±] .0167		
Meat injected controls	1.8825 [±] .0158	-.0196 [±] .0230	.85
<hr/> Females:			
Test animals	1.7731 [±] .0219	-.0052 [±] .0242	.02
Uninjected controls	1.7783 [±] .0102		
Meat injected controls	1.7182 [±] .0324	-.0601 [±] .0346	1.74

Table XVI--Showing mean brain volumes for all groups.

	Mean brain Sp. Gr. $D = \frac{M}{V}$	Deviation compared to controls	Critical ratio
Males:			
Test animals	1.0694 \pm .0307	+0.0174 \pm .032	.54
Uninjected controls	1.0520 \pm .0084		
Meat injected controls	1.0430 \pm .0078	-.0090 \pm .011	.82
Females:			
Test animals	1.0614 \pm .0086	+0.0037 \pm .012	.31
Uninjected controls	1.0577 \pm .0088		
Meat injected controls	1.0860 \pm .0093	+0.0283 \pm .013	2.17

Table XVII--Showing mean brain specific gravities for all groups.

	Mean difference between theoretical and observed brain weights	Deviation of the differences compared to controls	Critical ratio
Calc. wt.--Act. wt.			
Males:			
Test animals	+0.0757±0.0117	+0.0778±0.0214	3.63
Uninjected controls	-0.0021±0.0179		
Meat injected controls	+0.0167±0.0101	+0.0188±0.0205	.92
Females:			
Test animals	+0.0446±0.0181	+0.0765±0.0221	3.46
Uninjected controls	-0.0319±0.0127		
Meat injected controls	-0.0138±0.0133	+0.0181±0.0184	.98

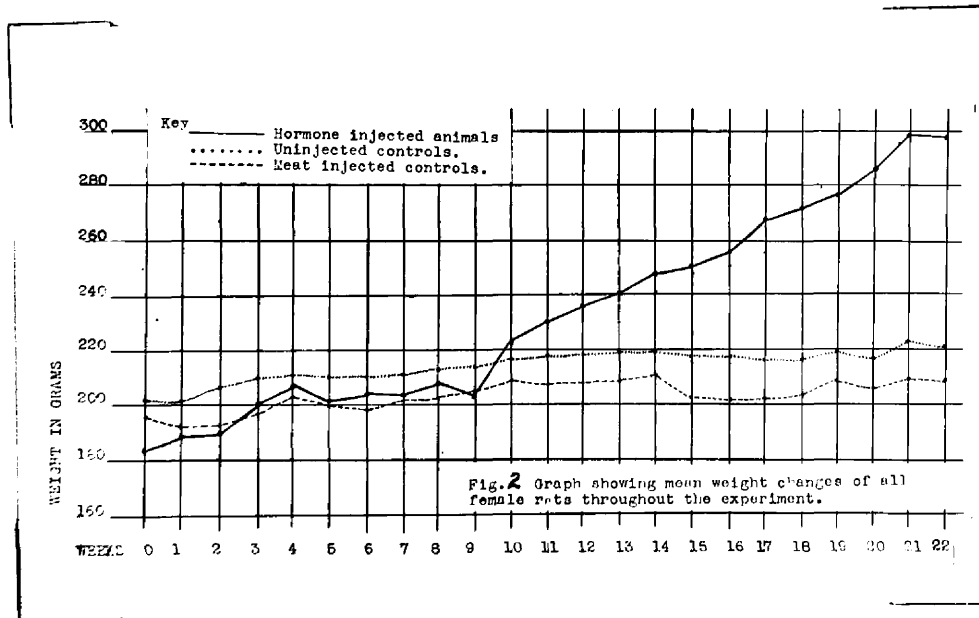
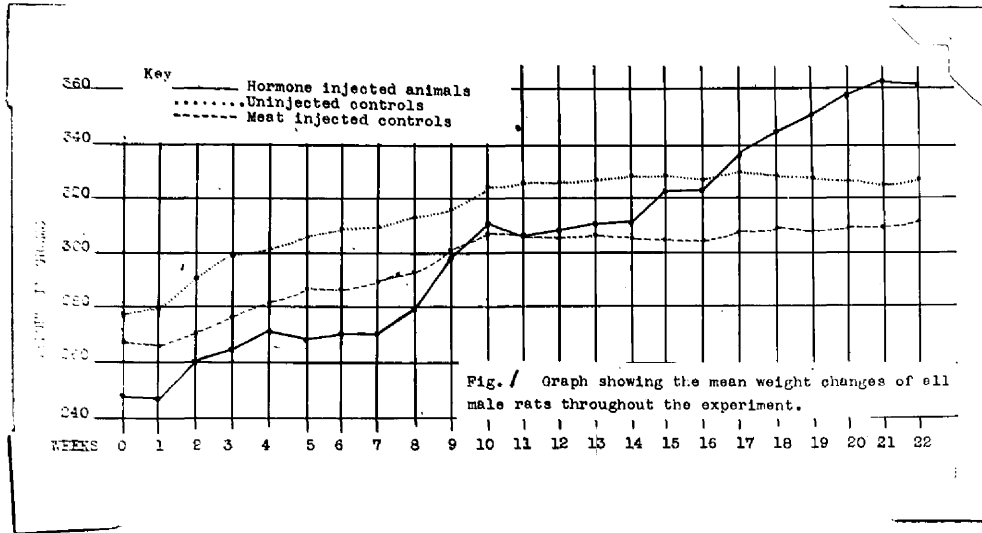
Table XVIII--Showing the mean differences between the theoretical and observed brain weights for all groups. Brain weight calculated according to $y = .569 \log (x - 8.7) + .554$.

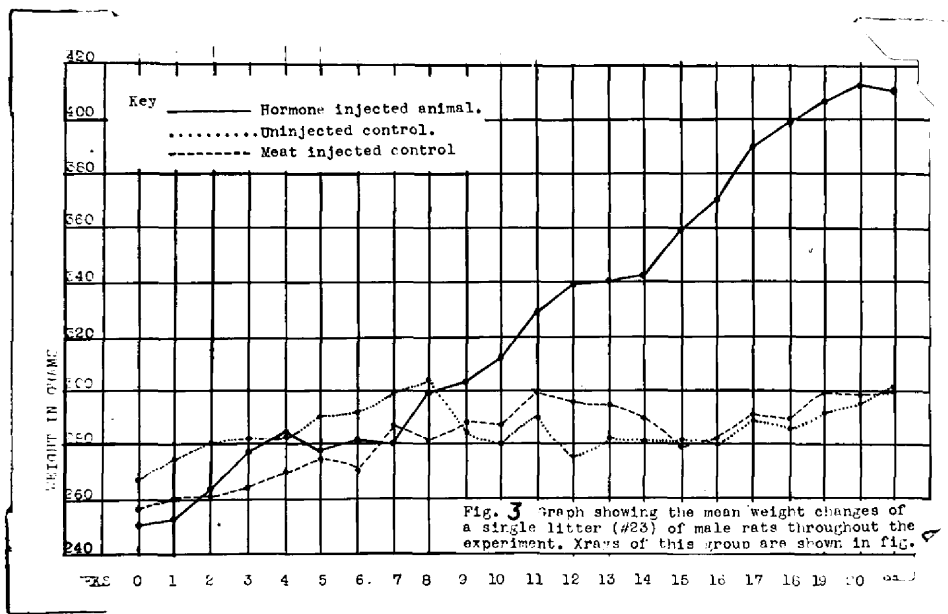
	Mean Pituitary Wt. gms.	Deviation from control	Critical ratio
Males:			
Test animals	.0134 \pm .00041	\pm .0033 \pm .00047	7.03
Uninjected controls	.0101 \pm .00022		
Meat injected controls	.0102 \pm .00037	\pm .0001 \pm .00043	.23
Females:			
Test animals	.0152 \pm .00052	$-$.0003 \pm .00069	.43
Uninjected controls	.0155 \pm .00046		
Meat injected controls	.0134 \pm .00057	$-$.0021 \pm .00073	2.88

Table XIX--Showing the mean final pituitary weights for all groups.

FIGURES

1 to 11





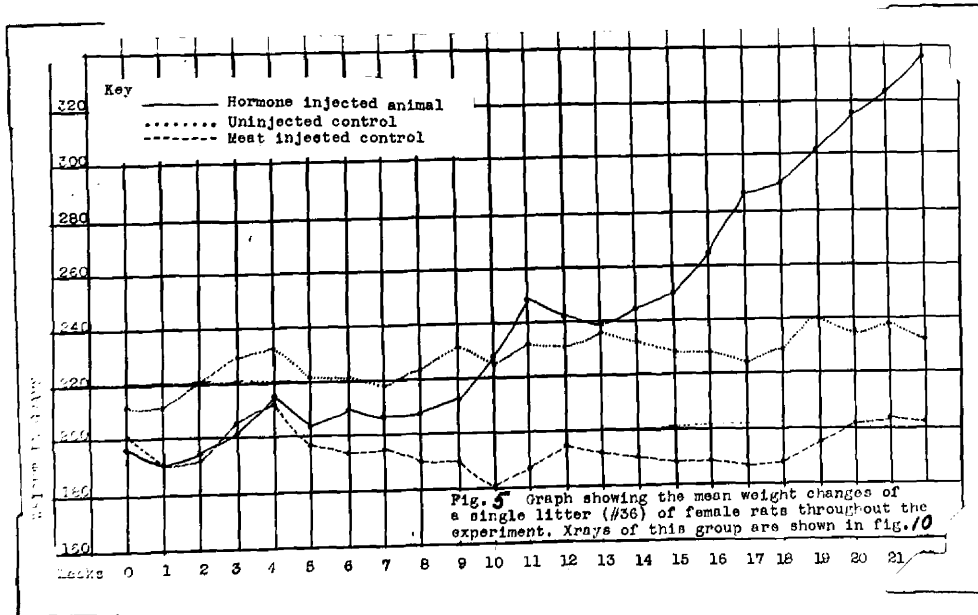
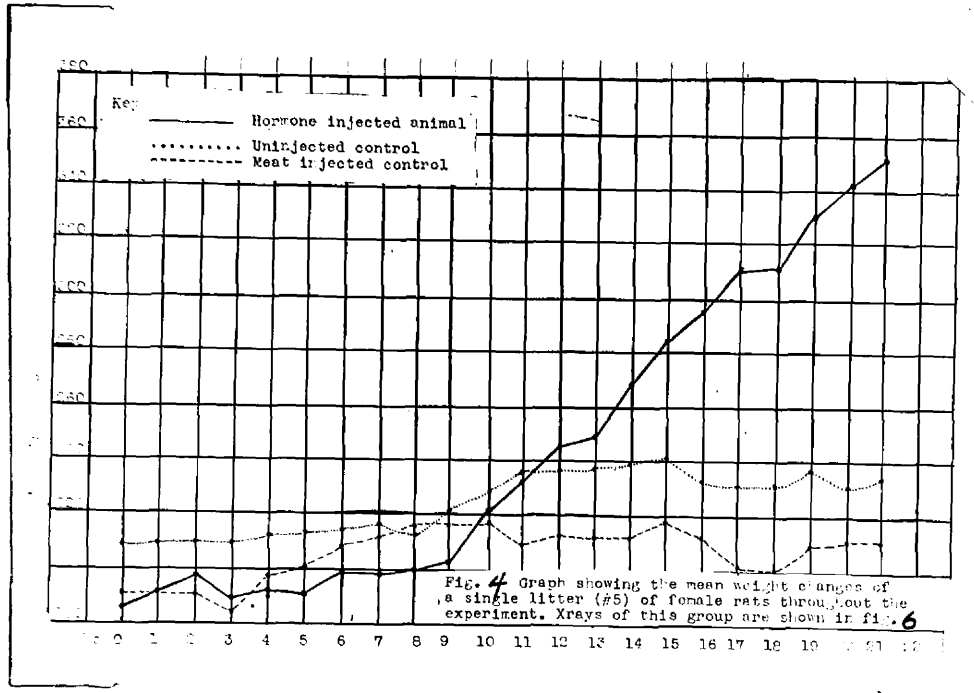




Figure 6. Roentgenograms taken at the end of the experiment of the antero-posterior view of litter #5, whose growth curves are represented in fig. 4. The control was the largest of the three animals before the experiment. Although it is still larger than the meat injected control, it is definitely smaller than the test (growth) animal.

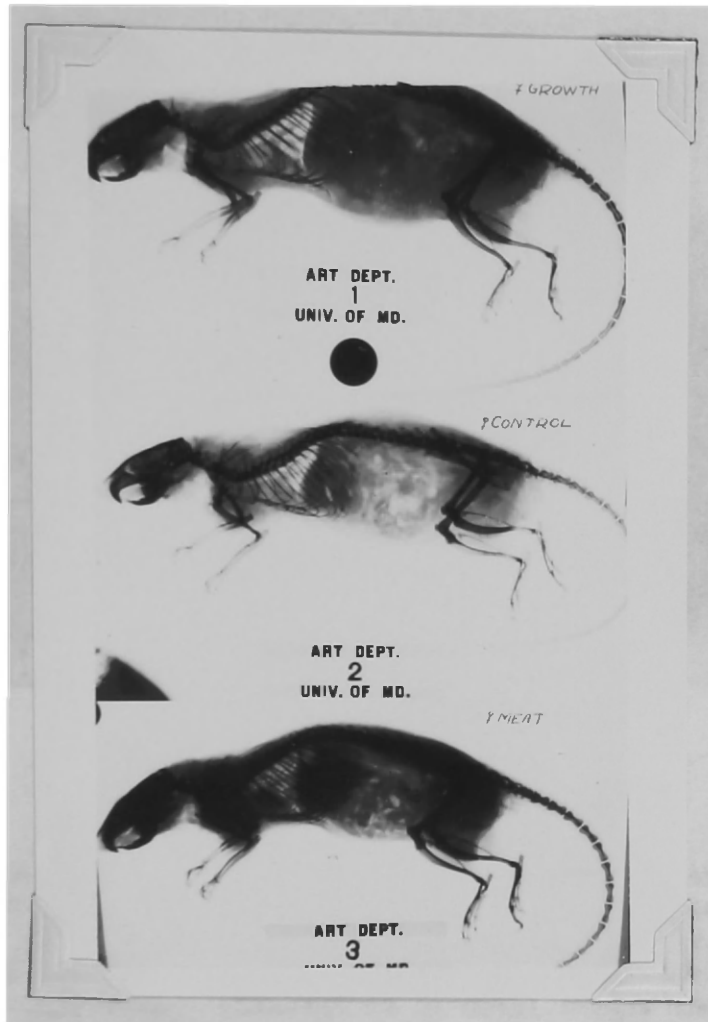


Figure 7. Roentgenograms taken at the end of the experiment of the lateral view of litter #5.

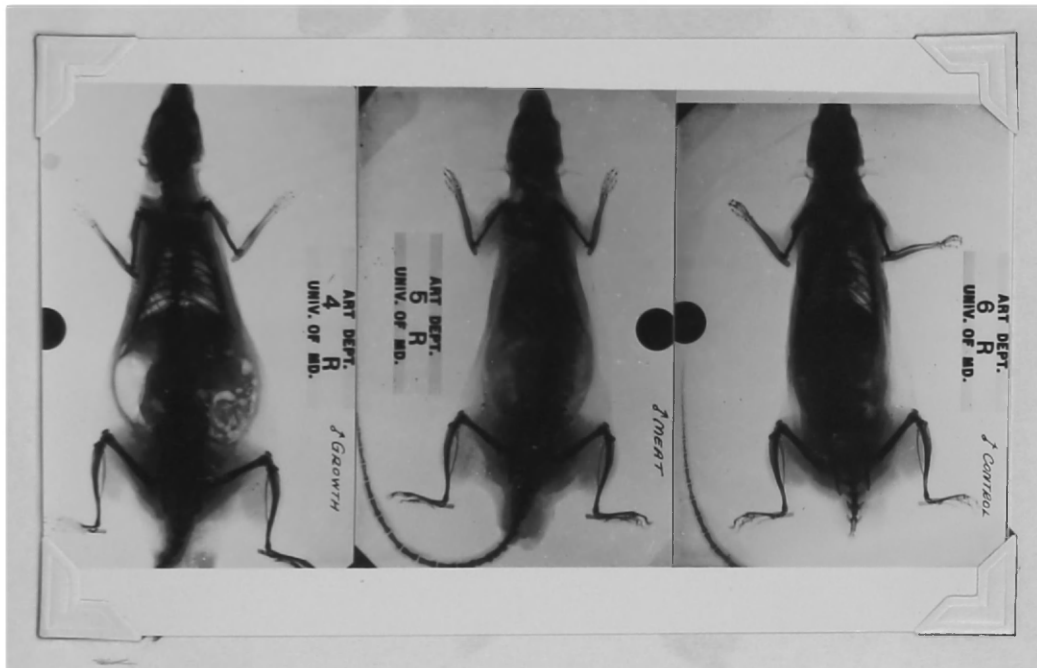


Figure 8. Roentgenograms taken at the end of the experiment of the antero-posterior view of litter #23, whose growth curves are represented in fig. 3. The control was the largest of these animals before the experiment. Although it is still larger than the meat injected control, it is definitely smaller than the test (growth) animal.

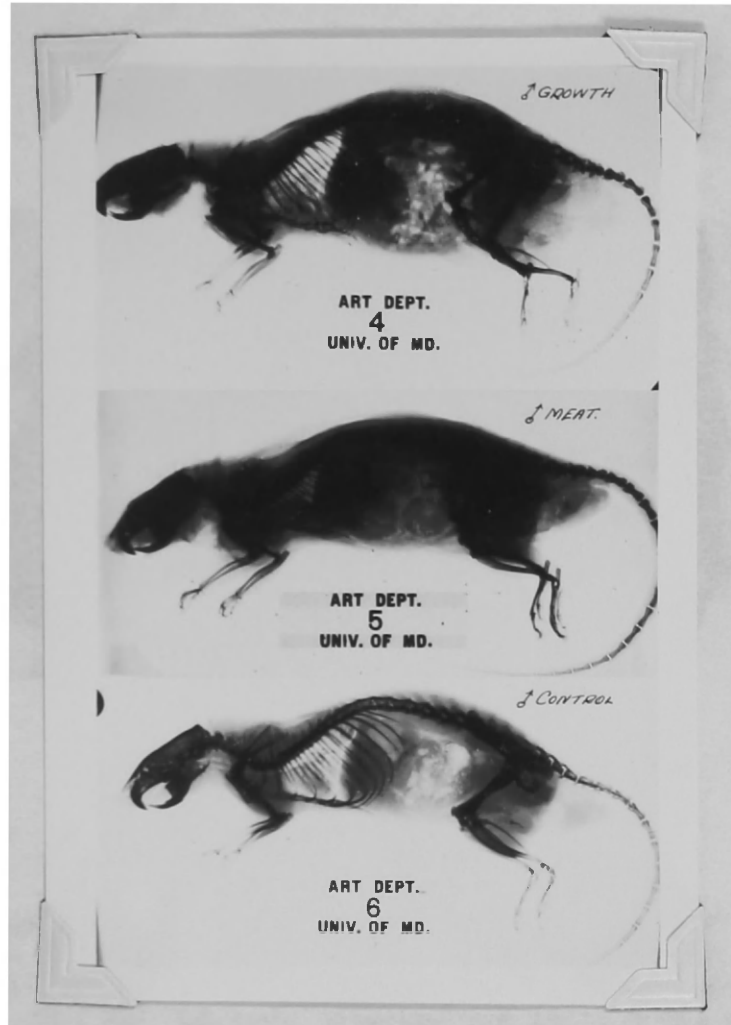


Figure 9. Roentgenograms taken at the end of the experiment of the lateral view of litter #23.



Figure 10. Roentgenograms taken at the end of the experiment of the antero-posterior view of litter #36, whose growth curves are represented in fig. 5. The meat injected rat still maintains a size smaller than the uninjected control, but the test (growth) animal which was the smallest at the beginning of the experiment is much larger than either control.

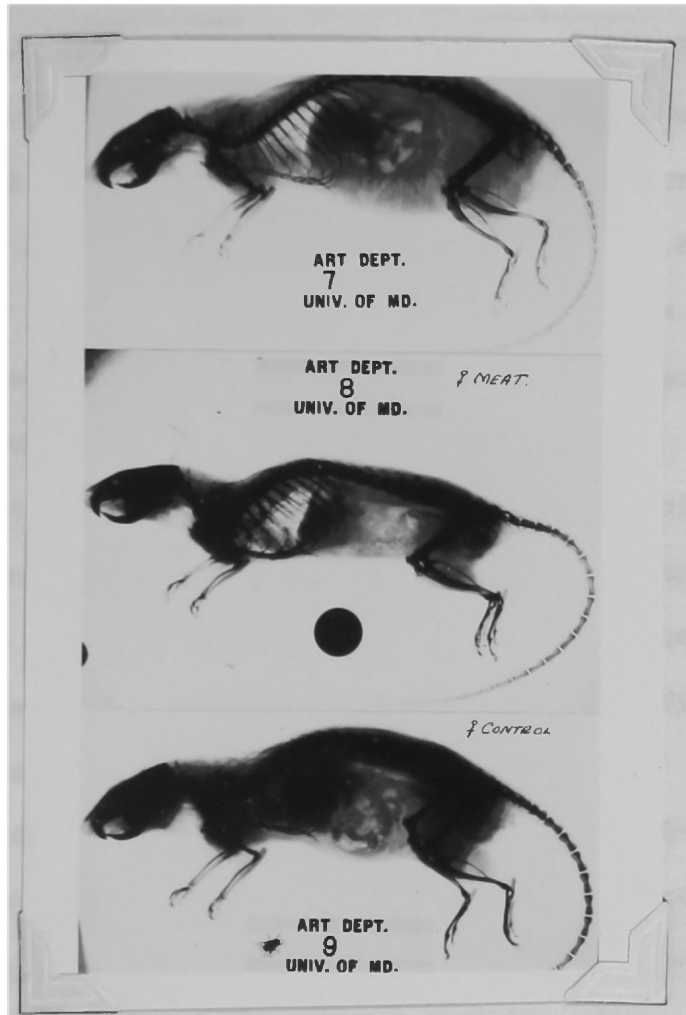


Figure 11. Roentgenograms taken at the end of the experiment of the lateral view of litter #36.

APPENDIX I

THE RELATION OF INTELLECT TO BRAIN WEIGHT

It is a matter of common knowledge that as we ascend the scale of life from species to species, the brain becomes relatively larger. This, of course, is due to a more intricate cerebral architecture and is in keeping with the demands for the more complex integrations which the more highly advanced animal must meet if he is to survive at his level of animal society. The relative size of the brain may thus roughly serve as a yardstick of the suprasegmental development which parallels the complexity of animal behavior.

Many investigators have attempted to show that within the human species the same factor; namely, relative intelligence is reflected in the size of the brain. Such, at least, have been the conclusions drawn from such studies as those of Davis (1868), Matiegka (1902), Spitzka (1903), Adam (1905), Draseke (1906) and others.

Davis (1868) considered the indirectly calculated brain weights of the six geographically distributed races* of man by estimating the volumes of their cranial cavities. From this study, he concluded that those nations in the various races that have the larger brains are the more assertive and successful. He cites, for example, that of all the European peoples, the Gypsies have the smallest brains. This, he believed to be in keeping with their social failure and, incidentally, to signify their

*Footnote: European, Asiatic, African, American, Australian, Oceanic.

origin anthropologically from the Hindoos, another backward race. Of the Oceanic races, he concluded that the Malays possess the heaviest (1334 gms.) brains and interestingly enough, believed this to coincide with the bold and enterprising nature of a people who "have pushed their migrations, chiefly for commercial purposes, over almost the whole ocean."

Spitzka (1903) studied the brain weights of ninety-six notables and was careful enough to exclude those whose weights were unverified and those who were insane. His cases were grouped according to occupation and included twelve men in the exact sciences (mathematics), forty-five in the natural sciences, twenty-five in fine arts and philosophy, and fourteen cases of "men of action" (politics and military). From this analysis he claimed that while the brains of these intellectuals were heavier than average brain weight, the brains of those men devoted to the higher intellectual occupations such as the mathematical sciences which involve the most complex mental synthesizations, were the heaviest of the entire series. Likewise those men characterized by their forcefulness, like Daniel Webster, also possessed brains heavier than the average. Spitzka lists all the men studied and appends an extensive bibliography on account of which his contribution, if for no other reasons, is valuable to the student of brain weights.

Adam (1905) basing his study on the figures of Matiegka, concluded that brain weight varies in the human according to:

1. intelligence	90 gm.
2. muscular development	77.5 gm.
3. height	72.3 gm.
4. nutrition	36.5 gm.
5. skeletal development	28.1 gm.

The high regard with which Adam holds intelligence as a factor in brain weight agrees essentially with the observations of Matiegka (1902) himself who reported the average brain weight of:

14 laborers to be	1410 gms.
34 tradesmen to be	1433 gms.
14 business men to be	1435.7 gms.
123 mechanics to be	1449.6 gms.
28 intellectual workers to be	1468.5 gms.
22 professionals (superior students) to be	1500 gms.

To the uncritical student, the above reports and conclusions of such an array of investigators appears quite convincing, especially if one adds to this the observations of Hauger (1921). Realizing the difficulty of obtaining reliable body weights from the usually emaciated hospital patients, the latter (Hauger) employed a method used in the earlier experiments of Mollison (1910) on primates. This consisted in substituting the usual brain weight-body weight correlation by a cranial cavity skeletal volume ratio. Accordingly, the skeletal volume was expressed by the total volume of the six large bones of the right limbs.* By this method Hauger found this relation exponent to be .25 which compares very favorably to the brain weight-body weight relation exponent discussed in this thesis (page 35).

After comparing this cranial-skeleton relationship in Europeans and Australians, this investigator assumed the bodily functions of these two races to be the same. Any differences noted, therefore, were explained

*Footnote: humerus, radius, ulna, femur, tibia, fibula.

as being due to differences in intellect. To his credit, it must be mentioned, that Hanger did take into consideration the fact that the domesticated humans had thicker bones than those less domesticated. In addition, his observations were calculated and his results checked in another way. Assuming that since the stature, development and bodily functions of those compared were similar, he reasoned that the brain and, hence, the cranial volume given over to governing somatic function was constant in all individuals. Hence, by subtracting this constant (for this somatic controlling portion of the brain) from the cranial volume, differences remained which to him indicated differences in intellect. By this method, he concluded that the Australian had a smaller intellectual cephalization than the European.

How significant such studies are remain for the future to decide. It appears, however, that if such intellectual coefficients are to be worked up for the human, that this will be achieved, as Kappers (1929) points out, by studying the brain-spinal cord relations in the various races. This has been done for many of the lower species (Ranke 1895; Mies 1897; Ziehen 1899) and a start has been made in man (Ranke 1895; Pfister 1903). Such studies seem to indicate that the higher the species the larger the brain in comparison to the spinal cord. In this connection it is perhaps interesting to mention that although many animals exceed man in brain weight-body weight ratio, the human presents a lower spinal cord percentage (in relation to brain) than any animal as yet studied.*

*Footnote: The cord percentage in man, as compared to the brain is about 2% (Ranke 1895).

However, since the more exact studies of Hanger, Kanke and Pfister are limited to either interracial comparisons or to the young (Pfister), any conclusions drawn from such studies can not with certainty be applied to men of the same race. In other words, a survey of all the foregoing studies still leaves one in a quandary concerning the intraracial relationship of intelligence to brain weight.

In order to overcome just such confusion, this question was taken up by such students of biometry as Pearson (1901-'02), Lee, Lewenz and Pearson (1912) and Pearl (1905; 1906). These men, after a most critical analysis of the data at hand, concluded that if any correlation between intelligence and brain weight does exist, such a correlation is indeed small.

An excellent review of such a scientific analysis on a rigorous statistical basis may be found in Pearl's "Studies in Human Biology" (1924).

The striking conclusion resulting from these more critical analyses is that if probable error were considered in the observations of Spitzka, Matiegka and the other proponents of high "intellect-brain weight" correlation, their relationship fades into insignificance. Hence, we may conclude that although a positive correlation does exist it is extremely small. Even this small correlation appears to Pearl to rest upon a physiologic rather than psychologic basis since "other things being equal groups of men with well-nourished bodies are on the average likely to be more able intellectually than groups in which bad conditions of nutrition prevail!"

This conclusion is in agreement with the facts as recently described by Paterson (1930) so that at present any intellectual differences which are found to exist between persons need no longer be explained on the basis of brain bulk but rather upon adequacy of blood supply, excellency in function, and, above all, the inherent quality of the cells making up that brain.

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