THE HYPOPHYSIS AND RESISTANCE TO INTOXICATIONS, INFECTIONS AND TUMORS*

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INTRODUCTION

IN the early days of the study of endocrine glands it was thought that they possessed antitoxic functions. The disorders due to glandular insufficiency were attributed to toxins arising from metabolic processes, or absorbed from the intestine. The toxins were thought to accumulate in the body because of the fact that they were neither destroyed in the gland itself, nor neutralized in the blood or tissues by the glandular secretions. This antitoxic theory has deservedly collapsed, since the supposed toxins have not been isolated, nor has their existence been demonstrated in a way that would explain the functional disorders of the different glandular insufficiencies. On the other hand, several hormones are now known, and some have been isolated in a pure state. These hormones prevent or cure the metabolic and other functional symptoms of the respective glandular deficiencies and, if given in excess, even produce signs of glandular hyperactivity.

The abandonment of the idea of an antitoxic function of the endocrine glands in favor of a hormonal function, has resulted in a loss of interest which reigned about a quarter of a century ago, in the study of the relation between the endocrine glands and immunity. Nevertheless this problem is of importance both in general pathology and immunology.

Very little work has been done on the pituitary from this point of view; probably because there are not many who have access to hypophysectomized animals, and also because it has been only recently that active extracts have been obtained, even though these latter are still very impure and complex.

The pituitary may play a part in immunity and resistance to intoxications in various ways: (1) By direct antitoxic action (intra- or extraglandular). (2) By its action on other endocrine glands. Since the anterior pituitary regulates the thyroids,‡ adrenal cortex,‡ gonads, parathyroids,‡ etc., the activity of these organs is decreased in pituitary insufficiency and increased when this gland is overactive. (3) By action on the hematopoietic or phagocytic organs, e.g., the spleen,‡ thymus,‡ etc. (4) By affecting metabolism and vasomotor reactions, the pituitary influences the resistance of the body to agents which lower the blood sugar and to those which lower the blood pressure. The action of such agents is intense in hypophysectomized animals. For the first of these mechanisms there is no proof, but the second, third and fourth occur in cases to be mentioned later.

Extirpation and destructive diseases of the pituitary produce an experimental or pathological deficiency in those functions which are directly performed by the gland. This deficiency is compensated for or may even be over-compensated for by restitution (implantation of the gland or injection of extracts). Hyperfunction (experimental or pathologic) produces opposite and different symptoms from those of glandular insufficiency. When the action is indirect, through the effect on another gland (e.g., thyroid, adrenal cortex, etc.), disturbances occur which are common to pituitary insufficiency and to insufficiency of the said gland. These disturbances are corrected both by preparations of the affected gland (thyroid, adrenal cortex, etc.) and by extracts of the pituitary which are capable of stimulating the gland (thyrotropic, adrenotropic, etc., pituitary extracts). The last-mentioned extracts are effective only when the respective gland is present and capable of responding to stimulation.

Specific neutralization of toxins or destruction of germs by the pituitary or its secretions has not yet been proved. There are, however, several ways in which it could take a part in immunity. Thus it might increase the general resistance of all the body cells or perhaps of only certain tissues to harmful agents; it might also enhance the capacity for antibody formation, or for the fixation and destruction of germs and toxins. Up to the present it is only possible to say that endocrine glands appear to play a certain rôle in immunity in an indirect way, by means of their metabolic functions or other nonspecific activities, such as stimulation of phagocytosis, or maintenance of the integrity and resistance of the skin, the mucous membranes, etc.

THE PITUITARY IN INFECTIONS AND INTOXICATIONS

Infective Lesions of the Pituitary.

The pituitary may be the site of infectious lesions,[13, 14, 17, 18, 28, 29, 33, 38, 47, 48, 55, 58, 59, 62, 68, 69, 70, 78, etc.] such as septic infarcts and abscesses, which in their ultimate evolution give rise to atrophy or fibrosis, the appearance of the syndromes of pituitary insufficiency and to Simmonds' hypophyseal cachexia.[1, 18, 38, 68, etc.] Circumscribed tuberculous lesions affecting the

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‡Besides the early publications of 1916, 1921 and 1922, etc., numerous studies on these subjects have been performed in our Institute from 1930 to the present date.

pituitary as well as metastatic lesions from distant foci and invasion from neighboring tissues have been described.[1, 5, 10, 20, 26, 36, 42, 44, 48, 50, 51, 52, 54, 63, 64, 68, 69, 74, 77, 84, 88, etc.] Syphilis[1, 8, 9, 10, 15, 21, 22, 24, 30, 32, 37, 45, 46, 48, 49, 51, 60, 62, 65, 67, 68, 69, 73, 75, 80, 81, 82, 83, 85, 87, etc.] may produce gummatous or fibrous lesions in the adult and congenital lesions in children. The Treponema pallidum has been found in the latter. (Duperié, Sabrazés.) Echinococcus[31, 40, 72] and cysticercus[1, 49] infections of the pituitary have also been known to occur. For further details the articles of Kraus[2] and Berblinger[1] should be consulted.

The Pituitary in Human Infections.

The pituitary has been studied macroscopically and, what is more important, microscopically in various general infections in human beings, such as tuberculosis,[19, 26, 48, 56, 65, 77, 79, etc.] typhoid,[25, 28, 41, 77, 79, etc.] diphtheria,[16, 23, 28, 35, 48, 56, 79, etc.] smallpox,[77, etc.] erysipelas,[77, etc.] scarlet fever,[56, etc.] tetanus,[77, 79, etc.] the septicemias,[11, 19, 77, 79, etc.] intestinal obstruction,[77, etc.] pneumonia,[25, 28, 77, 79, etc.] rabies,[57] typhus,[77, 79, etc.] encephalitis lethargica,[41] bronchopneumonia,[25, 28, 77] and also in distemper in dogs.[24] The older observations were made with imperfect staining techniques and it was believed that in acute infections an initial hyperactivity,[25, 79] followed later by exhaustion and hypoactivity (Delille) occurred while in chronic infections there was only hyperactivity. The cytological changes have been described more accurately by more recent workers.

Modifications of the Pituitary in Experimental Infections and Intoxications.

A number of descriptions have been given of the histological changes occurring in the pituitary of animals which had been subjected to various experimental procedures. The procedures used included the following: inoculation with diphtheria bacilli or toxins,[4, 16, 39, 77, 86, etc.] typhoid bacilli,[77] staphylococci,[11] streptococci[11] and tubercle bacilli,[11] also with the toxins of worms[12, 71, etc.] and with eel-serum;[39] ligature of the common bile duct,[39] the intestine[39] and the ureter;[39] injection of pilocarpine;[39, 77, etc.] alcoholic poisoning[66] and production of uremia.[1, 25, 39, 54, 56, 76, 77, etc.] Solely on the basis of interpretations of the histological changes, it has been supposed that there is an initial hyperactivity leading to exhaustion and functional insufficiency.

Functional Changes of the Pituitary During Infections.

The functional changes in the pituitary during infections and intoxications are not accurately known, since no method is available by which the pituitary secretion can be measured in the blood; neither has the relation between the histological aspect of pituitary glands and their activity, as demonstrated by implantation or by injection of extracts made from them, been investigated. Del Castillo, in unpublished work, found that there was no change in the gonadotropic effect of the pituitary of rats inoculated with *Trypanosoma equiperdum* on the immature ovary. The animals were killed eight to twelve days after inoculation with a strain that killed the majority of inoculated rats in ten to twelve days.

Azam[7] and Delille,[25] pupils of Renon, attribute the tachycardia, hypotension, insomnia, anorexia, sweating, etc., of acute infections to pituitary insufficiency, although it is by no means certain that these are the symptoms of such insufficiency. The fact that pituitary extracts produce some rise in blood pressure, strengthen the beat and slow the rate of the heart, increase diuresis, etc., is not enough proof to support their theory.

It has been thought possible that the exaggerated increase in height of young typhoid convalescents might be due to pituitary hypersecretion,[11, 24] though, of course, it might also be due to the direct action of the typhoid bacilli or of their products on the cartilage. Sometimes tuberculous children grow very rapidly when they reach adolescence and show signs of prognathism, but it has not been shown whether these symptoms can be attributed to hyperpituitarism or to a toxic action of the disease on tissue growth.[34, 53] Neither can it be affirmed that the sexual retardation and amenorrhea of tuberculous adolescents are due to overactivity of the pituitary.[53]

RESISTANCE OF HYPOPHYSECTOMIZED ANIMALS TO INFECTIONS AND INTOXICATIONS

Sensitivity to Anesthetics and Hypnotics.

Chloralose anesthesia is not well tolerated by hypophysectomized dogs.[153] In 1932 we started to use ether instead of chloralose and the mortality in the first week after operation dropped from 75 per cent to 15 per cent. On the other hand it is necessary to use a larger dose of chloralose than the usual one to anesthetize hypophysectomized or thyroidectomized dogs which have been previously treated with thyroid (1 to 4 Gm. daily of bovine extract for four to six days). This is also true in the case of hypophysectomized dogs after treatment with anterior pituitary thyrotropic extract. Ether anesthesia, however, gives unsatisfactory results in hypophysectomized toads.

The hyperglycemia due to morphia is less marked in hypophysectomized toads than in the controls, and implantation of the glandular lobe increases it.[139] In the hypophysectomized dog this hyperglycemia is on the average higher

than in the controls, but the difference is not statistically significant.[115] Ten hypophysectomized dogs presented similar symptoms to those seen in twenty controls when given a subcutaneous injection of 30 Mgm. per Kgm. of morphine chloride; one hypophysectomized animal, however, died two hours later in deep coma, while another had convulsions and respiratory failure, but was saved by artificial respiration. These two animals were the only ones which had practically no rise in blood sugar. Diabetogenic anterior pituitary extract increases the hyperglycemia due to morphia in dogs.[139]

Sensitivity to Operations.

Tadpoles deprived of the buccal pituitary anlage have a diminished resistance to unfavorable conditions.[89] Hypophysectomized toads, and those whose glandular lobe alone has been removed, remain active and appear to be in good condition for about three weeks after the operation. Soon after this they become asthenic and this disturbance increases progressively until death occurs.[132] In spite of their apparent good health, from the very beginning they are killed by many operations (e.g., on the testes, thyroids, adrenals and even cloacal ligature), which are well tolerated by the controls.[133, 142, 167, etc.] If, however, these operations are performed five to ten days before the hypophysectomy many animals survive.

Smith[193] stated, and it has been confirmed, that hypophysectomized rats present a general physical impairment, characterized by a lowered resistance to operative procedures, although the wounds heal well.[192] Hypophysectomized rabbits also have a diminished resistance to surgical trauma.[186, 188]

Hypophysectomized dogs are very sensitive to injuries, exposure and bad feeding. They readily become anorexic, which leads rapidly either to cachexia or death in hypoglycemia.[100, 135] Nevertheless with care a large number can be kept alive, even after the removal of one or more other glands besides the pituitary (e.g., ovaries, thyroid and pancreas).

The hypophysectomized - pancreatectomized animals, which have less hyperglycemia, glycosuria, azoturia and acidosis, live longer than the pancreatectomized animals with the pituitary intact, in which the diabetes is more intense. In the former group, with an attenuated diabetes, the wounds suffer less from infection and heal, even though no insulin treatment is given, but they never do so well as the hypophysectomized animals with the pancreas intact.

Sensitiveness to Infections.

According to Aschner[90] hypophysectomized dogs have a diminished resistance to infections, being particularly sensitive to mange, and Cushing[106] also states that hypophysectomized dogs are more susceptible to infections and that their resistance is diminished. We have not confirmed this increased susceptibility having found that mange is readily cured by sulphur,[141] but we have noted that when infected or ill these dogs readily become anorexic, hypoglycemic or cachectic and die. The wounds of hypophysectomized toads (or those without the glandular lobe) are more readily infected and heal slowly and with difficulty (Magdalena, Aubrun, Pasqualini, etc.). Also, their cutaneous glands are frequently invaded by cocci (Aubrun and Porto, unpublished). Hypophysectomized rats show the same sensitivity to caries of the molars as do the normal animals.[191]

Cushing[106] described acute or infectious processes as occurring in seven of his patients, notably in those with a primary hyperpituitarism. There also seemed to be a definite susceptibility to infection in his cases of pituitary basophilism.[210] Atkinson[6] found that out of 1319 published cases of acromegaly only twenty had tuberculosis as well, and that six of these died of the infection.

Sensitivity to Intoxications.

There are four groups of toxic agents which are poorly tolerated by hypophysectomized animals, namely, anesthetics, blood sugar reducing agents, blood pressure reducing agents and those agents which have intense adverse effects on thyroidectomized or adrenalectomized animals.

Blood Pressure Lowering Agents.

The hypersensitivity to histamine and to other shock inducing agents pertains to this group.

Amphibians. Removal of the pituitary does not alter the sensitivity of the frog (*Leptodactylus ocellatus*) to veratrine,[134] or of the toad (*Bufo arenarum* Hensell), twenty days after the operation, to morphine, atropine, curare, and veratrine.[124]

Rats. Three or more weeks after hypophysectomy in the rat the toxic dose of cobra venom is only two-thirds of that necessary to kill the controls.[93] The minimum lethal dose of histamine is halved if the hypophysectomy is total and there is an initial hypotension, but is unchanged if only the posterior lobe has been removed and there is no hypotension.[196] According to Perla[181] the toxic dose of histamine for hypophysectomized rats (one to ten weeks after operation), which show atrophy of the internal part of the adrenal cortex, may be one third, or even only one fifth of that for normal rats. When a sufficiently large part of the anterior lobe is left there is no alteration in the adrenal cortex or in the sensitivity to histamine. Perla believes that the increased sensitivity is due to hypofunction of the adrenal, particularly as

treatment with cortin increases the resistance to histamine, although it does not modify the adrenal atrophy.

Putnam[182] found that a dose of glycine which did not affect the controls caused a decreased metabolism and death in six to twelve hours in hypophysectomized rats.

Dogs. Ferrer Zanchi[118] injected several dogs with a suspension of dead typhoid bacilli. The eight controls survived, but two out of six hypophysectomized animals died, one an hour after receiving 2,500 million bacilli per Kgm., the other twenty-four hours after receiving 500 million per Kgm. This is not surprising since hypophysectomy in the dog produces a slight lowering of blood pressure and a slower recuperation of the normal blood pressure level after bleeding.[101] This slight hypotension has been observed in the rat[196] and is much greater in the toad.[177] Braier[100] noted that injections of B. Coli vaccine caused a less marked rise of the basal nitrogen and creatinin excretion in hypophysectomized dogs, than in the controls, but the rise of temperature was similar in both groups.

Agents Acting Through the Thyroid.

Anterior pituitary extracts, through their thyrotropic action, cause great sensitivity to anoxemia in rats, guinea pigs,[146] and mice.[190] This sensitivity is not observed when the thyroids have been previously extirpated.[146] It may be remarked that hypophysectomized rats tolerate anoxemia more or less as the normal animals do. (Chiodi and Rietti, unpublished.)

The fall in body temperature provoked by novocaine is reduced or prevented in guinea-pigs,[190] and anesthesia by chloralose is somewhat impeded in the dog, by treatment with thyrotropic pituitary extract.

It is known that the resistance of the white rat to the toxic action of acetonitrile is increased by the ingestion of thyroid. (Reid Hunt's effect.) Injections of thyrotropic preparations of the anterior pituitary lobe produce a similar effect,[173, 176, 178, 179, 190*] because they stimulate the thyroid to greater activity. This effect of anterior pituitary extracts has not been observed in thyroidectomized animals.[178, 179] The serum of men[175] and dogs[125] after treatment with anterior pituitary lobe increases the resistance of rats to acetonitrile, but the serum is without effect in the absence of the thyroid. Oehme, Paal and Kleine[176] believe that the active substance is other than the thyrotropic principle of the anterior pituitary, for it appears to be active *per os,* and does not cause histological changes in the thyroids. Posterior pituitary extract also increases the resistance to acetonitrile, without stimulating the thyroids.[154]

Hypoglycemic Agents.

In 1924 Magenta and I found that hypophysectomized dogs are very sensitive to the hypoglycemic action of insulin. Later, with Biasotti and Braier, we found that in these animals a number of different agents readily produce hypoglycemia, with severe symptoms such as convulsions and coma leading to death. This can be prevented by early treatment with glucose, posterior pituitary extract or adrenalin, it being necessary sometimes to repeat the treatment. The hypoglycemia can also be prevented by treatment with anterior pituitary extract for two to three days. It should further be noted that hypoglycemic crises occasionally occur spontaneously in hypophysectomized animals, whether the pancreas is present or not. They are frequent during the secondary fall in blood sugar which follows the hyperglycemia of adrenalin during fasting, and are constant after several days of fasting and also after the injection of phlorhizin or insulin.

Injection of phlorhizin produces fatal hypoglycemia in fasting hypophysectomized dogs[135] and in hypophysectomized toads.[113] This is prevented by feeding the dogs on a protein or carbohydrate diet, but not by fat diets.[97, 184] Treatment with alkaline anterior pituitary extract, before and during a fast of five to six days, prevents the hypoglycemia and death following phlorhizin.[137] Fasting hypophysectomized dogs, after adrenalin hyperglycemia, have an accentuated secondary hypoglycemia, giving rise to hypoglycemic crises.[100, 162]

Aschner[90] believed that although hypophysectomized dogs have a diminished resistance to intoxications, they tolerate subcutaneous injection of adrenalin better than the controls, since they do not develop local necroses and they show a lower glycosuria. Braier[100] injected adrenalin intravenously (0.5 Mgm. per Kilogram in twenty minutes) in fasting hypophysectomized dogs, and found during the first six to seven hours a slightly larger decrease in the excretion of nitrogen and urea than in the controls. There was also a lower hyperglycemia, with a marked secondary hypoglycemia, which gave rise to convulsions in three out of five cases; two of these were saved by treatment, but the other died during the night. When the animals were fed, the hyperglycemia was the same or greater than in the controls. In dogs and men suffering from pituitary insufficiency, Lucke[162] observed a much greater rise in blood sugar following adrenalin, followed later however by a larger fall and a higher renal threshold. In hypophysectomized rabbits the hyperglycemia occurs more slowly and is not so great as in the controls.[120, 156]

*Rietti could not confirm this, but his mice reacted very irregularly to acetonitrile.

The extreme sensitivity of hypophysectomized animals to insulin was discovered by us.[143] Doses, which in the controls cause very slight lowering of the blood sugar with no symptoms, cause an intense hypoglycemia in the hypophysectomized animals, with convulsions and coma invariably ending in death, unless intense and repeated treatment is carried out. This extreme sensitivity to the hypoglycemic and toxic action of insulin has been observed in dogs,[94, 95, 109, 117, 121, 123, 143, 148, 155, 162, 164, etc.] cats,[166] monkeys,[127] rabbits,[104, 105, 120, 157, 186, 187, 188] and man,[91, 108, 126, 162, 165, etc.] but apparently does not occur in birds;[129] it is also observed in hypophysectomized-pancreatectomized dogs (Regan and Barnes;[183] Houssay, unpublished data). It does not occur in dogs with severe lesions of the basal or retro-hypophyseal part of the tuber cinereum,[143] or in rabbits with the midbrain excised.[130]

According to Geiling and his collaborators the sensitivity to insulin is due to deficiency of the posterior pituitary lobe, but on the basis of our experiments we attribute it to anterior pituitary deficiency. Extracts of the posterior lobe can, to a certain extent, counteract the hypoglycemia and its severe symptoms in the dog[123, 143] and toad,[145] though vasopressin may not be efficacious in the rabbit.[105] Animals with inactivated adrenal medulla, which are hypersensitive to insulin, can also be successfully treated with posterior lobe extract.[122]

The protective action of the anterior pituitary lobe extract is very potent, far more so than that of the posterior lobe extract. It is able fully to counteract the sensitivity to insulin and also to raise the resistance both in hypophysectomized and normal toads,[145] dogs [114, 164*] and rabbits.[104] The anterior pituitary extract requires one to two days to increase the resistance,[114] and therefore is not efficacious in animals already in convulsions and coma.[143]

This protective action also occurs in thyroidectomized-hypophysectomized animals (di Benedetto, Houssay, etc.). The sensitivity of thyroidectomized rabbits and dogs to insulin[104] (Houssay, etc.) is greatly increased if hypophysectomy is also performed. For this reason we can exclude the explanation that diminished resistance to insulin following hypophysectomy is due to hypothyroidism.

It has been thought that this diminished resistance might be due to adrenal insufficiency,[96] because adrenalectomized animals are hypersensitive to insulin,[160, 161] and in pituitary insufficiency there is some atrophy of the adrenal cortex. The following objections may be raised against this theory. Anterior pituitary extract has a diabetogenic action in pancreatectomized toads, in adrenalectomized toads and in dogs lacking the adrenal medulla. It also protects these latter from insulin. According to Barnes, Dix and Rogoff, hypophysectomized animals require more adrenalin to prevent convulsions than do those with denervated adrenals. They interpret this observation as showing that hypophysectomized animals do not liberate adrenin during insulin hypoglycemia. On the other hand, Cope and Marks[104] demonstrated that there is adrenin secretion, for which reason they believe that the anterior lobe of the pituitary maintains the glycogenolytic action of adrenin normal.

There are insufficient observations to draw definite conclusions regarding modifications of the sensitivity to insulin in the diabetes of acromegalics. Some authors have observed an increase in the resistance to insulin,[110, 162, 168, 195, etc.] others have found it the same as in other diabetics,[98, 103, 128, 150, 158, 159, 185, 197, etc.] and even hypersensitivity has been described.[169]

Our opinion is that in pituitary insufficiency a hormone is lacking which plays an important rôle in carbohydrate metabolism; hypersensitivity to insulin is due to the absence of this hormone which acts as a stimulating agent for the production of glucose.

Antitoxic Action of the Extracts.

Much work has been done to find out if pituitary extracts can neutralize poisons or increase the resistance of animals to these agents, but the results are not conclusive. Delille[112] tried injecting pituitary extract and various poisons (potassium arsenate, atropine, mercury cyanide, strychnine, human urine) together and separately, but obtained no definite results. Marañon and Aznar[170] state that posterior pituitary lobe extract prevents the toxic action of strychnine in the guinea pig, so that convulsions and death do not occur. These results have not been confirmed by our experiments.[140] Mariante[172] stated that posterior lobe extract masked the toxicity of morphia, but this also was not confirmed by our experiments in guinea pigs and pigeons.[131, 149]

Phagocytosis and Opsonins.

There are a number of scattered observations on the relation of the pituitary to phagocytosis and opsonins of which the following may be mentioned. Carbon dioxide does not produce leucocytosis in hypophysectomized guinea pigs, but if these animals are treated with pituitary extract, they respond normally.[102] The injection of extract of horse pituitary causes a transitory increase in the phagocytic power of the leucocytes and later a diminution.[171] Injection of hypophysin increases the complement in the serum.[161] Pituitrin lowers the opsonic index

*The commercial extract used by Lucke, of unknown preparation, has posterior pituitary lobe properties, i.e., it has an immediate slight glycemic action which does not occur in the absence of the adrenals.

against staphylococci and tubercle bacilli in rabbits.[194]

Parodi (unpublished work) in our Institute has found a marked decrease in the phagocytic powers of the polymorphonuclear leucocytes in the blood of hypophysectomized dogs; using Radsma's modified method he found that 50± 1.9 per cent of the leucocytes ingested starch in the controls, but only 20 ± 5.2 per cent in the hypophysectomized animals. Peritoneal injection of alkaline extract of anterior lobe greatly increases phagocytosis, but this cannot be considered a specific action, as extracts of muscle and kidney will also do this. It is possible that the diminished phagocytosis found in hypophysectomized animals is due to hypothyroidism.

Antibody Formation.

Borchardt[99] states that injection of pituitrin raises the agglutinating power of the serum in animals or men injected with typhoid bacilli. Cutler,[107] however, found an equal formation of these agglutinins in normal and in incompletely hypophysectomized guinea pigs, and also an equal formation of hemagglutinins and hemolysis on injection of chicken erythrocytes. He further showed that neither ingestion nor intraperitoneal injection of pituitary extract altered the course of immunization.

Ferrer Zanchi[118] in our Institute immunized four hypophysectomized dogs and five controls with doses of 2,000 to 5,000 millions of dead typhoid bacilli per Kgm. of body weight. The agglutination curves and maximum titres were similar in both groups.

Savino,[189] also in our Institute, immunized five normal and seven hypophysectomized dogs with diphtheria anatoxin during twelve weeks. The individual titres of the sera tested every two weeks, showed a more rapid immunization in the hypophysectomized animals, the serum of which always reached a higher final antitoxic value. The average was 38 ± 6.1 A. U. for the hypophysectomized, compared with 26 ± 5.5 A. U. for the controls, a difference of 12.3 ± 2.6 A. U. This may be explained as due to hypothyroidism,[119] to hypersensitivity, to slower absorption of the anatoxin, or to general nutritive changes.

In contradistinction to Jungeblut and Engle,[151] Hudson, Lennette and King[147] found that gonadotropic pituitary extract did not cause the appearance of any activity antagonistic to poliomyelitis virus in the serum of monkeys, nor did it increase the resistance of these animals to intracerebral inoculation.

THE PITUITARY AND CANCER

Tumors of the Pituitary.—The pituitary frequently is the site of adenomatous proliferation or of true adenomas of acidophilic, basophilic, chromophobic or mixed types, which give rise to more or less specific symptoms. Malignant adenomas or adenocarcinomas may also occur. Besides these, angiomas, fibromas, teratomas, adamantinomas, etc., have been found. There is a special group of tumors known as tumors of the pituitary canal, which consist of craniopharyngiomas and teratomas.[1, 209, 210, 211, 220, 238, 275, etc.] In addition, metastases from various origins occur in the pituitary[230, 236, 238, 266, 274, 280, etc.] giving rise to certain symptoms (polyuria, etc.). When sarcoma is implanted into the gland in the rabbit it does not proliferate as much as in other tissues.[227]

The Pituitary in Cancerous Patients.

Various histological[1, 201, 215, 233, 236, 261, 265, 273, 279, 280, etc.] changes have been described in the pituitary gland found at autopsy on cancerous patients, e.g., increase in the principal cells,[233] increase[215] or decrease of the basophiles,[238] increase in the weight of the gland and in the number of the eosinophiles,[280] signs of hyperactivity of the anterior lobe, and of hypoactivity of the posterior.[273]

In rats with subcutaneous implantation of tumors, there is an increase and vacuolization of the basophile cells of the pituitary, with enlargement of their Golgi apparatus. The changes are similar to those produced by castration, although the sexual cycle is not affected. If these pituitary glands are then implanted into immature rats it can be demonstrated that they have an increased gonadotropic activity.[225] If the cancerous implantation is made into the uterus there is a larger increase of the eosinophile cells of the pituitary and less of the basophiles, and the pituitary appears like that of pregnancy or after the injection of estrin.[225]

Hypophysectomy and Cancer.

Hypophysectomy before or after implantation of tumors causes a retardation of their growth in rats[199, 262] but does not completely stop it,[243, 255, 269] although it has been observed occasionally that shrinkage occurs and fewer of the implants take.[244, 262, 263] There are also fewer metastases, but the resistance of the animals is diminished.[244] In hypophysectomized rabbits also a diminished growth of implanted sarcoma has been observed,[227] although with partial hypophysectomy tar carcinoma may develop more rapidly than in the controls.[234] Irradiation of the pituitary with x-rays diminishes the growth of cancer in rats,[203, 247] but it has not been proved that this treatment produces any real change in the gland.

Gonadotropic Substances in the Urine of Cancer Patients.

The urine of certain cancer patients will cause ripening of the follicles in the ovary of immature rats and mice.[198, 281, etc.] Zondek attributes

this effect to a substance he calls prolan A. This occurs in 60 to 80 per cent of cancers of the female genital apparatus[198,208, 212, 216, 221, 222, 281, etc.] and almost constantly in cases of moles or chorioepitheliomas.[198, 204, 205, 218, 221, 228, 229, 235, 248, 252, 253, 260, 267, 281, etc.] In the latter there may be as many as 200,000 to 700,000 rat units per litre, which is of great diagnostic value.[205, 229, 241,etc.] In cases of testicular tumors, particularly in those of embryonic nature, enormous quantities of gonadotropic substances occur,[200, 214, 215, 218, 226, 228, 277, 281, etc.] which are described as prolan A, but differ from this. The high content found in moles and tumors compared with the small amount in the pituitary, leads one to the conclusion that it originates in the tumors and not in the pituitary; this is also borne out by the differences in the action of prolan A and anterior pituitary extracts.

Carcinogenic Action of Pituitary Extracts.

Hofbauer[231] insists repeatedly on the danger of anterior pituitary extracts, since prolonged administration in guinea pigs produces hyperplasia of the endometrium and precancerous lesions of the uterine neck. Overholser and Allen[251] also found atypical epithelial proliferation, and possible metaplasia, which seemed to be precancerous lesions; other investigators[206, etc.] do not admit that these are precancerous.

Action of Pituitary Extracts on Cancer.

Posterior pituitary extracts (pituitrin, etc.) have no influence on the growth of implanted tumors or human cancers.[203, 219, 237, 257, 271, 273] With several anterior lobe extracts various results have been obtained, depending on the injected substances, the type of tumor, and the rapidity of its growth; in some cases an accelerating effect was observed;[203, 219, 223, 227, 255, 258, 272, etc.] in others there was no alteration. The inhibitory action on tumor growth by prolan A described by both Zondek and Hartoch[282] has received some confirmation,[207, 212, 242, 250, 264, etc.] but other investigators have not observed this effect, or else obtained merely a nonspecific weakening in growth.[223, 224, 232, 239, 240, 278, etc.] The disturbing effect on tumor growth *in vitro* described by Reiss and Hochwald,[256] Kriesch and Victorisz[240] has not been confirmed.[249]

GENERAL DISCUSSION

The existence of a direct antitoxic or antiinfectious action of the pituitary gland or its secretions has not been proved, but the gland can modify the resistance of the animal by its metabolic action, its regulating action on the thyroid or adrenal and on the vascular or nervous systems.

The gland can show certain histological changes during infections or intoxications, but their functional significances are not understood. It has been thought that the increased growth in typhoid convalescents or sexual retardation and amenorrhea in adolescent tuberculous patients, may be due to functional changes in the gland but as yet there is no proof of this.

Anesthetics and hypnotics are not tolerated well by hypophysectomized animals, and after operation some species are more susceptible to infections, poisons of the nervous system (cobra venom, morphia, chloralose), blood pressure lowering agents (histamine, etc.) and blood sugar lowering agents (insulin, phlorhizin, etc.). Hypophysectomy, because it produces hypothyroidism, provokes a decrease in phagocytosis and accelerated formation of antitoxins (in dogs), the agglutinin production not being changed. The thyrotropic hormone of the anterior pituitary, by stimulating thyroid activity, causes hypersensitiveness to anoxemia in rodents; in the mouse an increased resistance to acetonitrile and in the dog a slightly increased resistance to chloralose occur.

The pituitary can be the site of benign or malignant new growths, also of metastases. The structure of the pituitary is modified in patients suffering from cancer. Hypophysectomy retards, but does not prevent the growth of tumors and diminishes the number of implantations which take; probably this is due to a metabolic action which should be studied. The urine of cancerous patients (especially cases of uterine tumors, moles, testicular tumors) has a powerful gonadotropic activity. Pituitary extracts can accelerate the growth of certain tumors. In some cases prolan A has an inhibitory action but its specificity and its practical importance are doubtful.

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FOODS CONTAINING ARSENIC AND LEAD

The Department of Agriculture has consistently maintained that foods containing added arsenic and lead in amounts held by qualified scientific opinion to be poisonous or deleterious constitute a definite menace to public health and, under the pure food law, are subject to action. As the result of intensive activities over a period of many years the Food and Drug Administration encounters today relatively few interstate consignments of fruits or fruit by-products containing dangerous quantities of lead and arsenic.

The Washington Dehydrated Food Company was found guilty in 1933 in the Federal court in Yakima, Washington, of a violation of the Federal Food and Drugs Act in shipping in interstate commerce stocks of apple chops carrying residues of poisonous lead and arsenical sprays which might render them injurious to health. The firm later marketed apple chops containing lead and arsenic in amounts deemed by eminent toxicologists to be capable of injury to health. One of these shipments involved a consignment destined for export to France. The Government instituted seizure proceedings when lead and arsenic in such amounts were found, taking the position that the pure food law does not sanction the practice of making foreign countries a dumping ground for foods not measuring up to the criteria of fitness set for our own country. The lower Federal court in that instance, however, ruled against the Government, holding that the shipment fell within a proviso in the food law exempting, under certain conditions, violative shipments consigned to foreign shores. The court also expressed doubt as to the deleteriousness of the material.

An outgrowth of this adverse decision was the institution of a suit for damages by the president of the Washington Dehydrated Food Company against administrative officials of the Department of Agriculture who, in carrying out their duty, had reported the facts as to the arsenic and lead content of the export shipment. The civil suit for damages resulted in a hung jury and is of vital interest to every consumer since in its larger aspects it involved the question as to whether a Federal officer, in the discharge of his official duties under the Food and Drugs Act, can be held personally liable for damages for reporting facts to his superiors in the event of an adverse court decision under the Food and Drugs Act. The action in St. Louis is the most recent chapter in the various legal actions which have grown out of shipments by the Washington Dehydrated Food Company.—*Bulletin*, U. S. Department of Agriculture.

COOK PORK WELL TO PREVENT TRICHINOSIS

Reports received by the Department of Agriculture of several recent cases of illness and some deaths from trichinosis justify a repetition of the warning to cook pork thoroughly before serving. The parasites occur in a small percentage of hogs, which themselves suffer no apparent inconvenience. But the meat of such hogs, unless well cooked, constitutes a considerable danger to human health.

The assumption that pork which has passed inspection by a federal organization is safe even when eaten raw or undercooked is erroneous. There is no test that will show definitely whether trichinae are present in a sample of pork, except in some cases of severe infestation. Certain products that are customarily eaten without cooking in the home are given a special processing at federally inspected establishments, and are free from live trichinae. Pork products of the kind that ordinarily are cooked in the home are not processed in meat-packing establishments, since thorough cooking is a complete safeguard.

When infested pork is eaten by human beings in a raw or insufficiently cooked state, the trichinae are set free in the digestive tract where they give rise to numerous young worms. The latter invade the muscles, thus causing the painful disease, trichinosis, which somewhat resembles typhoid fever, meningitis, and several other diseases that are characterized by fever. Severe cases of this disease are likely to result in death. — *Bulletin*, U. S. Department of Agriculture.