in the treatment and prognosis of such cases, as the surgeon is liable to be misled by the innocent appearance of the external wound and the absence of immediate symptoms of an alarming character. Mackenzie relates several cases in which the patients walked considerable distances after receiving the injury and then fell dead.

The result of a *gunshot wound* of the orbit will depend upon the direction that the ball takes. In a large proportion of cases the brain is injured and death ensues; but a ball passing obliquely through the temporal region may destroy one eye only, and cases are reported in which sight was entirely destroyed, without other injury, by balls crashing through both orbits behind the eyes. I met with one such case, during the civil war, in which very little deformity resulted, and the external appearance of the eyes was not affected.

Fractures of the base of the cranium frequently extend into the walls of the orbit, generally the roof. In the post-mortem examination of eighty-six cases of fracture of the base, von Hölden found fracture of the orbit in seventy-nine. (Berlin, *loc. cit.*) Blindness may result immediately from rupture of the optic nerve, or from hemorrhage in its sheath, or it may be subsequently induced by neuritis. Intracranial hemorrhage and hemorrhage and emphysema of the orbit, as results of fracture of the orbital walls, have already been referred to.

It is important to remember that *foreign bodies*, even of considerable size, may easily escape detection in the orbit. A number of striking instances of this have been recorded. Mr. Carter has reported a case in which a piece of iron hat-peg, nearly three inches and a half long, remained concealed in the orbit for several weeks, without the knowledge of the patient. It was removed, and the eye remained uninjured. Hennen found a flattened musket ball which had lodged in the orbit, without injury to the eye. Shot from fowling-pieces and chips of iron driven with force by the hammer or lathe sometimes pass through the ball and lodge in the orbit. Shot may become encysted and cause no irritation, and even larger and rough substances may give little indication of their presence. A man presented himself at the Wills Hospital, in Philadelphia, with a wound near the corneoscleral junction, but he was very positive that the foreign body that inflicted it had rebounded. The eye was but slightly inflamed, and the patient continued to improve and would have been discharged if a little sympathetic irritation of the other eye had not been noticed. In enucleating the ball great difficulty was experienced in cutting the optic nerve, and a splinter of iron, one inch long, was found lying by its side.

x-Ray examination may be made useful in detecting the presence of a foreign body and even in determining its location.

Cases were formerly reported in which impaired vision was attributed to injury of the supra-orbital or infra-orbital nerve by blows upon the edge of the orbit, but it is probable that the ophthalmoscope would have revealed some intra-ocular lesion produced by concussion, or that a fracture involving the apex of the orbit may have injured the optic nerve. Contusion of these nerves is not now recognized as a cause of amblyopia.

Dislocation of the eyeball may be caused by a foreign body thrust into the orbit behind it. It has frequently been produced by the "gouging" thumbs of brutal fighters. The ball lies upon the malar bone and the orbicularis muscle contracts behind it, retaining it beyond the lids. The optic nerve is, of course, violently stretched, but is not usually permanently injured if the dislocation is soon reduced.

In the *treatment* of injuries of the orbit it is important to bear in mind the dangerous character of its anatomical relations, and the serious mischief that may easily be inflicted by probing. It is better to treat many trivial cases with unnecessary caution than to underestimate the danger of one that may have a serious or even fatal termination. Complete rest, cold applications, and sometimes leeching will be required in the early stages, and if pus forms subsequently it should be allowed prompt and free escape. If incisions are necessary for the removal of foreign bodies, they should be made through the conjunctiva rather than through the lids, to avoid the danger of ectropium or other deformity that might follow the contraction of cicatrices. In reducing dislocation of the eyeball, the upper lid should be stretched and drawn forward, while the ball is gently pressed back. It may be necessary to divide the external commissure. A compress bandage will be required to retain the eye in position for a few days.

Diseases of the Neighboring Sinuses may seriously affect the orbit by pressure upon its walls or by extension into its cavity.

The *frontal sinus* is sometimes greatly distended by the accumulation of retained muco-purulent secretion in chronic inflammation of its lining membrane. The upper and inner wall of the orbit is bulged by pressure, and the eyeball is forced downward and outward. These accumulations are sometimes very extensive, and involve the ethmoid sinus or the frontal sinus of the other side by destruction of the intervening walls. Dr. Bull (Trans. Am. Oph. Soc., 1885) reports a case of chronic abscess involving both frontal sinuses and the ethmoid sinus of one side, the result of an injury received fourteen years before. The disease may also result from direct extension of inflammation from the mucous membrane of the nose. The pus may finally escape into the nose, into the orbit, or externally, but the opening that gives it exit is not likely to be free enough to lead to a cure. The most common locality for spontaneous discharge is at the inner canthus, above the tendo oculi, and a permanent fistula is likely to result. When the bone over the swelling is very much thinned by distention and absorption it yields to pressure by the finger with a kind of crackling sensation, which has been well compared to that produced by pressure upon the lid of a tin box, and which will distinguish the case from one of solid growth. The sinus should be freely opened with a strong knife, or, if necessary, with a drill, near the inner canthus or beneath the superciliary arch, and a silver tube inserted, through which the cavity can be washed out frequently with disinfectant and stimulating solutions. It may be necessary to open the cells through the inner wall of the orbit, remove all carious bone, and establish drainage through the nose.

Similar distention of the *maxillary antrum* by fluid accumulation forces the floor of the orbit upward. It may result from any cause that produces chronic inflammation of the lining membrane of the cavity, but the most frequent cause is a diseased tooth. Pus may escape into the nostril, through the alveolus at the canine fossa, or into the orbit. When it enters the orbit it causes an infiltration and swelling of the lower eyelid, and finally a fistula. When there is a diseased tooth, the best plan of treatment is to extract it and puncture the antrum through its socket; or, if the abscess points in the alveolar process, an opening may be made behind the upper lip. In either case a tube should be inserted and injections used.

A few cases of retention tumor of the *ethmoid cells* have been met with. Dr. Knapp (Trans. Fifth Internat. Oph. Cong.) reports one in which the wall felt so dense that he took it for an exostosis and proceeded to remove it, when the chisel pierced a bony shell, and a quantity of muco-purulent discharge escaped. And a similar experience occurred in my own practice (Trans. Am. Oph. Soc., 1900).

Cysts, polypi, or solid tumors of any of these cavities, or of the nares, may press upon the walls of the orbit or destroy them and extend into its cavity. A discussion of all of these diseases would lead into too wide a field for the limits of this article, and the reader must be referred to works on general surgery and to the elaborate chapter on this subject in Mackenzie's treatise on "Diseases of the Eye." Intracranial growths sometimes involve the roof of the orbit, and in chronic hydrocephalus its cavity is narrowed by pressure, and the eyeball is pushed forward.

George C. Harlan.

OREXIN. — (Phenyl-di-hydro-quinazoline hydrochlorate.) This is the trade name applied to a complex derivative of quinoline. It forms in bright, colorless, lanceolate crystals, without odor, containing two molecules of water, which effloresce on exposure. It has a bitter, pungent, and almost caustic taste. It is freely soluble in hot water. It is almost free from toxic effects, as two grains per pound weight were insufficient to cause death in a rabbit.

Orexin was introduced by Professor Penzoldt, of Erlangen (*Therap. Monat.*, February, 1890), as a stomachic, as it was found to exert a tonic influence over the digestive organs, and a stimulant action on the appetite. It possesses neither antipyretic nor antiseptic properties. Penzoldt used it in a great number of cases of anorexia in healthy individuals, as well as in others suffering from various diseases accompanied by loss of appetite. Its use is contraindicated when there are gastralgia, acute catarrh, ulcers, or any condition in which there is hypersensibility of the mucous lining of the stomach, on account of its local irritant action. The class of cases in which it proved most serviceable were those in which the stomach was not diseased, but in which the loss of appetite was due to some general condition, such as anæmia, phthisis, or debility. It was said to be of special value in commencing pulmonary tuberculosis, its employment being followed by a considerable increase in body weight. The dose is from three to seven grains, once or twice a day. Within the last few years the *iannate* of this agent has been brought forward as being superior to the hydrochlorate. It is a yellowish-white, odorless, and almost tasteless powder, soluble in water.

Although favorable reports of its use appear from time to time, it has failed to gain the confidence of the profession and is rarely employed.

Beaumont Small.

ORGANOTHERAPY. — (Synonyms: Histotherapy—from ἱστός, tissue; cytotherapy—from κύτος, cell).

History.—The oldest medical manuscript in existence, the "Papyrus Ebers," mentions the use of animal extracts in medicine. Among the writers of antiquity Homer, Democritus (450 B.C.), Aretæus, Dioscorides, Galen (600 A.D.), among writers of the Middle Ages, Guido de Chauliac (1300 A.D.), John Hunter, Burton (in his "Anatomy of Melancholy") all speak of the treatment of disease with various animal products. It is interesting to note some of the bizarre preparations that were recommended, *e.g.* (Dr. William Salomon, "New London Dispensatory," 1677), human heart, *cor hominis*, in powder for epilepsy, human skull and human brain, *tinctura cranii*, *essentia cranii hominis*, *spiritus cerebri humani*, for a variety of disorders, chiefly "debility."

Brown-Séquard, in 1869, advanced the hypothesis of the "internal secretion" of the glands and tissues; he held that all the cells of the body manufacture specific soluble products which, entering the blood, exercise "an important if not necessary" influence on other cells. Insufficiency of this function in certain organs, he argued, produces certain definite disorders that can best be remedied by supplying the deficient secretion. The extravagant and sensational claims advanced by over-enthusiastic disciples of this "method" have done much to discredit organotherapy. Of recent years, however, many clinical and experimental data have accumulated to show that certain organs actually do manufacture internal secretions, and that these products profoundly influence metabolism. The postulates of Brown-Séquard were in part, therefore, correct and his method was not altogether irrational.

It is manifestly a precarious and an unscientific procedure to introduce substances of unknown properties into a sick organism without first determining their effect on the healthy body. Before organotherapy could be raised above the level of crude empiricism and could attain the dignity of a rational system of treatment, the power of organ extracts to influence physiological processes had to be studied. This problem was approached in two ways, viz.: on the one hand, different animal preparations were administered to normal animals or human subjects and the effects determined; on the other hand, different organs (chiefly ductless glands) were removed and the perversions of function that followed established. The knowledge, moreover, obtained from operative ablation of organs was in many instances supplemented by clinical observations on human subjects in whom spontaneous degeneration or atrophy of these organs had occurred. In this way a fund of knowledge was acquired that based organotherapy on a rational foundation, and furnished concise indications for the administration of definite organ preparations in definite diseased states. Organotherapy was finally rendered still more exact by the discovery and isolation of "active principles" that possessed all the specific properties of the organs from which they were derived; these, it was shown, could be advantageously administered in the place of the crude extracts, of indefinite and uncertain composition, that were formerly employed.

I. The Ductless Glands.

1. Thyroid Gland.—The *administration of thyroid gland* in large doses accelerates proteid and fat metabolism, causes increased elimination of nitrogen, phosphorus, and chlorine, and leads to an increased absorption of oxygen. Clinically, polyuria, polyphagia, polydypsia, sweating, tachycardia, palpitation, tremor, emaciation, fever, and occasionally glycosuria are observed. This syndrome is called *thyroidism*, and has so many cardinal features in common with exophthalmic goitre (Basedow's, Graves' disease) that this affection is held by many to be due to excessive activity of the thyroid gland, *scil.*, *hyperthyroidism*.

Removal of the thyroid gland is followed in a few days or often after a longer time (as late as nine months) by anæmia and oligæmia (*cachexia thyreopriva*, if the normal gland is removed, *cachexia strumipriva* or *operative myxœdema* if the diseased gland is removed); there is often an initial rise of temperature usually followed by a descent to subnormal; the growth of the bones is retarded in young animals, and various trophic disturbances develop; the rate of respiration increases; a variety of nervous phenomena are observed that may be either irritative or depressive in character, viz.: at first fibrillary twitchings of the muscles followed later by tetany and contractures, or again paresis and diminished sensibility. Other symptoms are palpitation, tachycardia, vomiting, loss of mental vigor, irritability followed by languor and lassitude, apathy, and finally idiocy.

A similar syndrome is presented in myxœdema and cretinism (synonyms: infantile or fœtal myxœdema, myxœdematous idiotism); myxœdema is undoubtedly due to arrest or insufficiency of thyroid function, *scil.*, *athyroidism*. We witness the same arrest of development of bones and external soft parts, the impairment of psychic and of nearly all somatic functions. The infantile type is maintained throughout, the physiognomy is typical, there are characteristic disturbances of the organs of sense and of the intellect, the skin is bloated, the sweat glands are depressed, the heat regulation is disturbed. There are general muscular quiescence, apathy, and idiotism. Exact metabolic studies have so far not been made. In one case the oxygen absorption was found subnormal and the nitrogen excretion reduced. It is probable that metabolism becomes retarded after ablation or atrophy of the thyroid gland.

The function of the thyroid is either nutritive or antitoxic, *i.e.*, it either supplies something to the blood that is necessary to normal life or it removes something that is harmful. The most plausible theory advanced to explain hyperthyroidism and athyroidism is the following: The blood normally contains certain bodies that can inhibit metabolism; the origin of these bodies is obscure; the thyroid secretion possesses the power of neutralizing these substances and rendering them inert. Normally metabolism is regulated in this way. Hyperthyroidism causes complete neutralization of these inhibitory sub-

stances followed by acceleration of metabolism; athyroidism, on the other hand, by permitting the accumulation of excessive quantities of the inhibitory bodies, favors retardation of metabolism.

The active principle of the thyroid gland is thyroidin (iodothyrin), a proteid body containing over nine per cent. of iodine. Removal of the iodine renders this substance inert. Iodothyrin administered to healthy animals produces the same effects as fresh thyroid gland or thyroid extracts. When administered immediately after ablation of the thyroid it is capable of arresting the convulsions that frequently follow this operation. The action of iodothyrin is cumulative, but only of short duration. In order to do good it must be administered continuously. When iodothyrin is given to dethyroidized animals all the iodine appears in the urine in a short time and is wasted. In animals with a thyroid the bulk of the iodine is retained. The thyroid, therefore, seems to be concerned in arresting and preserving the valuable iodine that is ingested with the food and that is intended to play some physiological rôle.

It appears, from experimental investigation, that the iodine body of the thyroid is an indispensable regulator of oxidation, and is also needed to preserve the normal function of the brain and nervous system and possibly of other organs. The "colloid substance" of the thyroid that was long believed to be the active ingredient of the gland has been shown to contain an organic iodine compound, probably iodothyrin.

Various *preparations of thyroid gland* are in use in medicine. Bircher in 1889 implanted a piece of thyroid gland under the skin. Later different extracts were prepared with glycerin alone, or with glycerin and carbolic acid or thymol. These extracts were administered hypodermically. The French favor fluid extracts made with carbolized physiological salt solution sterilized under pressure with carbonic acid gas and pressed through clay candle filters; this extract, too, is used for hypodermic injections. Vermehren precipitates the glycerin extract of thyroid with alcohol, gathers the sediment, desiccates it, and administers it in pill form (Vermehren's thyreoidinum). Many clinicians give the fresh gland raw by mouth; some boil the gland to make it more palatable, and claim equally good results as from the raw organ.

Still others give clysmata of thyroid gland. The most popular preparations nowadays are compressed thyroid tablets made from the desiccated gland. These are less disagreeable to the patient, and if prepared by a reliable house enable the physician accurately to determine the dose. True, very little is known of the amount of active principle which they contain, but the same objection applies to all the other preparations. As it is essential to individualize in thyroid medication, it is at all events of advantage to know that the qualitative and quantitative composition of the tablets is approximately uniform. For the many methods in use for preparing dry thyroid extracts and tablets we refer to text-books of pharmacology.

The *dose* to be administered naturally depends on the preparation employed. Many subjects manifest an idiosyncrasy for thyroid products, so that it is always well to begin with very small doses and carefully to watch for symptoms of thyroidism (see above). Dried thyroid powders frequently contain ptomaïns and peptonized proteïds that are toxic; they may consequently give rise to additional untoward symptoms. The best guide is the pulse. Quickening of the heart beat and palpitation should lead us to stop the administration of the drug until the heart action becomes normal. Gastric disturbances or rapid loss of flesh should also put us on our guard. Occasionally a change of preparation or a different mode of administration will enable the patient to tolerate the drug, but it is usually best either to stop its exhibition, or at least materially to diminish the dose.

The fresh gland furnishes about twenty-seven per cent. of dry powder, so that each unit of powder corresponds to about four times its equivalent in fresh gland. Manufacturers of thyroid tablets always indicate the amount of thyroid powder contained in each tablet. Beginning with a fraction of a tablet a day the dose may be gradually increased to seven or eight tablets in the twenty-four hours. Of the raw gland one-eighth to two may be given in the course of a day. The common dose of the desiccated powder is from one to five grains three times a day.

Therapeutics.—Thyroid preparations are employed most successfully in all those diseases which are due to insufficiency of thyroid function, viz., infantile myxœdema (*cretinism*), operative myxœdema (*cachexia strumipriva*), and adult (*sporadic*) *myxœdema*. Thyroid treatment in these states is a true substitution therapy.

In all forms of myxœdema thyroid medication as a rule produces amelioration of all the symptoms; in a minority of the cases only the main symptoms are relieved, while the minor and probably secondary manifestations persist. In adult myxœdema, for example, the swelling may recede while the anæmia persists. In cretinism the results are particularly brilliant. The skin becomes soft and moist, the bloating disappears, the physiognomy changes, healthy growth of the bony structures and of the soft tissues is stimulated, normal development of the teeth sets in, and the mental condition improves.

The younger the subject the better apparently the result, although all ages seem to react favorably. A case is on record, for instance, of a woman of seventy-two years who had been a sufferer from myxœdema for twenty-six years, and who was completely cured in three months. Some authors maintain that the older the disease the more rapidly does it yield to thyroid therapy. The sex of the patient is without influence. Each individual seems to react differently.

In a very small proportion of cases thyroid treatment is without result, and one or two cases are on record in which the disease was aggravated. The unsuccessful cases constitute not quite two per cent. of all the cases reported in the literature. As it is not excluded that in some of these instances the thyroid preparation employed was worthless, this is a remarkably good showing, and one that warrants the use of thyroid, with the precautions outlined above, in all cases of myxœdematous disease.

Thyroid preparations have also been employed in a large number of other diseases; the indications for the exhibition of thyroid being based either on our knowledge of its physiological effect or, in many instances, on pure speculation. In some diseased states the results obtained have been sufficiently favorable to warrant recording.

As trophic disturbances of the skin are common in sporadic and operative myxœdema, thyroid preparations have been used in the treatment of many *skin diseases*. The best results have been obtained in psoriasis. The sphere of usefulness in this disease is, however, limited, and thyroid should be employed as a last resort, only after all other standard remedies and measures have failed. In lupus, cutaneous tuberculosis, leprosy, keloid, alopecia, eczema vulgaris, acne rosacea, ichthyosis, thyroid has also been tried with varying effect. The results are often negative and uncertain throughout. Scleroderma does not yield to thyroid therapy. It is probable that thyroid gland acts favorably in some cutaneous affections by stimulating the circulation of the skin. Improved vascular supply leads to improved nutrition, increased activity of the cutaneous glands, and increased vitality of the epidermal layer, all tendencies that must act beneficially in correcting the trophic perversions that form the basis of many skin lesions. Thyroid preparations, either in the form of the dry powder or as an ointment, have also been applied locally to *serpiginous ulcers*, *suppurating buboes*, syphilitic and soft *chancres*. Good results are claimed for this method.

Loss of weight is a common result of thyroid medication. This observation has led to the employment of thyroid gland for the reduction of *obesity*. A loss of fat undoubtedly can be brought about in the majority of

cases. Patients with anæmic obesity are more suitable for thyroid therapy than patients with plethoric obesity. In the latter the results are as a rule indifferent; in the former oxidation is increased, as shown by the increased amount of oxygen that is absorbed and the greater amount of carbon dioxide that is eliminated. Together with the fat some proteid is, however, always lost in these cases, so that from this point of view alone thyroid medication is to be condemned in the treatment of obesity. As obesity, moreover, is frequently complicated by various cardiac disorders, gout, diabetes, and kidney lesions (all conditions in which thyroid preparations may do harm), this therapy is dangerous also on these grounds. It must further be remembered that as soon as the administration of thyroid gland is discontinued the fat returns; consequently the drug must be taken continuously. This leads to the indiscriminate use of thyroid preparations by the laity, a procedure that is manifestly dangerous. Finally, the exhibition of thyroid is totally unnecessary in obesity, for correct dietetic treatment produces results that are equally favorable, more constant, more permanent, and not at all dangerous. In carefully selected cases which are rigorously supervised by the physician small doses of thyroid, together with rational dietary regulations, produce satisfactory results and may be permitted.

In *insanity* the results of thyroid therapy are not constant; some cases are strikingly benefited, others are not affected at all. It is probable that in many sufferers from melancholia, recurrent mania, delusional insanity, and the insanities of adolescence, the climacterium, and the puerperium there is at the same time some derangement of thyroid function, and that these cases precisely, and possibly these cases alone, derive benefit from the use of thyroid preparations. The insanities of myxœdema, needless to say, often improve under thyroid medication. The largest statistics on the subject show that of 1,032 such cases 16.8 per cent. recovered, 24 per cent. were improved, and 59.2 per cent. remained unimproved. The results, therefore, in this particular form of mental derangement are fairly good.

Because infantile myxœdema and *rachitis* are both characterized by disturbances of the bony development thyroid medication has been employed in the latter disease. The relation between the two diseases is, however, purely superficial and their pathogenesis radically different, so that we need not be surprised to learn that thyroid therapy has led to absolutely negative results in rickets.

There is a superficial resemblance between *acromegaly* and myxœdema, and in some cases of acromegaly the thyroid has been found degenerated or atrophied. Some experiments are also on record that seem to show that the pituitary body hypertrophies after removal of the thyroid. These observations have led to the employment of thyroid in acromegaly. The results of this treatment are not satisfactory. A few isolated cases are on record, however, in which thyroid medication seemed to do good after all other measures, including the exhibition of pituitary extract, had failed. The method deserves further trial.

Simple goitre often yields to thyroid treatment. Some statisticians report improvement in two-thirds of the cases. Young persons, it is claimed, are more benefited than older subjects. It is necessary to continue the administration of the remedy for a long time, as otherwise the goitre is liable to return. The swelling rarely if ever disappears completely. The treatment must be considered symptomatic and in no case curative. The treatment is useless in goitre that has undergone secondary degeneration (colloid, cystic). The simple parenchymatous form is the most suitable for treatment with thyroid gland. Of 60 cases of the latter kind 14 were cured, 29 improved, and 19 not benefited. One author reports improvement in all of a series of 79 cases, another one improvement in 92 per cent. of a large series of cases.

The treatment of *Basedow's Disease* (exophthalmic goitre) with thyroid preparations seems altogether paradoxical, for, as we have seen, the cardinal symptoms of this disease are actually produced by the administration of thyroid. To expect a cure would be to avow faith in the homœopathic "law" of similars. Nevertheless the remedy has been extensively employed in this disease either empirically or from ignorance of the physiologic action of the thyroid extract, and finally on the basis of various hypotheses that are not worth recording. The consensus of opinions, as was to be expected, is that thyroid has a tendency to do harm in this disease. In many instances no effect was noticed when small doses were given. A few cases of improvement are also reported, chiefly by American and French authors, but the case reports (which have been carefully studied by the author) do not show that the amelioration of symptoms could in any way be attributed to the action of the thyroid preparations given. In exophthalmic goitre, therefore, the use of thyroid should be discouraged as useless.

A more rational method of treating Basedow's disease has recently been tried, apparently with good results. It consists in injecting the serum of dogs whose thyroid has been removed. This method is at least based on sound physiologic reasoning. It warrants further trial, for of the nine cases treated all improved.

Thyroid preparations have at one time or another been tried in nearly every known disease. Benefits have been claimed in tetany, the various disorders of lactation (galactagogue action), certain middle-ear disorders, muscular and osseous dystrophies, hemorrhages in uterine diseases, cancer of the breast, and syphilis. Very little value, however, attaches to isolated case reports, for in the majority of them grave sources of error are not excluded, and no conservative judgment in regard to the therapeutic value of the thyroid preparations administered can be rendered.

2. The Suprarenal Glands.—Injection of suprarenal extract produces a very marked rise of blood pressure. This is primarily due to vaso-constrictor action, for suprarenal extract exercises its chief effect on the peripheral circulatory apparatus. This is made manifest after section of the medulla or the cord (even complete removal of the cord), section of the vagi, of peripheral nerves, or paralysis of the nervous end apparatus with atropine, for all these operations do not hinder the rise in blood pressure after injection of suprarenal extract. Direct application, moreover, to mucous surfaces causes rapid contraction of the blood-vessels of the part. It is not established whether suprarenal extract acts directly on the muscle cells of the arterial muscularis or on the ganglion apparatus of the vessel walls. Suprarenal extract also acts directly on the heart, causing retardation and strengthening of the heart beat, and in this way, too, a rise in blood pressure. It seems that the extract directly stimulates the heart muscle and at the same time irritates the vagus centre. The former action strengthens the heart beat, the latter retards it. If the medulla is destroyed or the vagus severed, the heart beat is greatly accelerated after the exhibition of suprarenal extract, more so than after simple section of the vagi. Applied to the excised heart of a frog suprarenal extract also causes quicker and more forcible contractions. The *direct* effect of the extract on the heart muscle is accelerating, in other words, excitory, as in the case of the arterial muscularis.

Other effects that follow the injection of suprarenal extract are: (1) The excretion of dextrose (suprarenal glycosuria); (2) local pigmentation around the point of injection; (3) destruction of red blood corpuscles and deposit of hæmosiderin in the spleen and lymph glands; (4) excretion of pigments related to bile pigments.

Removal of the suprarenal glands, a very difficult operation, is invariably followed by the death of the animal. If one gland alone is removed or if accessory adrenals are left behind, compensatory hypertrophy of the remaining organ occurs and the animal may survive for months or even years.

The statements made by different authors in regard to the effect of removal of the adrenals on general nutrition are contradictory. The same applies to the effect on the

temperature; some report a rise, some no change, some subnormal temperatures. The effect on the nervous system is marked. All authors agree that degenerative changes in the brain, cord, and sympathetic plexuses follow removal of the adrenals. The statements in regard to the clinical nervous phenomena observed are not uniform. There is always great muscular asthenia. The digestion is always impaired; there are increased peristalsis and diarrhœa. The blood pressure always falls. No uniform changes in the pulse rate or the respiration have been noted. Occasionally, when the animals survived for a period of several months, abnormal pigmentation of mucous and cutaneous surfaces has been noted. The most marked changes occur in the chemical composition of the blood. (The statements in regard to changes in the hæmoglobin content and the number of red blood corpuscles are absolutely contradictory.) The blood of an animal whose adrenals have been removed becomes very poisonous and acts like curare on healthy animals. It accelerates the death of other animals whose adrenals have been removed, whereas the injection of normal blood into such animals improves their condition. It appears that after removal of the adrenals certain substances accumulate in the blood that paralyze the motor endings of the nerves and maybe the muscles themselves. We are justified in assuming, therefore, that one of the functions of the suprarenals is to disintoxicate the blood. There is much experimental evidence to show that the toxic principle which the adrenals normally arrest or neutralize is a fatigue product of muscle and nerve activity.

Our knowledge of the *function* of the suprarenal glands is supplemented by clinical studies in Addison's disease. Here we find in the majority of cases spontaneous degeneration of the adrenals (usually tuberculous) and a symptom complex which corresponds in many features with some of the symptoms that follow *removal* of the adrenals, viz., asthenia, cardiac weakness. In other features Addison's disease resembles the syndrome following *injection* of adrenal extract (pigmentation, glycosuria).

This observation makes it probable that the function of the suprarenals is twofold, viz., that on the one hand they supply a substance that stimulates the sympathetic ganglia and striped and unstriped muscle fibre; on the other hand, that they arrest or disintoxicate certain poisonous principles which are the product of nervous and muscular activity. The latter fatigue products, we must imagine, when present in excess produce asthenia, blood impoverishment, and occasionally pigmentation and glycosuria. Only on this duplex basis can we explain how insufficiency of suprarenal function or absence of the glands can produce the whole syndrome of Addison's disease.

The "*active principle*" of the suprarenal glands has recently been isolated; it is called adrenalin. Older impure preparations are sphygmogenin (a syrupous liquid), suprarenin, and epinephrin (both albuminoid bodies). Other substances (lecithin, jecorin, pyrocatechin, neurin, etc.) that have been isolated from adrenal extracts, do not possess the specific properties of the fresh glands. With the discovery of adrenalin and its manufacture on a large scale all the other preparations have been superseded with the exception possibly of the desiccated and powdered gland itself.

Dose and Administration.—In one case of Addison's disease a piece of fresh gland was implanted under the skin of the patient. No effects were observed and death occurred in three days. The dry powdered extract is given by mouth in capsules or in compressed tablets, in doses varying from twenty to forty grains a day. The gastric juice does not destroy the action of suprarenal preparations. It must be remembered, however, that the drug when given by mouth exercises no effect on the blood pressure.

For hypodermic use, for administration by mouth, and for local application adrenalin is the most convenient, the most accurate, and the safest preparation at our disposal. It is usually dispensed in the form of the hydrochlorate (adrenalin chloride) as a white crystalline powder. It is a most powerful remedy. One part to ten thousand blanches the conjunctiva in from thirty to sixty seconds; 0.000008 of a grain, injected intravenously, causes a rise of blood pressure that is equal to the effect of 0.005 gm. of the dry powdered extract; 0.0000014 gm. per kilogram of body weight exercises a distinct physiological effect. It is the most powerful hæmostatic and astringent known, and the strongest stimulant of the heart. The preparation is non-irritating and non-cumulative. It is generally employed in the strength of 1 to 1,000 for hypodermic and local as well as for internal use. Hypodermically a few drops (two to ten) usually suffice to bring about the desired immediate effect (see below). By the mouth, from five to ten drops should be given every fifteen to thirty minutes for two or three times, and then every three hours, as needed.

Therapeutics.—In *Addison's disease* suprarenal preparations have been extensively employed. The results are not altogether unfavorable. In many instances improvement seemed to be maintained as long as the drug was exhibited. In one case the patient improved for two years under adrenal treatment. As soon as the remedy is stopped in these cases relapses are liable to occur; they are often sudden and severe, and may even terminate fatally. In the majority of cases the remedy is altogether without effect. In a few cases the patient's condition seemed to grow worse. No case of a complete cure is on record.

A number of statistics on the treatment of Addison's disease with suprarenal preparations have been published, but they are essentially without value because the stage of the disease, the time during which the cases were under observation, the quality of the suprarenal preparation are not included in the tabulation. In many instances the diagnosis is not even positive. One series, the most accurate one, includes 48 cases. Of these 6 were greatly improved, 22 slightly improved, 16 were not affected, and 2 grew worse. The results obtained so far are withal sufficiently encouraging to stimulate further trial.

Suprarenal preparations are the most rapid *cardiac tonic* which we possess. In sudden heart failure due to shock or hemorrhage, narcotics, anæsthetics, etc., hypodermic injections of adrenalin are very effective. The action of adrenalin is very transitory, however, so that in chronic heart lesions it cannot take the place of nitroglycerin, digitalis, or strychnine, but should merely be employed as an adjuvant to these remedies.

As rapid and powerful *vaso-constrictors* suprarenal preparations have a large sphere of usefulness. They can be given by mouth for the arrest of *internal hemorrhages* of all kinds (hæmoptysis, hæmophilia, etc.), and can be applied locally as *hæmostatics* to all bleeding surfaces. In the treatment of epistaxis adrenalin is particularly useful. In *inflammation of the conjunctiva* depletion of the engorged vessels with relief of pain and redness is rapidly brought about by the instillation of a few drops of adrenalin solution into the eye. In *glaucoma, episcleritis, vascular keratitis,* and *kerato-conjunctivitis* suprarenal gland is a valuable adjuvant to other treatment. In *operations on the nose* or other mucous surfaces the application of a spray of adrenal extract or of adrenalin will produce rapid ischæmia of the parts and consequently render surgical interference practically bloodless. Whenever it is desired to apply cocaine to intensely inflamed surfaces suprarenal extract may be first applied with profit, as it relieves the congestion of the tissues and in this way renders the action of cocaine more powerful. For the details of the employment of suprarenal preparations in ophthalmology, in intratympanic surgery, and in nose and throat work we refer to special articles on these subjects.

Suprarenal gland has been used in the treatment of *diabetes* (this use being based on the view that certain forms of disturbed carbohydrate metabolism are due to "lack of vaso-motor tension"), but the results of this treatment have been quite unsatisfactory. In view of the fact that fluctuations always occur in the condition of diabetic subjects, the reports in regard to temporary amelioration

following the use of suprarenal extract, must be judged with caution. The discovery of suprarenal glycosuria has also led to the employment of adrenalin in diabetes, but the results obtained are altogether negative so far. In a few cases the dextrose excretion was even increased for a short time.

In *asthma* with vaso-motor ataxia occurring in neurotic subjects the drug apparently has a certain application, and beneficial results from its administration are reported.

In the *asthenia* of certain nervous diseases, both functional and organic, the drug may do good as a muscle tonic. It is said to cause the feeling of profound fatigue so frequently complained of by neurasthenics to disappear. It also acts on the uterine muscles, and has been successfully employed to stimulate uterine contractions and to arrest uterine bleeding.

Other conditions in which suprarenal preparations are reported to have exercised favorable effects are acute maniacal excitement with low blood pressure, cyclic albuminuria, and the pain of cancer of the breast and the œsophagus.

3. Thymus Gland.—*Removal of the thymus* in animals in which it persists during life is not followed by any characteristic perversions of function. In man the gland spontaneously decreases in size from the second year, and is almost totally obliterated in adult life. The organ is therefore not essential to life, nor apparently of physiological importance in adult man. Of its function we know nothing.

Injection of thymus extract produces a fall of blood pressure, acceleration of the pulse rate, restlessness, dyspnœa, and in large doses collapse and death.

No *active principle* has been isolated. The gland contains iodine in smaller quantity than the thyroid. Dogs who are fed on thymus excrete a peculiar purin body, and the theory has consequently been advanced that the thymus is concerned in the metabolism of nuclein and the genesis from nuclein of uric acid and its chemical congeners.

The *dose* of thymus is much larger than the safe dose of thyroid. From ten grains to several ounces of the fresh gland have been given per day. Of the dry extract the common dose is from twenty-five to sixty grains a day. No thymus preparation is used hypodermically.

Therapeutics.—Thymus is particularly useful in *simple goitre*. In this disease it acts very much like thyroid, only not so energetically. The statistics in regard to the efficacy of thymus treatment of simple goitre vary greatly In many of the successful cases reported other treatment was given at the same time; and some of the cases were not kept under observation for a sufficiently long time to justify final conclusions in regard to a cure. The consensus of opinions is, however, very favorable. A critical review of the whole literature of the subject seems to show that about one-half the cases of simple goitre are much benefited by thymus. In several instances thymus brought improvement after thyroid had failed.

In *exophthalmic goitre* the reports are very much at variance. A few authors report aggravation of all the symptoms; others report altogether negative and indifferent results; a few report improvement. One author studied twenty cases of Basedow's disease treated with thymus, and contrasted with them twenty cases treated by various other means. The balance in regard to the retardation of the pulse rate, the decrease of the thyroid swelling and of the exophthalmus inclined toward treatment without thymus. The statistics as a whole are better than for thyroid treatment, but not as good as for other standard methods of treating exophthalmic goitre.

4. Pituitary Gland.—*Removal of the pituitary body* constitutes an operative inroad of such magnitude that only very few statements in regard to the effects of ablation of this organ are recorded in the literature. All the symptoms described, moreover, are ambiguous, and may be ascribed to shock or to injury of neighboring vital parts. From this source, then, we gain no reliable information. Spontaneous degeneration consisting in hypertrophy of the connective-tissue portions, cystic degeneration, sclerosis, atrophy, and tumor formation on the other hand is almost invariably followed by the syndrome of acromegaly. One case of hypertrophy of the pituitary body is on record in which acromegaly was absent, and a few cases of acromegaly are reported in which the gland was not found diseased. The connection between disease of the organ and acromegaly is nevertheless sufficiently apparent to warrant the employment of pituitary preparations in the treatment of this disease. In two cases of adiposis dolorosa the pituitary is also reported enlarged.

Injection of the infundibular portion of the organ produces a rise of blood pressure. Injection of the hypophyseal portion does not produce such a rise, but merely retardation of the pulse beat that persists to a certain extent, even after division of the vagi. A substance has also been isolated from the gland that causes contraction of arterioles and augmentation of the heart beat.

The *function* of the gland is not understood. Some authorities claim that it regulates the intracranial blood pressure, and is also concerned in the regulation of general metabolism. It is finally believed to exercise some effect on the growth and development of the bony structures and the cutaneous tissues of the body.

No *active principle* has been isolated.

The gland is usually administered in the form of a trituration or desiccated as a powder ("hypophysin"). The *dose* varies from one and a half to ten grains a day.

Therapeutics.—Pituitary gland is used exclusively in *acromegaly*. It seems to exercise no effect on the course of the disease, but does seem to be efficient in relieving some of the most distressing symptoms, as, for example, the headache, the neuralgic pains in the limbs, the general lethargy, and the loss of memory. In a series of thirteen cases seven showed relief of symptoms, five showed no improvement, and one case grew worse. Some authors claim to have seen marked benefits accrue from the combined use of pituitary gland and thyroid, particularly in regard to the relief of headache; but it is difficult to determine how much of this good effect must be attributed to the thyroid (see above) and how much to the pituitary gland. It is best in the present state of our knowledge to give sufferers from acromegaly the benefit of the combined use of thyroid and pituitary, in connection, of course, with other established measures for the relief of symptoms.

II. The Blood-Forming Organs.

The rôle which the spleen, the lymph glands, and the bone marrow play in blood formation has suggested their employment in various diseases of the blood. Extracts made from the three organs are used rather indiscriminately, either singly or in combination. Very few clinicians in administering these preparations apparently have clear conceptions in regard to the physiologic function in blood formation which these different organs perform. A summary of our present knowledge in regard to the hæmatopoietic function of the spleen, the lymph glands, and the bone marrow reads as follows:*

The *spleen* plays only an insignificant part in blood formation. It is not at all concerned in the formation of red blood corpuscles (in man!) nor in the formation of granular mononuclear and polynuclear leucocytes, nor of eosinophile leucocytes. It appears to manufacture a small proportion of the lymphocytes. Its chief rôle is to arrest the fragments of red and white corpuscles that are carried to it in the blood of the splenic artery (spodogenic tumor of the spleen in infections).

The *lymph glands* manufacture only lymphocytes and have no other function in hæmatopoiesis. The lymph glands are closely related to the spleen; both contain lymphoid tissue.

The *bone marrow* forms the granular mononuclear and polynuclear leucocytes, and in all probability the red

* The views held by different authors are greatly at variance in some respects. I have in the main followed Ehrlich, who is *facile princeps* in this field.