

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 diarrhoea. 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 disintegrate 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 disintegrate 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, 23 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, anesthetics, 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, dyspnea, 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 degener-

ation, 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.

blood cells. It is not related to the spleen and lymph glands and consists largely of myeloid tissue.

There are then two types of leucocyte-forming tissue—the lymphoid (spleen, lymph glands) and the myeloid (bone marrow). Metaplastic vicarious transformation of lymphoid to myeloid tissue may, however, occur. In myelogenous leukaemia, for example, large quantities of myeloid tissue are found in the lymph glands and the spleen. Under these conditions, therefore, the spleen may be said to play an important part in blood formation.

1. THE SPLEEN.—*Extirpation of the spleen* is invariably followed by vicarious hypertrophy of numerous lymph glands, and in many instances by enlargement of the thyroid. A colossal lymphocytosis develops very soon, but no increase is witnessed in the number of mononuclear and polynuclear granular leucocytes. If the animal survives for a year or longer, marked eosinophile leucocytosis develops.

The injection of splenic extracts produces a fall of blood pressure followed by a continuous rise and often by elevation of temperature. Splenic juice is irritating and may produce abscesses when injected hypodermically, and inflammation of the upper digestive tract when given by the mouth. "Eurythrol" is a salt-water extract of spleen that is given in the dose of one or two teaspoonfuls a day, and is said to be non-irritating and not disagreeable to the taste.

Therapeutics.—On physiological grounds splenic extract should be administered only to increase the lymphocytes. The spleen, however, contains much nuclein, and it is well known that this substance produces a marked general leucocytosis. From this point of view spleen may be used to produce general leucocytosis, but it seems much more simple and expedient to employ pure nuclein for this purpose.

It is very difficult to render conservative judgment in regard to the efficacy of splenic extracts in diseases of the blood. Innumerable reports have been published, but very few of them are free from ambiguity.

The most careful and exact observers report very little benefit. In the majority of cases other preparations were used together with the organ extract, so that no positive conclusions in regard to the latter can be reached. How splenic extract should produce an increase of red blood corpuscles, as some writers claim, or how, e.g., red bone marrow should cause a marked lymphocytosis, as others relate, it is difficult to understand on the basis of the physiological considerations we have outlined above.

In leukaemia, in which disease we have a relative decrease of lymphocytes, and also often a decrease of polynuclear neutrophiles, splenic extract might be expected to act beneficially. Physiologically, the supplying of spleen would raise the number of lymphocytes; chemically, the presence of nuclein would raise the number of granular leucocytes. What effect, however, splenic extract would have on the development of the myelocytes that are so colossally increased in this disease, what effect finally on the primary process, it is hard to foresee. Some good results have been claimed from this therapy, notably in regard to the increase of polynuclears (nuclein) and the improvement in the subjective sensations of the patient. It does not appear from the case reports that the course of the disease is appreciably modified.

In other blood diseases no valid reports of good results are on record. In typhoid fever and in tuberculosis splenic extract has been given, apparently with some benefit. We are inclined to attribute this to the nuclein leucocytosis.

As the spleen is occasionally found enlarged in operative and sporadic myxoedema, splenic extract has been employed in this condition. It seems to improve the general condition of the patient and to ameliorate the distressing mental symptoms. Combined with thyroid it seems also to enhance the efficacy of the latter. In this disease spleen has been given in the form of the dry desiccated organ (four hundred to six hundred grains a week) and as fresh gland (twenty grains per dose three times daily in capsules).

A few cases of exophthalmic goitre and of paludism (cachexie paludienne) are on record in which great benefits were claimed from splenic medication.

2. LYMPH GLANDS.—*Total extirpation of all the lymph glands* is manifestly impossible. In many clinical cases, however, the lymph glands are found extensively degenerated or involved in tumor formation. In all such cases the number of lymphocytes is greatly reduced.

What has been said in regard to the physiological function of the spleen applies with equal force to lymph glands; they, too, may possibly increase the lymphocytes, and they, too, contain much nuclein and consequently can produce leucocytosis. Theoretically, therefore, lymph gland extract is indicated wherever splenic extract is indicated in blood diseases. As a matter of fact, lymph-gland preparations have not been extensively used. All the case reports describe the administration of lymph-gland extract in combination either with spleen or with bone marrow.

3. BONE MARROW.—*Removal of all the bone marrow* is of course impossible. Comparative counts of corpuscles in the afferent and efferent blood-vessels of the marrow have yielded essentially negative results. In clinical cases in which the bone marrow was largely displaced by other tissues (malignant tumor formation), the number of polynuclear leucocytes was found greatly decreased. In the bone marrow are found preliminary forms of red blood corpuscles, and after great loss of blood the yellow marrow of certain bones is converted into red marrow, showing that a process of regeneration is stimulated here. It seems, therefore, that bone marrow should be employed to stimulate the formation of red blood corpuscles and of leucocytes other than lymphocytes. In addition it contains iron in organic combination, and many clinicians recommend its use on these grounds. They argue that the iron in the form found in bone marrow is more readily assimilable than iron in other combinations or metallic iron.

These claims are probably exaggerated, and are not based on experimental or clinical evidence of value. In fact, the majority of clinicians obtain equally good and equally bad results with the standard inorganic preparations of iron.

Bone marrow is either given raw in doses of several ounces a day or in the form of glycerin extracts. As the marrow of young animals is more active in blood formation than the marrow of adult animals, it seems advantageous to employ the former alone. The anterior extremities of the ribs are crushed so as to expose the cancellous tissue. The fragments of bone are then extracted with glycerin for a number of days, the extract is filtered off and given in teaspoonful doses from three to six times a day.

What good effects have been claimed from bone marrow can hardly be attributed to any ingredient that might be utilized to build up corpuscles, or, as we have seen, to the iron which it contains. We must hypothetically assume the presence of some body in bone marrow that is capable of stimulating blood formation.

In leucocythæmia (leukaemia) the employment of bone marrow is altogether irrational, because in this disease we have already hypertrophy and overactivity of the bone marrow.

In progressive pernicious anemia some good results are claimed. No case is on record, however, in which bone marrow was given alone. The best that can be said, therefore, is that as an adjuvant to other remedies it may be tried. It certainly cannot replace arsenic.

In chlorosis and in secondary anemias the results have been more favorable than in the primary anemias. Here again it may be used in combination with iron, but cannot replace the latter.

In pseudoleukæmia (Hodgkin's disease) the best results have been recorded. The exhibition of bone marrow is a more rational procedure in this disease than in all the other diseases of the blood, for here the spleen and the lymph glands are extensively diseased and the bone marrow, we must suppose, vicariously assumes the greater portion of

the hæmatopoietic function. Anything that can stimulate the bone marrow to increased blood formation is indicated. It is not impossible that bone marrow does this (see above). The best results are reported from the combined use of bone marrow, thyroid, and arsenic.

### III. THE GENERATIVE ORGANS.

The use of orchitic and of ovarian extracts is of historical interest. Brown-Séquard, when an old man, performed his first experiments with "*suc testiculaire*" on himself, and claimed to experience "a return of vital energy and rejuvenescence with renewed and efficient peristalsis and control over the bladder and sphincter." His conclusion was that the testicles secrete into the blood a substance that profoundly influences nervous and possibly muscular metabolism and increases mental vigor. There can be no doubt that the ridiculous claims of charlatanistic advocates of this particular application of the "Brown-Séquard method" have done much to bring organotherapy into disrepute. Nevertheless, the use of testicular and ovarian extracts, if we carefully weigh all the clinical evidence, cannot be absolutely condemned as useless. Favorable symptomatic results at least, that are not due to suggestion, are obtained without question in certain conditions.

1. THE TESTICLES.—*Removal of the testicles* in children exercises a very marked effect on growth and development. The voice remains treble, the subjects usually grow obese, show lack of mental vigor, and manifest psychic perversions of various kinds (eunuchs). The injection of testicular extract into normal subjects produces indifferent results.

Several so-called active principles have been manufactured from testicles. The best known is spermin. There are two different kinds of spermin. The one can be converted into its polymer piperazin (dispermin), the other cannot. Poehl discovered the latter, and claims the most startling effects from its exhibition. His statements are borne out by many Russian and some French authors, but the reports are not convincing. The majority of conservative French and German authorities failed to witness any physiological effects from Poehl's spermin and report negative results from its administration in all the morbid conditions for which it is recommended. Brown-Séquard states that spermin is not the active principle of testicular extract. Charcot's crystals which are found in testicle juice are phosphate of spermin.

Testicular extract is best made from the testicles of young animals by maceration of the glands, extraction with normal physiological salt solution, to which may be added a little carbolic acid, thymol, or glycerin. The extract is sterilized according to d'Arsonval, under pressure with CO<sub>2</sub> and filtered through a clay candle filter. No uniform data in regard to the concentration of this extract nor the exact dosage are given by the different authors who have written on the subject. The best results are claimed from hypodermic injection, and Brown-Séquard states that testicular extract is inactive when given by mouth.

The most interesting results are claimed in the treatment of locomotor ataxia. The destructive sclerotic lesions of the spinal cord that form the anatomic basis of tabes cannot of course in any way be influenced by the injection of testicular fluid. A cure is, therefore, a priori out of the question. It appears, however, that many of the symptomatic manifestations of the disease can be ameliorated by orchitic medication, so that the remedy may be tried. The statistics published are altogether contradictory. Brown-Séquard and d'Arsonval have published the most comprehensive tabulation of results. Three hundred and forty-two cases were treated. All improved, and some, they claim, were "cured" (!). Other French authors report eighty-five and ninety per cent. of successful cases. German clinicians, on the other hand, claim essentially negative results throughout.

In neurasthenia, hysteria, hypochondriasis, melancholia, and kindred psychoses transitory improvement is

reported by many writers, but the element of suggestion can hardly be excluded in cases of this character.

In general debility from wasting disease and in senility a certain tonic effect is conceded by nearly all authorities. It appears, therefore, that the chief therapeutic sphere, and probably the only sphere of testicular extract is to act as a tonic to the cerebrospinal centres. This power, it seems, is also inherent in many other organs, though possibly not to such a marked degree as in the testicles. Whether the latter produce a specific internal secretion that is distributed to other organs, or whether all organs secrete such a tonic principle, cannot be determined.

For the arrest of surface hemorrhage minced testicle, locally applied, has been found to be of value.

2. THE OVARIES.—*Removal of the ovaries* before the age of puberty prevents the appearance of the characteristic phenomena of puberty. The pelvis does not enlarge, menstruation fails to appear, the mammae and the genital organs atrophy, and occasionally certain male attributes develop. In adults, aside from the cessation of menstruation (a few cases are recorded in which periodic uterine bleeding persisted even after removal of the ovaries) and atrophy of the genital organs, a variety of distressing nervous phenomena and in many patients obesity are apt to develop. In cows removal of the ovaries causes the milk to become richer in fat.

The administration of ovarian extract to healthy animals has been known to cause death from hemorrhage into the spinal cord. Males are claimed to be more susceptible to this influence than females.

No active principle has been isolated. Ovary is administered as dry powdered gland in doses of from one to five grains. The powder is conveniently dispensed in compressed tablets. Glycerin extracts have also been recommended for hypodermic use.

Therapeutics.—Ovarian extract is a useful remedy for all the symptoms following double oöphorectomy. The nervous and vaso-motor disturbances (insomnia, headache, psychoses, flatulence, lumbar pains, etc.), of the climacterium and of certain uterine disorders also often yield to ovarian medication. The drug is not, however, reliable in all cases, and it is impossible to predict in any given case whether or not ovary will do good.

Senile debility in old women seems to be counteracted by the use of ovary. Of sixty-four old women treated in one of the Paris hospitals all, we are told, were greatly benefited and rejuvenated.

In hysteria good results are also related. In a young child hysterical contractures disappeared after a few doses; "*mais que n'obtient-on pas dans l'hystérie!*"

In chlorosis ovary is of greater benefit than spleen, lymph glands, or bone marrow. It is believed by leading authorities that the ovaries secrete a substance that stimulates blood formation, and that in chlorosis this function is insufficient. On these grounds they supply ovary and claim very favorable results.

Ovarian extract has finally been given with success as an aphrodisiac.

### IV. THE NERVOUS SYSTEM.

Brain cortex, cord, and nerve tissue have been employed either singly or in combination in many nervous or mental disorders. The most common preparation used is a sterile glycerin extract that is injected hypodermically.

All nervous tissues contain cholin and neurin, two bodies that are highly toxic. They are probably catabolic products of brain and nerve activity, for in nervous diseases in which nerve metabolism is increased the cerebrospinal fluid contains abnormally large quantities of cholin. It is probably due to the action of the latter substance that the injection of nervous extracts often produces a rise of temperature, leucocytosis, increased absorption of oxygen, and increased excretion of nitrogen. In addition to this toxic action nervous tissue, and particularly brain cortex, seems to exercise a distinct tonic effect, i.e., in healthy subjects a feeling of exaltation and of in-

creased energy. There is no record of any influence having been exerted on the pulse and respiration.

**Therapeutics.**—The best results, it is claimed, are obtained in *neurasthenia*, but suggestion cannot be excluded. In *epilepsy* and in a case of *bulbar palsy* one authority reports excellent effects. In *mental diseases* the psychopathic disorders seem to remain unaffected, whereas the physical condition of the patients improved greatly under this treatment. Of eleven cases of *tubercles* treated with nervous extracts seven are reported benefited.

As against many favorable reports we find an equal or even greater number of absolutely negative results. Nerve-tissue extracts probably possess tonic properties for the nervous system and merit employment in this sense. Many other remedies that we possess are, however equally efficacious, so that nerve extracts are by no means an indispensable adjuvant to our therapeutic armamentarium. Charlatans in and out of the profession have utilized these preparations extensively to impose on a credulous laity, so that their employment has fallen into considerable disrepute among conservative physicians.

#### V. THE SECRETING GLANDS.

Aside from their external secretion some of the glands of the body seem to furnish an "internal secretion" that plays an important part in intracellular digestion. In the case of the pancreas and the kidneys this may be practically considered established; in the case of the liver, the intestinal glands, the mammaræ, and the salivary glands it is highly probable.

1. **THE PANCREAS.**—Complete extirpation of the pancreas is invariably followed by the complete syndrome of diabetes mellitus. If a small portion of the gland is left behind, or if a piece of the extirpated pancreas is subsequently grafted under the skin, diabetes does not develop. Ligation of the pancreatic duct does not cause diabetes. There are numerous theories in regard to the rôle of the pancreas in carbohydrate metabolism; they cannot all be discussed in this place. The preponderance of experimental evidence points to the secretion by the pancreas of a glycolytic, *i. e.*, dextrose-destroying ferment. If this secretion becomes insufficient or is arrested, the blood sugar is not destroyed, consequently it accumulates. This leads to hyperglycæmia and glycosuria. Diabetes may also be due to other causes. Degeneration of the pancreas in man may and may not produce diabetes. From very recent investigations it appears that in nearly all cases of diabetes certain cell groups in the pancreas (the "islands of Langerhans") are found degenerated. These cells are not connected with the efferent ducts of the gland, but pour their secretion into the lymph spaces. It is probable that they furnish the specific internal secretion. Ligation of the pancreatic duct causes atrophy of the cells furnishing the external secretion, whereas the islands of Langerhans remain intact for a long time. The writer is at present engaged in studying the effects of pancreas prepared in this way, *i. e.*, of "isolated" islands of Langerhans in carbohydrate metabolism, both *in vitro* and *in vivo*. It is expected that these researches will throw light on the nature of the internal pancreatic secretion, and will advance the organotherapy of diabetes. For the present this method of treatment, although so clearly indicated on theoretical grounds, has furnished essentially negative results. This may be due to the fact that all pancreatic extracts contain digestive ferments and certain nucleoproteids that are toxic and produce local necrosis when injected hypodermically; thromboses, pyrexia, tachycardia, increased diuresis, and increased N-excretion when administered intravenously. The administration by mouth is negative in diabetes. It is probable that the trypsin contained in pancreas extracts destroys the "internal secretion" as it destroys the fat-splitting enzyme that we know to be present. An extract of pancreas containing no digestive ferments, prepared as suggested above, may act more favorably.

The administration of pancreas by mouth is practised

for the relief of *steatorrhœa* and other *intestinal disorders* that are due to perversion or absence of the external secretion of the gland. This treatment is not, however, organotherapy proper, and will therefore be discussed under other headings.

2. **THE KIDNEYS.**—Complete anuria may persist for many days without causing the development of uræmic symptoms (*e. g.*, hysterical anuria). If a double nephrectomy is performed in a dog and kidney extract is injected intravenously, the life of the animal will be prolonged beyond that of a nephrectomized control animal that is not treated with renal extract. The onset of uræmic symptoms can be delayed in this way. From these observations the conclusion has been drawn that the kidneys furnish an internal secretion that is disintoxicating for certain urinary bodies, and that prevents the occurrence of uræmia. It has also been shown that the toxicity of the blood of uræmic animals is greatly reduced by its passage through healthy kidneys. Uræmia is not, therefore, considered to be due to the retention of urinary bodies alone, but also to insufficiency of the internal disintoxicating secretion of the kidneys. In harmony with this theory kidney extract has been employed in the treatment of a considerable number of uræmic cases, apparently with good results. Kidney therapy is too modern, and case reports are too scanty to warrant extended analysis. The subject, however, seems capable of fruitful development.

3. **THE LIVER.**—Liver extract contains many substances with active physiologic and toxic properties, and no less than ten well characterized ferments besides. It is difficult therefore to understand how those who employ liver extract for the sake of an hypothetical internal secretion of the hepatic cells can exclude the action of all these bodies. It has been claimed that the virtues of cod-liver oil are due to the presence in this product of an internal secretion. A few good results are reported from the use of hepatic extract (prepared according to d'Arsonval's method) in *diabetes*. The preparation is said to stimulate the liver cells to increased activity in the sense that it enables them to store more glycogen. A great reduction in the sugar excretion has been reported by reliable clinicians. Some authors have also used liver extract symptomatically for "*hepatic insufficiency*" following alcoholic cirrhosis, and report improvement of many of the subjective symptoms.

4. **MAMMARY GLAND.**—Mammary gland extracts are believed to exercise an influence on the female generative organs. Desiccated sheep's mamma has been given by mouth in twenty-grain doses for *uterine hemorrhages*. It is said to cause contraction of the uterine muscles and to arrest bleeding. Good results are also claimed from this therapy in the leucorrhœa and irregular bleeding of sub-involution, and in benign tumors of the uterus it is said to relieve many of the reflex symptoms, to control the leucorrhœa and bleeding, and to improve the general health of the patient.

5. **INTESTINE.**—There is some experimental evidence to show that the intestinal wall neutralizes many of the toxic products that are generated in the bowel lumen. Insufficiency of this function would lead to autochthonous intestinal intoxication. It has also been shown that the injection of sterile feces does not produce death so rapidly in animals which have been treated with intestinal extract as in animals which have not. The disintoxicating action of the cells of the intestinal wall is believed to be carried out with the aid of a soluble internal secretion which they produce. It does not seem improbable that the violent systemic disturbances of intestinal strangulation, volvulus, and invagination are in part due to insufficiency of this function and the resulting self-intoxication. The same applies to certain anæmias, psychoses, etc., which may be attributed to auto-intoxication from the bowel.

Extract of intestine has, in fact, been employed with some success in *chlorosis*, and in several cases of stercoræmic poisoning following *strangulation* of intestinal hernias. We are told that in a few of the latter cases the general condition of the patients improved so much un-

der this treatment that operative interference was rendered more safe. This field of organotherapy also merits further cultivation.

6. **PAROTID GLAND.**—The parotid gland and the ovaries appear to stand in some sympathetic relation to one another. Parotid extract has been used with success by eminent clinicians in Germany and Scotland for the relief of certain symptoms due to ovarian disorders, notably the pain and reflex manifestations of ovaritis in cases in which the glands were enlarged and prolapsed.

#### VI. MISCELLANEOUS TISSUES.

Nearly every tissue of the body has at some time been made to yield an extract. No exhaustive experimental or clinical data relating to their employment are, however, recorded excepting in the case of muscle tissue, lung tissue, and heart. We will therefore discuss these three alone.

1. **MUSCLE TISSUE.**—Muscle extracts contain abundant quantities of potassium salts and consequently are toxic when given hypodermically. In addition, muscle juice has a distinct thermogenic action and can produce salivation. Reliable investigators claim that small quantities of muscle extract prepared in the cold and sterilized under CO<sub>2</sub> pressure act as distinct muscle tonics.

Muscle extract has been employed apparently with some success in all primary myopathies in which there was no injury to the anterior horns or the peripheral nerves. A leading French neurologist recommends its use in all "*dystrophies musculaires progressives*" with lesions of the fibrillæ of the muscle and connective tissue.

2. **LUNG TISSUE.**—Pulmonary extract has been successfully employed in the treatment of pulmonary arthropathies. It is believed that destructive lesions of the lungs, in addition to interfering with the respiratory interchange of gases, inhibit the formation of an internal secretion of the pulmonary cells, and that the lack of this secretion in the blood leads to the development of the osteo-arthritis lesions of lung disease. Very good results are reported from pulmonary therapy in a case of Marie's disease (*ostéo-arthropathie hypertrophique pneumonique*). The arthritic process was arrested, the dynamometric pressure rose from 9 kgm. to 19.5 kym., and the general health of the patient was markedly improved after the twenty-ninth injection. In pleuro-pulmonary suppuration with osteo-arthritis pulmonary extract is also said to act beneficially, and recently "pulmozyme," a pulmonary preparation, has been advised for the treatment of lesions of the lungs themselves. Case reports are scanty and results not uniform, so that judgment cannot as yet be rendered on this therapy.

3. **HEART.**—Heart extract was extensively used a few years ago in the treatment of a large variety of disorders. The effects claimed from the injection of this preparation were, among others, an increase in the pulse rate, a rise of arterial pressure, increased diuresis, and a general tonic effect. The extract used by the chief advocate of cardiotherapy unfortunately contained appreciable quantities of alcohol, so that we need not be surprised to learn that it exercised the above effects. The literature on cardiotherapy is large and many cures are reported. A careful analysis of the case reports, however, reveals the method to be utterly devoid of value and the claims of its advocates to be unfounded. Cardiotherapy is mentioned only to be condemned. *Alfred C. Croftan.*

**ORPHOL.** See *Naphthol-bismuth*.

**ORRIS ROOT.**—(*Rhizoma Iridis*, Ph. G.; *Iris de Florence*, Codex Med.) The peeled rhizomes of three or more species of *Iris* are cultivated for this object in the south of Europe, especially in the vicinity of Florence. They, and a few other species also, are familiar garden flowers both there and in this country. The three following are recognized as the sources of "Orris": *I. florentina* L., with very sweet-scented, white, or pale slaty-blue flowers; *I. germanica* L., with dark, violet flowers; and *I. pallida*

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Lam., with flowers light blue, very large, and fragrant. They all resemble each other in respect to the more important particulars. The former is a native of the southern and eastern Black Sea regions, the others of Europe; all have been cultivated for a long time.

The rhizomes are gathered in the latter part of summer, trimmed and peeled, and then dried in the sun, and afterward separated into grades, according to size, symmetry, and appearance. The pieces are more or less long and flattened, with rounded surfaces and ends, often curved or twisted in drying, of a nearly white color, a hard but brittle texture, and a yellowish fracture. Pieces with the branches attached are called "hands"; the detached branches, "fingers." The scars where the roots have been cut away may be seen on the lower surface. Taste bitterish, aromatic, and sharp. Odor, for which it is valued, mild and pleasant, recalling that of violets. Orris which has been kept for one or two years is more fragrant than that just dried. This product has been for centuries used as a perfume, and less generally as a medicine, and is mentioned by most of the classical writers upon medicine. It yields, upon distillation, about 0.1 per cent. of a so-called volatile oil, "*orris camphor*," a buttery-looking substance. This consists chiefly of *myristic acid*, with a trace of *irone*, a liquid with a violet-like odor. *Iridin* is a glucoside, occurring in acicular crystals, in very small amount. There is a specific amaroïd, giving the bitter taste. Orris contains also a little resin and fixed oil, and a very little tannin. Starch is abundant.

**ACTION AND USE.**—Internally given, orris, like our Blue Flag (*Iris versicolor* L.), is a cathartic and occasional emetic, but it is almost never employed in this way. It is a common ingredient of tooth powders, as well as of sachet powders (violet), and is otherwise used as a perfume. The oil is also used in tooth washes. Large, fine pieces are now and then given to teething children to chew upon. *Henry H. Rusby.*

**ORTHIN.**—This is one of the numerous compounds introduced for its antipyretic properties. It is a combination of hydrazin and para-oxybenzoic acid; the base is an unstable body, but the hydrochlorate is a stable preparation, and is the salt supplied under the name of orthin. It is very soluble in water. The solution should always be freshly prepared and preserved from the light. It is recommended as an antipyretic in typhoid fever, pneumonia, rheumatism, and all febrile disorders. Kobert, who introduced it into therapeutics (*Deutsche med. Wochen.*, 1890), claimed that it was non-toxic and free from all ill effects. Its use, however, has been accompanied by sweating, prostration, and other symptoms of poisoning. The dose advised by Kobert is from five to eight grains. *Beavmont Small.*

**ORTHOFORM**—meta-amido-para-oxybenzoic methyl ester (C<sub>6</sub>H<sub>5</sub>.OH.NH<sub>2</sub>.COOCH<sub>3</sub>)—is a white powder without odor or taste, and permanent in the air. It is soluble in alcohol, ether, chloroform, and some of the oils, but very slightly soluble in glycerin or water. It is precipitated, but not rendered inert, by formaldehyde and mercuric bichloride (Luxenburger), produces a brown color with bismuth subnitrate, and decomposes silver nitrate and potassium permanganate. It is not affected by zinc oxide, iodoform, salicylic acid, carbolic acid, lysol, aluminum acetate, or iodine, and may be safely combined in prescription with most of the ordinary antiseptics and dusting powders. It is said to remove most of the odor of an equal amount of iodoform.

Acting on the sensory end-organs, orthoform produces a local anesthesia, which, owing to the insolubility of the drug, is mild and long continued. This slow action, together with a distinctly antiseptic power, makes it a valuable dusting powder for raw surfaces. It is therefore applied to burns, fissures, painful ulcers, ulcerating hemorrhoids, etc. The anæsthetic effect from a ten-per-cent. powder or ointment lasts for from two to forty-eight hours (Kindler). As the drug has no penetrating power,