

luteum; the striking effect of the remedy in these patients would thus easily be accounted for.

STERILITY; INFANTILE GENERATIVE ORGANS; HABITUAL ABORTION; HYPEREMESIS OF PREGNANCY.—Additional conditions in which corpus luteum has proved beneficial, though less consistently than in the disorders already referred to, are sterility, infantilism of the reproductive organs, repeated abortions, and hyperemesis in the early months of pregnancy. Sterility is, of course, influenced only in the absence of gonococcal or other infection as well as of cervical stenosis. Elliott¹⁴⁸ has reported the case of a married woman of 27 years, masculine of figure, with uterus of walnut size and ovaries impalpable, menstrual show only three or four times during life, epistaxis, and sexual feeling almost absent, in which corpus luteum therapy, coupled with uterine massage, was followed by a partial return of menstruation and by pregnancy. Dannreuther found the drug of similar value in 2 cases of repeated abortion of obscure origin. In the hyperemesis of pregnancy corpus luteum has been employed by a number of observers with variable, but often distinctly favorable results. J. C. Hirst¹⁴⁹ obtained excellent results in 4 out of 5 cases and deems it superior to any other for the treatment of nausea in pregnancy.

The two most important prerequisites to success in the use of this drug appear to be (1) the selection of a preparation made exclusively from the corpora lutea of pregnant animals and (2) due attention to the fact that the action of the drug is frequently slow in asserting itself, and that the drug should be given up only when thorough trial has demonstrated its lack of efficiency.

The material now chiefly employed consists of the dried corpora lutea of cows or sows, exhibited in tablets, capsules, or cachets in doses of 5 to 10 grains three times a day. The dried substance represents usually about five to six times its weight of fresh luteal tissue. Preparations made exclusively with the corpora lutea of pregnant animals are considered the most efficient. A preparation termed "luetin," now on the market, is administered in 20-grain doses three times a day.

¹⁴⁸ Elliott: Jour. Am. Med. Assoc., April 4, 1914.

¹⁴⁹ Hirst: Jour. Am. Med. Assoc., Feb. 26, 1916.

ORCHITIC OR TESTICULAR ORGANOTHERAPY.

From the standpoint of therapeutics, testicular preparations can hardly be regarded as of more than historical interest. The influence of the testicles on the body at large is well known. Castration influences the development of the organism in many particulars. Eunuchs preserve to a certain extent the characteristics of infantilism, the skin remaining soft and white, their muscles flabby and weak, and the voice high pitched. Yet they are usually tall, owing to inordinate growth of the bones. They lack courage, initiative, and intelligence. This suggests, therefore, that the testicles do not carry on genital functions only. Brown-Séquard taught that they carried on a dual rôle: 1st, procreation; 2d, the production of an internal secretion which stimulates and sustains the energy of the nerve-centers and cord, and capable, moreover, of endowing the individual with physical, moral, and intellectual characteristics of sex. His own physical and intellectual activity having been greatly improved at the age of 72 years, by injections of an extract prepared from the testes of young dogs, he concluded that it possessed marked therapeutic value. No one who, as I did, saw Brown-Séquard before and after he had submitted himself to this treatment could stretch his imagination sufficiently to attribute the change in his appearance to auto-suggestion. He literally looked twenty years younger.

The prevailing opinion is that the beneficial effects obtained from testicular preparations are not due necessarily to an internal secretion, though the existence of such is not denied, but to nucleo-albumins, substances that are rich in phosphorus, resembling greatly lecithins and glycerophosphates. From my viewpoint (see page 473), they are mainly due to extracts of the adrenal rests they contain, in organic combination with nucleins.

Dixon states that a constituent of orchitic extract is unaltered by boiling; McCarthy holds that it increases the force and regularity of the heart muscle as does digitalis. It enhances the resistance to disease, increases the production of urea, and also acts directly upon the cardio-vascular system. Moreover, as shown by Poehl—a fact which indicates that it is not specific

to the testis—it is a ubiquitous constituent of the whole organism, in the female as well as the male.

Testicular preparations, including spermin, have been recommended in a host of disorders, particularly tabes, neurasthenia, melancholia, impotence, and paralysis agitans; in several cutaneous disorders, eczema and psoriasis; in disorders of nutrition, gout, obesity, and glycosuria; but others again have failed to obtain any favorable results. Spermin has also been recommended by Poehl and his followers not only in the majority of the foregoing disorders, but in many others besides, in acne, rheumatism, syphilis, marasmus, and in various infections, such as typhoid fever, diphtheria, and even cholera. It has been tried in Addison's disease, but adrenal preparations are to be preferred.

In the light of the analysis submitted above, however, there is good ground for the belief that beneficial effects were obtained in all these maladies. That the nucleo-albumins of orchitic extract acting as would glycerophosphates could be beneficial in the disorders enumerated, no one can deny. This can hardly be said, however, of the cutaneous and nutritional disorders, unless the spermin the extract contains, by enhancing oxidation and the destruction of toxic wastes, proves to be the active agent. Spermin itself—as adrenoxidase—is unquestionably capable of doing this actively, and in syphilis and marasmus to markedly enhance the functional activity of all tissues. Again, the beneficial rôle of spermin in infections finds its explanation in a fact I have repeatedly emphasized, viz., that the oxygenized adrenal secretion, the active agent of spermin, from my viewpoint, is an active participant in all immunizing processes, local and general. The main point to determine, however, is whether orchitic extract, or spermin, affords better or as good results in any of the disorders enumerated than other remedies at our disposal. The evidence available indicates that such is not the case.

KIDNEY ORGANOTHERAPY.

That the kidneys produce an internal secretion is still problematic. Brown-Séguard, having removed the kidneys and caused uræmia, found that the injection of a glycerin extract of

kidney prolonged the life of the animals as compared to those in which the same operation was not followed by the use of the kidney extract. This experiment, which has been repeated by others, forms the basis of the belief that the kidney produces an internal secretion. That such a conclusion may not be warranted is suggested by the fact that the kidneys, along with some of the organs so far reviewed, are also rich in adrenal tissue—the so-called “adrenal rests” from which hypernephroma sometimes develops—and that as such they are capable, as an active factor in the immunizing functions of the body, of counteracting temporarily the toxæmia or “uræmia” brought on by removal of the kidneys. Indeed, the relief afforded is but ephemeral, death being postponed but one to two days in rabbits, in which Bitzou¹⁴⁷ repeated Brown-Séguard's experiments. Dromain and de Pradel Bra¹⁴⁸ had also noticed that injections of kidney extract lessened the fits of epilepsy, another toxæmia. Dubois¹⁴⁹ and Renaut¹⁵⁰ have also found that kidney extracts were endowed with antitoxic power.

That we are again dealing mainly with a manifestation of the adrenal principle is further suggested by its powerful blood-pressure-raising property. Tigerstedt and Bergman found that rennin possessed this power; Bingel and Strauss¹⁵¹ recently confirmed their observation, and found that its action corresponded with that of adrenal and pituitary extracts, those of other organs causing depressor effects. The rise of pressure produced by kidney extract was high, *i.e.*, from 40 to 60 mm. Hg, and lasted from fifteen to thirty minutes. The authors concluded, moreover, that “the action of rennin, like that of adrenalin, is exerted in the muscles of the peripheral vessels.” Its general action, however, is more like that of pituitary body extract, the adrenal principle being doubtless combined organically, as in the pituitary, with bodies which prolong and perhaps control advantageously the action of the former. Like adrenal preparations kidney extract produces dilatation of the pupil. This sustains my opinion that its action is due to adrenal principle.

¹⁴⁷ Bitzou: Jour. de physiol. et de path. génér., Nov. 15, 1901.

¹⁴⁸ Dromain and de Pradel Bra: C.-r. heb. des sci. et mém. de la Soc. de Biol., Paris, 1895.

¹⁴⁹ Dubois: Soc. de Biol., p. 287, 1903.

¹⁵⁰ Renaut: Bull. gén. de thérap., T. 147, pp. 3 and 37, 1904.

¹⁵¹ Bingel and Strauss: Deut. Archiv f. klin. Med., xcvi, S. 476, 1909; July 26, 1895.

Even the oxidizing power I have attributed to the adrenal secretion seems to be reproduced; Batty Shaw,¹⁵² who also finds "very little justification for the existence of an internal secretion" in the kidney, remarks that "possibly nephrin and other renal preparations provide a means of stimulating oxidation in general, the kidney merely sharing in this oxidation"—a very accurate estimate from my viewpoint. Shaw adds, moreover, that "similar good results have been reported as a result of treatment by means of spermin and testicular extract," both of which, as I have shown, also owe, in all probability, their therapeutic effects to the adrenal principle they contain.

The *therapeutic application* of kidney preparations has received considerable attention, and favorable results have been reported in about one-half of the cases of chronic nephritis, or Bright's disease, in which it was tried. The mode of action, in the light of the facts submitted above, is mainly an increase of the antitoxic power of the blood and diminution, therefore, of the irritation of renal apparatus. Page and Dardelin,¹⁵³ for example, report marked amelioration in 18 cases, using a maceration prepared as follows: A very fresh kidney from a pig is cut into minute pieces, washed with fresh water to remove the excess of urine, then hashed and pounded into pulp. This pulp is put into 300 grammes (9 ounces and 5 drachms) of fresh water to which the physiological proportion of salt, 7.50 to 1000, has been added. It is then allowed to macerate for three hours, stirred occasionally, and kept in a cool place to avoid fermentation. The red water of the maceration is divided into three parts to be drunk by the patient during the day. It is more conveniently given, however, in tablet form, as "nephritin" prepared in this country by Reed and Carnrick. Only the active substance of the kidney is used in this preparation, the dose being from 10 to 15 5-grain (0.33 Gm.) tablets daily in divided doses, given between meals.

Kidney preparations have also been used with more or less advantage in puerperal intoxications and epilepsy, but their field is essentially the various forms of nephritis, and particularly for the prevention of uræmia. They also tend to increase

¹⁵² Shaw: *Loc. cit.*, p. 216.

¹⁵³ Page and Dardelin: *Presse médicale*, Dec. 21, 1904.

diuresis and reduce the albumin. As stated above, however, favorable effects are to be expected in about one-half of the cases.

MAMMARY GLAND ORGANOTHERAPY.

It is held by some that the mammary gland produces an internal secretion, but what evidence there is on the subject is so weak that it can hardly be taken into account. Introduced by Bell, of Glasgow, and in this country by the late John H. Shober, it has shown therapeutically marked stimulating action upon the uterus, but the manner in which it produces this effect has remained obscure. An extract lowers somewhat, and but temporarily, the blood-pressure and the pulse. According to Shober, it diminishes the blood supplied to the uterus and thus controls hæmorrhage, its action resembling that of ergot, though free of the unpleasant effects of the latter drug. From my viewpoint, therefore, it would act by causing constriction of the arterioles.

Mammary gland is prepared in the form of a tablet made of the desiccated gland of the sheep, each tablet representing 20 grains (1.32 Gm.) of the fresh gland. The dose is from 3 to 6 tablets daily.

The *therapeutic application* is restricted to the genital apparatus. In cases of uterine fibroids characterized by excessive menorrhagia and metrorrhagia the bleeding was found by Shober to be controlled in a few weeks and the periods become regular, normal, and free from pain. There is improvement in the patient's health and weight, and the tumors themselves diminish in size up to a certain point. The patient is thus placed in a better condition for any needed operation, and often the necessity for an operation is postponed. Where there is evidence of inflammatory or degenerative changes, or when serious pressure symptoms are not controlled after a reasonable trial, operation should not be delayed. In 43 cases of uterine fibroma treated by Fedoroff, cure is claimed to have been obtained in 33, while there was a marked reduction of the growth in 43 per cent. Mammary gland is also useful in cases of subinvolution unassociated with malignancy or structural changes. Pozzi has advocated its use in uterine hemorrhage of any kind attending metritis.

Mammary gland has also been recommended to assist uterine involution and to enhance lactation. But the reports on the use of this agent have been antagonistic.

THYMUS ORGANOTHERAPY.

In the sixth chapter (p. 280), I submitted the experimental and clinical evidence which led me to suggest, in 1907, that the function of the thymus was to supply an excess of phosphorus in organic combination during the growth of the body, *i.e.*, particularly while the development of the osseous and nervous systems demanded such a reserve. This was sustained by the recognized fact that certain diseases of children and adolescents, especially marasmus, rachitis, and trophic disorders of the brain and nervous system, were due, in part, to the functions of the thymus. While it cannot be affirmed that this theory actually represents the function of the organ—the thymus having been the graveyard of many hypotheses—all that can be said for it is that it seems to account for the clinical results obtained under its use better than any hypothesis so far advanced, besides corresponding with the laboratory findings of its effects.

DISEASES OF THE THYROID.—In simple goiter it was first tried by Mikulicz,¹⁵⁴ who obtained sufficiently favorable results in 5 out of 11 cases to render operation unnecessary, at least for the time being. Reinbach¹⁵⁵ considers it probably superior to thyroid because the unpleasant effects of the latter are avoided; for the same reason it is especially suitable when organotherapy has to be used continuously. This view is based on the employment of thymus in a large number of cases in the Breslau clinic. Mikulicz gave from 2½ to 4 drachms (10 to 16 Gm.) of the raw sheep thymus on bread three times a week, increasing the dose to 7 drachms (28 Gm.) if required.

We have seen that in exophthalmic goiter it had proven efficacious in the hands of Owen¹⁵⁶ in advanced cases, and also in those of Maude¹⁵⁷ when other remedies had been used fruitlessly. The latter gave 45 grains (3 Gm.) daily to a severe case, which greatly improved, relapsing whenever the treatment was

¹⁵⁴ Mikulicz: Berlin. klin. Woch., Bd. xxxii, S. 342, 1895.

¹⁵⁵ Reinbach: Mittheil. aus den Grenzgebiet. d. Med. u. Chir., B. i, S. 202, 1896.

¹⁵⁶ Owen: Brit. Med. Jour., Oct. 10, 1896.

¹⁵⁷ Maude: London Lancet, July 18, 1896.

interrupted. S. Solis-Cohen¹⁵⁸ also advocates its use in this disease, having found that it exerted its beneficial influence mainly upon the nervous symptoms of the disease without affecting the exophthalmus. Huston White¹⁵⁹ found that the nervous symptoms were alone improved.

These observations coincide with my own view of the manner in which thymus gland produces its beneficial effects. The excess of thyroiodase produced in exophthalmic goiter causes, we have seen, too rapid oxidation of the phosphorus in organic combination in the tissues, particularly in those of the nervous system which are extremely rich in phosphorus. Thymus, supplying phosphorus in organic combination, replaces that lost by the nervous system, thus procuring marked benefit in this one direction. As 5 grains (0.33 Gm.) of the dried thymus are equivalent to 30 grains (2 Gm.) of the fresh gland, this dose can readily be given three times daily.

RACHITIS, OR RICKETS.—The same explanation, *i.e.*, the purveying of phosphorus in organic combination—to the osseous system, in the present connection—accounts for the undoubted benefit thymus has procured in this disorder. Mendel,¹⁶⁰ having used thymus gland in 1½ to 3 drachms (6 to 12 Gm.) daily in over 100 cases, obtained marked benefit in a large proportion, but especially in the nervous symptoms, including spasm of the glottis. It had previously been tried by Stoppato,¹⁶¹ but without marked benefit. In Mendel's cases both fresh and commercial tablets were tried, the cases being subdivided as follows: 1, those which showed prodromal symptoms only; 2, those in which deformity of the osseous system was the chief feature; 3, those marked by spasm of the glottis, and, 4, those in which splenic enlargement was the most important sign. Marked improvement was noted in all after from three to four weeks, and dentition and the closure of the fontanelle proceeded satisfactorily. No untoward symptoms were noted—a marked advantage over thyroid preparations. In a case of stunted growth, obviously of osseous origin, in a boy of 14 years, R. Webb Wilcox¹⁶² ob-

¹⁵⁸ Solis-Cohen: Jour. Amer. Med. Assoc., Aug. 18, 1900.

¹⁵⁹ White: Brit. Med. Jour., vol. i, p. 786, 1899.

¹⁶⁰ Mendel: Münch. med. Woch., Bd. xlix, S. 134, 1902.

¹⁶¹ Stoppato: Policlinico, April 15, 1897.

¹⁶² Wilcox: Boston Medical and Surgical Journal, Aug. 13, 1908.

tained $9\frac{1}{4}$ inches growth in three years by the persistent use of 2 grains (0.13 Gm.) thymus night and morning.

The view that these effects are due to the addition of phosphorus in organic combination to the body is further sustained by the results of experimental observation by Hart and Nordmann,¹⁶³ that the thymus had a definite relation to assimilation, and that it took an active part in the resistance of the organism to infection. As I will show in the second volume, page 878, nucleo-proteid, in so far as its phosphorus in organic combination is concerned, is an active participant in the immunizing process.

BRAIN AND NERVE SUBSTANCE ORGANOTHERAPY.

While these agents have given good results, the theory that brain and nerve substance possess or produce an internal secretion has never been sustained scientifically.

The clinical results, though quite discordant, particularly in the neuroses and psychoses in which these preparations have been tried, have shown a tendency to harmonize since the introduction by Sciallero¹⁶⁴ of an oily extract. Page,¹⁶⁵ who has obtained unusually good results in neurasthenia by means of injections of this extract, ascribes them to its antitoxic and antispasmodic effects. Wassermann and Takaki had previously shown that tetanus toxin was neutralized by contact with brain substance, and that when a fatal dose of tetanus toxin was injected with brain substance the fatal effects were prevented. The same observations were made in the case of hydrophobia by Babes; in strychnine and morphine poisoning by Widal and Nobécourt; in tetanus by Krokiewicz; in epilepsy by Lion and also Kaplan, using Poehl's opocerebrin—in accord with Dana's experience several years earlier. Sciallero, who obtained encouraging results in neurasthenia, hysteria, chorea, tic, and epilepsy, used his oily extract "cephalopin" in doses varying from 1 to 5 c.c. (16 to 81 minims). No untoward effects were obtained.

Although it is very improbable that brain extracts injected into the tissues act as they do in the test-tube, it seems established that they act much as do the lecithins on the market, *i.e.*,

¹⁶³ Hart and Nordmann: Berlin. klin. Woch., May 2, 1910.

¹⁶⁴ Sciallero: Riforma Medica, Jan. 27, 1904.

¹⁶⁵ Page: C.-r. de l'Académie de Méd., March 30, 1909.

by furnishing phosphorus to the organism in an assimilable form, or as nucleo-proteids in enhancing the immunizing process. Be this as it may, these substances seem to have produced effects which suggest that they are worthy of further study.

THE PINEAL GLAND ORGANOTHERAPY.

The functions of this organ have not as yet been determined to any degree. It is no longer regarded as a purely vestigial structure, however, tumors of the pineal as noted by Marburg¹⁶⁶ and others being capable of causing obesity, while Ogle, Frankl Hochwart,¹⁶⁷ and other clinicians have recorded marked precocity in young subjects, as to stature, genital development, and hair growth. These effects have also been ascribed to a secretory function, but the results obtained from extracts of the gland have been contradictory, though these agents appeared to increase the strength of the heart-beat.

A kinship with the functions pituitary is suggested by many facts. From my viewpoint, it does not possess the characteristics of a secreting gland but, seemingly, those of a nervous organ working in harmony with the pituitary body, through fibers which meet those originating from the latter organ, in the region of and in the corpora quadrigemina. The fact noted by Biedl¹⁶⁸ that in the adult animal the organ is "a negligible quantity" sustains my view, since a co-ordinating center can be sacrificed without permanent harm more readily than a secreting organ whose product should, as in the present case, deeply influence metabolism, if the effects of organic lesions of the organ are taken as standard.

As a therapeutic agent, Dana and Berkeley¹⁶⁹ claim to have obtained improvement in backward children owing to its stimulating influence on general metabolism.

HORMONE THERAPY.

The word "hormone" was applied by Starling to the group of substances secreted by various organs—the ductless glands in the group studied in this work—which could enhance the functions of other organs. Precisely as I had held three years earlier

¹⁶⁶ Marburg: Deutsch. Zeitschr. für Nervenheilk., B. xxxvi, S. 112, 1908.

¹⁶⁷ Frankl Hochwart: *Ibid.*, B. xxxvii, S. 455, 1909.

¹⁶⁸ Biedl: The Internal Secretory Organs, p. 355, 1913.

¹⁶⁹ Dana and Berkeley: Medical Record, May 10, 1913.

(the adrenal secretion exciting the thyroid, the pituitary, the pancreas, etc.); these hormones were shown by Starling to reach the distant structures they influenced, through the intermediary of the blood.

While certain hormones influence various organs, others affect only one organ or a system of them. Bayliss and Starling termed "secretin" a hormone formed in the duodenal mucous membrane under the influence of hydrochloric acid from the stomach. Carried by the circulation to the intestinal mucosa, the pancreas, and the liver, it activates the production of the secretions produced by these organs. As I suggested in 1907 (see vol. ii, p. 861), this hormone presents several properties of adrenal extractives.

Another hormone has been obtained from the gastric mucosa by Zuelzer, Dohrn, and Marxer¹⁷⁰ which has been found to enhance peristalsis. It being impossible to obtain it in sufficient quantities from the stomach, it was sought elsewhere, and was found in ample quantities in the spleen—that junkshop in which red corpuscles (which, as I suggested in 1903, are the common carriers of the adrenal principle) are broken up along with other cells. This splenic hormone specifically stimulates intestinal peristalsis to a degree so remarkable that the intestinal movements in the experimental animal may be shown cinematographically ten to fifteen minutes after an intravenous injection.

This hormone (available as *hormonal* in the trade) has been found of considerable value in chronic constipation, intravenous injections (20 c.c.—5 drachms—in children and 40 c.c.—10 drachms—in adults). In intestinal paralyses following abdominal operations or volvulus it has also given satisfactory results in some cases. Henle's¹⁷¹ favorable results did not seem to be lasting. In intestinal occlusion care is necessary lest the violent peristalsis provoked aggravate any intestinal lesion that may be present. The observations of Saar¹⁷² and Unger¹⁷³ suggest, however, that the peristaltic action promoted by the hormone is not violent. The untoward effects reported by various clinicians, however, emphasize the need of great care in the use of this agent.

¹⁷⁰ Zuelzer, Dohrn, and Marxer: Berl. klin. Woch., Nu. 46, 1908.

¹⁷¹ Henle: 50th German Congress of Surgery, April, 1911.

¹⁷² Saar: Medizin. Klinik, Nu. 2, 1910.

¹⁷³ Unger: Berliner med. Woch., Nu. 11, 1911.

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