Several instances of rupture of the uterus under the use of pituitrin have also been reported.

Ott and Scott[116] found infundibulin, *i.e.*, extract of the posterior lobe, to act as a powerful galactogogue in the goat. So far, however, it has not been tried in women.

Infectious Diseases.—In this general class of disorders the use of pituitary acts, from my viewpoint, and in keeping with the effects of adrenal preparations, by enhancing the immunizing activity of the blood and the tone of the cardio-vascular system.

Rénon and Delille[117] found that in typhoid fever it raised the blood-pressure, slowed the pulse, increased diuresis, and improved the patients in general, hastening convalescence noticeably. In diphtheria, in which the toxin reduces the vascular tension and promotes cardiac complications, it lowered the pulse-rate, raised the blood-pressure, and increased diuresis. In erysipelas it seemed to hasten the favorable evolution of the disease. In pneumonia it raised the blood-pressure when this became low, but without influencing favorably the evolution of the disease. In bronchopneumonia, however, the opposite proved to be the case, considerable benefit being noted. Influenza was found to be very favorably influenced, rapid recovery resulting in patients aged, respectively, 80 and 63 years. This was confirmed by Azam,[118] in the infectious form. Rénon and Azam enumerate the phenomena which, in infectious diseases, indicate the need of pituitary: 1, a fall of the arterial tension; 2, quickening of the pulse and, as complementary minor phenomena, insomnia, anorexia, abnormal sweating, and heat flushes. Under the influence of pituitary there occur: 1, increase of arterial tension; 2, slowing of the pulse, with increase of power and amplitude; 3, increased diuresis; 4, increase in weight; 5, hastening of convalescence.

In several cases of tuberculosis treated by Rénon and Delille, the results were not, on the whole, encouraging. In a case of Addison's disease complicating tuberculosis, however, there was a notable rise of the blood-pressure and diminution

[116] Ott and Scott: Monthly Cyclopædia and Medical Bulletin, Nov., 1910.
[117] Rénon and Delille: Bull. gén. de Thérap., Feb. 8, 1907, and Delille: *Loc. cit.*
[118] Azam: Jour. de méd. et de chir. pratiques; Practitioner, March, 1908.

of the asthenia. Trerotoli had already noted the beneficial effects of pituitary body in Addison's disease—a fact which further suggests that the active agent of pituitary substance is its adrenal component.

Acromegaly.—The possible value of pituitary extracts in acromegaly, a disease of the pituitary body, has naturally suggested itself, but, although a few of the symptoms, the headache, lethargy, and amnesia, were relieved in some, no cures were obtained. This subject has already been referred to on page 607.

Analysis of the cases reported as benefited suggests an explanation of its mode of action, however, one quite apart from any functional relationship with the organ as the source of an internal secretion, but entirely in keeping with the presence in the pituitary preparation of adrenal secretion in organic combination. Marinesco[119] observed that it was the extremely violent headaches that were relieved, there being no benefit otherwise excepting perhaps increased diuresis. Kuh,[120] obtaining no favorable result, withdrew the remedy, but the patient begged to be given the powders again, having found his headache much more intense when he failed to take them. The same observation had been recorded by Cyon,[121] the patient, an obese child of 12 years, having besides lost twenty pounds in weight. What benefit was obtained in 1 case out of 7 cases treated by Kinnicutt[122] was also limited to the headache and neuralgia. Leszynsky,[123] after a prolonged trial in 2 cases, wrote: "While some published reports as to the efficacy of the preparations of the sheep's gland have seemed quite encouraging in so far as the relief of headache and of paræsthesia of the hands is concerned, it is the general consensus of opinion that it in no way influences the progress of this disease."

Still, the relief of the headache and paræsthesiæ indicates some potent action. This is accounted for if the adrenal principle is considered as the active agent of pituitary preparations, since, as Langley has shown, it is principally upon the

[119] Marinesco: Semaine Médicale, Nov. 13, 1895.
[120] Kuh: Jour. Amer. Med. Assoc., Feb. 1, 1902.
[121] Cyon: Progrès Medical, Nov. 26, 1898.
[122] Kinnicutt: London Lancet, vol. ii, p. 173, 1896.
[123] Leszynsky: Medical Record, June 30, 1900.

arterioles that the adrenal principle acts, a view which has now become classic. Such being the case, the tumor of the pituitary, or the compressed tissues around it, receive less blood through their constricted arterioles, and the sensory terminals of the peripheral likewise. The resulting ischæmia of these tissues thus accounts for the diminution of pain—as long only as the remedy is administered.

Exophthalmic Goiter.—Rénon and Delille[124] obtained considerable improvement in this disease by the use of pituitary gland. From the fourth to the fifth day, the sleeplessness, tremor, digestive disturbance, sweating, and sensation of heat were considerably lessened. The tachycardia improved less rapidly, the pulse becoming slower gradually and attaining its slowest rate toward the fifteenth day. The arterial tension also rises steadily, attaining the maximum toward the third week, falling again somewhat, but not to the former low level. Some diminution of the exophthalmus occurred, but the goiter was not reduced. The dose administered was 4½ grains (0.30 Gm.) of the whole pituitary (ox) gland daily, a dose which they deem advisable to increase to 7½ grains (0.50 Gm.) in divided doses daily. The symptoms tend to return, however, on discontinuing the remedy. Cases subsequently treated were also benefited, but no cures were effected.

This mode of action, from my viewpoint, corresponds precisely with that referred to under the preceding heading. We have seen in the fifth chapter that the main pathological condition, that to which all the prominent symptoms of exophthalmic goiter were due, was a general dilatation of the arterioles. Pituitary extracts causing constriction of these vessels as long as it is administered, it offsets for the time the morbid phenomena enumerated. That such is actually the case was demonstrated by Hallion and Carrion,[125] who found, experimentally, that pituitary extracts "always produced their effects by raising the arterial tension," producing at the same time "an intense vasoconstrictor action upon the thyroid body." Briefly, we have here precisely the physiological action necessary, the vasoconstrictor power of the adrenal component of

[124] Rénon and Delille: Soc. Oesthérap., March 13, 1907.
[125] Hallion and Carrion: *Ibid.*

the pituitary gland superseding the vasodilator action of the thyroid, the underlying cause of the disease.

Nervous and Mental Diseases and Myopathies.—Rénon and Delille used pituitary in 10 neurasthenics in whom tachycardia, irregular vascular tension, often below normal, a sensation of oppression, myasthenia, insomnia, and anorexia were present. In these cases, 3 to 5 grains (0.2 to 0.3 Gm.) daily proved remarkably useful, though no complete recovery was noted.

Delille and Vincent[126] obtained a complete recovery in a grave case of bulbo-spinal myasthenia by the simultaneous use of pituitary and ovarian extracts. Parhon and Urechia and Léopold-Lévi and de Rothschild[127] had also obtained favorable results with pituitary in similar cases. Browning[128] observed good effects in cases of chorea in which this disorder occurred in conjunction with stunted growth, as shown under the next heading.

In epilepsy, it was tried by Mairet and Bosc,[129] but only served to increase the number of attacks—a result to be expected, since Spitzka has shown that these were due to abnormal elevation of the blood-pressure. In some instances it provoked delirium.

Sollier and Chartier[130] tried pituitary in mental disorders and found it useful in depressive states. It raised the blood-pressure, reduced the pulse, suppressed profuse sweating, and improved the asthenia. The synthesis of perceptions and the association of ideas were improved, and mental operations were incited more promptly.

Stunted Growth and Imbecility.—In the case of a child of 3 years, which had shown the evidences of hypothyroidia with idiocy sufficiently to suggest the use of thyroid, Léopold-Lévi and de Rothschild found this agent useless. The case being attended with marked myasthenia, they administered pituitary extract 1½ grains (0.1 Gm.) twice daily, which corresponded with 7½ grains (0.5 Gm.) of the fresh gland. Marked signs of improvement appeared within a few days. The intelligence

[126] Delille and Vincent: Soc. de Neurol., Feb. 7, 1907.
[127] Léopold-Lévi and de Rothschild: *Ibid.*
[128] Browning: New York State Journal of Medicine, Sept., 1909.
[129] Mairet and Bosc: Arch. de Physiol., p. 600, 1896.
[130] Sollier and Chartier: Congrès de Dijou, Aug., 1908.

developed to a remarkable degree, and soon reached that of a child of a corresponding age, 3 years, though before the treatment it did not exceed that of a 7 or 8 months' infant. Two similar cases, one of which showed symptoms of Little's disease, were similarly benefited.

Browning[131] used pituitary only in undersized or backward children and youths with marked success. The reader is referred to the fifth and sixth chapters, in which these disorders are treated in full.

Intestinal Paresis.—Bell and Hicks[132] have found pituitary extract of value in paralytic gaseous distention of the intestines. It never failed either in post-operative or other paresis if given intramuscularly, when the intestine begins to distend, in 15-minim (0.92 c.c.) doses, repeated in an hour, if required. The effect is then sustained by daily doses if need be. The beneficial influence of the injections was, as a rule, noticeable in a few minutes. Duffy[133] concludes that its effect on the peristalsis in cases with tympanites seem more marked than in cases with no intestinal distentian.

According to E. H. King[134] by-effects of pituitary extract are: rise of blood-pressure, dyspnea, air hunger, and pallor; but these are transitory, and are negligible when contrasted with the lasting benefit secured in the majority of instances. Vomiting may be expected, and be welcomed, if the stomach contains intestinal excrement; for in intestinal paresis the upper, rather than the lower, alimentary tract functions inadequately as the vent. Pituitary extract is injected, under aseptic precautions, into a vein—usually one near the elbow, though in fat persons a vein on the back of the hand is more available. In a given case of intestinal paresis, it affords an additional means of emptying the bowel, which is peculiarly applicable and transcends in efficiency any previously known. In uncomplicated post-operative cases its action is promptly curative, and it is possibly curative of functional, actual obstruction. Pituitary extract should be given very carefully when the heart rate is unusually high, 140 or more, when there is marked intermittence

[131] Browning: *Loc. cit.*
[132] Bell and Hicks: British Medical Journal, March 27, 1909.
[133] Duffy: New York Med. Jour., Jan. 9, 1915.
[134] King: Med. Record, June 30, 1914.

of the heart, or in cardiac decompensation. In angina pectoris, on account of the vasoconstriction produced by it, this agent is probably absolutely contraindicated.

Arthritis.—B. H. Whitbeck[135] describes 13 cases of rheumatic arthritis treated by the daily intramuscular injection of a 1 per cent. solution of pituitary extract; only 2 failed to improve. Relief of pain, joint-fluid absorption, and increased activity were noted rather early in the treatment. General improvement and equalization of the pulse- and blood- pressure were also noticeable.

M. S. Macy[136] obtained good results in 3 consecutive cases of gonorrheal arthritis. All 3 had been under autogenous vaccines, as well as local antiseptic treatment for the infection of the genitourinary tract; but the arthritis, of some months' standing, had been very slightly, if at all, benefited. The treatment consisted in ionizing into the affected joints, by the high-frequency spark, of pituitary gland substance (in the form of tablets) triturated to a powder. Usually, 1 grain of the powder was employed at each treatment, but in one of the patients this was increased to 2 grains.

Rachitis.—R. Klotz[137] tried pituitary with calcium carbonate in 5 infants, from 1 to 2 years of age, some of whom had received no benefit from the usual remedies. Although all 5 cases were severe, in two weeks all were able, for the first time, to stand upright and walk. Previously wasted from diarrhea, the children increased in weight and strength.

Asthma.—We have seen that adrenalin is used with benefit in the treatment of asthmatic paroxysms; unfortunately the arrest of suffering is ephemeral. Pituitary gland has been found equally effective and more lasting in its effects. Moreover, it may be administered orally and the paroxysms thus prevented. Suggestive in this connection, in so far as my own view that the effects are mainly due to the adrenal extractives it contains, is the observation of Reiss[138] that the first injection in his cases gave all the by-effects of adrenalin. Crookshank[139] treated 20 cases of bronchial asthma, giving 2-grain tablets of pituitary

[135] Whitbeck: Am. Jour. of Orthopedic Surg., Jan., 1915.
[136] Macy: Med. Record, June 19, 1915.
[137] Klotz: Münch. med. Woch., May 21, 1912.
[138] Reiss: Berliner klin. Wochensch., July 19, 1915.
[139] Crookshank: London Lancet, March 14, 1914.

substance. The attacks became comparatively mild. In 2 of the cases the use of antispasmodics—stramonium, etc.—were rendered unnecessary. F. C. Warfel[140] also obtained "very marked improvement in the distressing train of symptoms in forty-eight hours," by means of 2½-grain tablets of the anterior lobe.

Hemoptysis.—This distressing condition, so often rebellious to classic methods, was found amenable to treatment by means of extract of the posterior lobe by Rist[141] when injected intravenously. The results in 20 cases, ranging from the stage of consolidation to that of cavities, and including 1 case of pulmonary cancer and of pulmonary infarct, were instantaneous as to arrest of the hemorrhage, excepting in 1 case in which the patient failed to subject himself to rest and quiet. Recurrence having occurred in several instances, the second injection proved as efficient as the first. In only one instance did a third injection become necessary. Konikow[142] refers to a case, in which he injected 15 minims of pituitary liquid hypodermically, as "magical." Recurrence was also followed by arrest of the flow by the same measure.

OVARIAN ORGANOTHERAPY.

The fact that destruction or absence of the ovaries caused girls to grow without the general physical attributes of the female sex led Brown-Séquard to consider these organs as the source of an internal secretion. This view has been upheld by many observers who found that ovaries transplanted in the abdominal cavity, *i.e.*, elsewhere than in their normal location, restored to the other genital organs the power to develop and carry on their physiological functions. The identity of this internal secretion and the manner in which it carries on its function have, however, remained obscure.

My own view, submitted on page 478 with ample evidence, is that its effects are similar to those awakened by adrenal substance, and that it is to the presence of this substance, though in organic combination—not necessarily an internal secretion—in the ovaries that they must be attributed.

[140] Warfel: Indianapolis Med. Jour., July, 1915.
[141] Rist: Echo Medical du Nord, No. 903, 1914.
[142] Konikow: Boston Med. and Surg. Jour., Sept. 30, 1915.

The *preparation* in general use is the desiccated gland, which may be given in doses of 2 to 5 grains (0.132 to 0.33 Gm.) twice daily. The fresh organ may be employed in 10- to 15- grain (0.6 to 1 Gm.) doses where the pharmaceutical product is not available. It soon loses its effect; small doses should first be given, then gradually increased.

Ovarian preparations have been tried in many disorders, but it is mainly in connection with those of the genital apparatus that they have been found of actual value.

Natural and Artificial Menopause.—In disorders occurring in the course of the physiological menopause, or when the latter is produced by bilateral oöphorectomy, ovarian preparations have proven of considerable value in a large proportion of cases since Brown-Séquard first introduced their use. Experience has shown, however, that the improvement lasts only as long as the agent is administered, and that, furthermore, certain phenomena—the palpitation, trembling, and "nervousness"—disappear earlier than the others, *i.e.*, the asthenia, flushes, irritability, and psychoses, though effects in all symptoms, including the cutaneous disorders,—especially acne rosacea and eczema,—are promptly realized, sometimes as early as the fourth day.

These effects are normally explained by the influence of the remedy on general oxidation and the improvement of the antitoxic functions of the blood, the imperfect hydrolysis of tissue wastes being the underlying cause of the phenomena other than the general asthenia.

The best results are obtained in young women who have grown obese after removal of the ovaries, or in whom obesity is due to ovarian insufficiency. In physiological menopause they are less marked, as a rule, and sometimes fail altogether to appear. In such instances, good results may sometimes be obtained by giving simultaneously 1 grain (0.066 Gm.) desiccated thyroid, or by depending upon the latter remedy alone. In congenital ovarian insufficiency, desiccated ovary has caused the appearance of menstruation.

Of late, however, the general attention has been centered upon the therapeutic use of corpus luteum, which often affords benefit where ovary alone fails.

The mode of action of ovarian preparations is suggested by

the personal view submitted on page 479, concerning the general effects of the ovaries attributed to an internal secretion. This is that we are not dealing with a true secretion, but with the products of the adrenal rests in the organ, and particularly the corpora lutea. The chemical properties, tests, physiological effects, etc., were shown to correspond precisely; the cellular elements also showed the characteristic features of the adrenal cortex, that the kinship had been noted by Mulon and others.

An important fact which should not be overlooked, however, is that the active agent occurs in organic combination with other bodies. Hence the fact that, although investigations having for their purpose to isolate the active constituent of the corpus luteum have been numerous, they proved successful only in a relative degree. Iscovesco,[143] of Paris, has extracted from the corpus luteum as well as the entire ovary a number of lipoid substances, one of which, a yellowish, waxlike body, soluble in oil, was found to exert a pronounced stimulating action upon the genital system, injections into young female rabbits causing a striking enlargement of the ovaries and uterus to several times the size noted in control animals. He believes the lipoids isolated by him to represent the active internal secretion of the ovary, and produces evidence to the effect that the most active of the lipoids exists both in the corpus luteum and in the remaining tissue of the ovary. Some investigators, on the other hand, cling to the older view that the active ovarian principle is a protein substance occurring in conjunction with a lipoid or lipoids. Herrmann,[144] in a recent research, obtained from the corpus luteum, as well as from the placenta, a thick yellow oil, which turns brown upon oxidation in the air and powerfully excites the growth of the reproductive organs. In common with Frank and Rosenbloom,[145] he believes that the active substance is not a lipoid, but is simply carried along with the lipoids when these are extracted from the luteal tissue as a whole. No preparation of an active principle of the corpus luteum is as yet available for therapeutic use, unless the lipoid preparations of Iscovesco, already used by him with satisfactory results in clinical work, are to be considered such.

[143] Iscovesco: Revue de Gynécol. et de Chir. Abdom., vol. xxii, p. 161, 1914.
[144] Herrmann: Monatshefte f. Geburts, u. Gynek., Jan., 1915.
[145] Frank and Rosenbloom: Surgery, Gynec. and Obst., Nov., 1915.

CORPUS LUTEUM ORGANOTHERAPY.

Menstrual Disorders; Menopause; Oöphorectomy.—Corpus luteum therapy has been applied chiefly in disturbances of menstruation and for the removal of the symptoms of the menopause, physiological or artificial, such as hot flashes, spells of psychoneurotic manifestations, digestive difficulties, vesical irritation, etc. The best results have been obtained in the climacteric group of cases. Marked, though not always complete, relief is usually experienced by these patients, the use of the remedy for an indefinite period being, however, necessary if permanency of result is to be secured. Dannreuther[146] has reported 2 cases of pruritus vulvæ associated with the menopause in which the itching was relieved with striking promptness by corpus luteum. He urges routine administration of the drug in all cases approaching the menopause as well as after hysterectomy and oöphorectomy, whether partial or complete. In some cases where but one ovary has been removed, compensatory activity by the other proves insufficient; corpus luteum therapy under these conditions is likely to prove beneficial.

Menstrual disturbances amenable to corpus luteum include, in particular, functional amenorrhea and dysmenorrhea of ovarian origin. Among patients with the former condition Dannreuther lays stress on the slightly obese, anemic, pale type of young woman who begins, soon after puberty, to complain of headache, malaise, nervousness, and constipation, together with scanty menstruation and, possibly, acne vulgaris. In such patients, by combining corpus luteum with hygienic treatment and tonic remedies, marked general improvement as well as stimulation of the menstrual flow can often be secured. Leighton[147] reports excellent results from the use of corpus luteum in a certain proportion of cases of dysmenorrhea, in particular those showing symptoms of ovarian insufficiency, such as irritability, malaise depression, headache, and scanty menstruation, with pain, especially on the first day of the period. This observer has become convinced that there occur cases of dysmenorrhea of which the chief cause is deficient action of the natural corpus

[146] Dannreuther: Jour. Am. Med. Assoc., Jan. 3, 1914.
[147] Leighton: Amer. Jour. of Obstet., Nov., 1915.