transplanted human parathyroids in a critical case with a successful result, and mentions 3 recorded cases.

An essential feature of parathyroid implantation is that the improvement may prove temporary only, *i.e.*, until, probably, the secretion the organ happens to contain is exhausted. This may last a couple of weeks and the symptoms return. It is only when the implanted organ assumes its normal functions *in situ* that cure occurs if the secretion produced is sufficient. Halsted's[66] valuable researches on the subject should be read by all operators in this class of cases.

That the oral use of parathyroid gland is of value in parathyroid tetany has been shown by MacCallum, Vassale, and others, though the first-named observer found that large quantities were necessary. Berkeley refers to other well-known observers, James, Putnam, and Halsted, as having obtained favorable results. In 2 cases recently reported by Bircher,[67] thyroid gland had first been tried, but without effect; parathyroid, however, caused prompt recovery.

An emulsion of fresh parathyroids may be given subcutaneously. Branham[68] reported a case thus treated successfully. Five fresh beef parathyroids were placed in a 1:1000 solution of bichloride of mercury and allowed to soak about ten minutes. The glands were cut, under strict asepsis, into 5 pieces under physiological salt solution. These pieces were placed in a mortar and ground into a homogeneous mass, 400 c.c. of sterile salt solution being poured into the mortar. This was then filtered through a sterile gauze and given as salt transfusion into the patient's breast. The oral use of thyroid and parathyroid extracts and the feeding of raw parathyroids had proved entirely useless. The recovery in this case, however, seems to me to be due to the fact that only one parathyroid was totally removed, and the three others only partly so, the remaining segments having eventually resumed their secretory activity. The injected emulsion thus acted as a palliative pending the functional recovery of what had been left of the organs. In Brown's case in which the parathyroids were removed, the

[66] Halsted: Amer. Jour. Med. Sci., vol. cxxxiv, No. 1, July, 1907, and Annals of Surgery, vol. xlvi, p. 489, 1907.
[67] Bircher: Medizinsche Klinik, Oct. 30, 1910.
[68] Branham: Amer. Jour. Med. Sci., vol. xlviii, p. 161, 1908.

benefit obtained from the emulsion lasted eleven days, and was then followed by violent tetany. Bircher's[69] 2 cases, also treated successfully with thyroid tablets, were probably of the same kind. Kocher[69a] obtained recoveries "by energetically pushing the thyroid extract and iodothyrin in large doses." Biedl[69b] urges that it should always be tried.

On the whole, what evidence there is tends to show that implantation of fresh glands should alone be depended on for a cure when the parathyroids have been destroyed.

Calcium lactate has been found efficacious by MacCallum and Voegtlin[70] and others. It may be given in 10-grain (0.66 Gm.) doses every hour or two, or in larger doses in saline solution per rectum, or in emergency cases, intravenously, 4 grammes (1 drachm) being given in 100 c.c. (25 drachms) of salt solution, as recommended by Winternitz,[71] in a case of non-operative tetany. In Brown's case, however, calcium lactate, given orally, proved useless, as did all organic agents, including parathyroids. Large injections of normal saline solution are used by Gomez[71a] and copious hypodermoclysis by Chvostek[71b] with washing of the stomach, stopping food for a couple of days.

The diet should receive considerable attention, and all substances rich in nucleins, including meats, should be strictly avoided, to reduce to a minimum the formation of spasmogenic wastes. A milk diet, farinaceous foods, and the free use of water to facilitate the elimination of what toxic wastes are formed are most useful in this connection. Exercise of any kind is also harmful, owing to the formation of muscular wastes that it entails. Rest in bed, or in an armchair, tends greatly to reduce the number and severity of the spasms.

Paralysis Agitans.—This is a particularly interesting syndrome from the standpoint of physiology, for it clearly sustains the view that the thyroid and parathyroids are functionally united. Indeed, while Möbius, in 1883, found paralysis agitans associated with exophthalmic goiter, Lundborg, in 1891, met it in connection with myxœdema, the autopsy show-

[69] Bircher: Medicinische Klinik, Oct. 30, 1910.
[69a] Kocher: Quoted by Biedl, "Internal Secretory Organs," p. 50, 1913.
[69b] Biedl: *Ibid.*
[70] MacCallum and Voegtlin: Johns Hopkins Hosp. Bull., vol. xix, p. 91, 1908.
[71] Winternitz: *Ibid.*, vol. xx, p. 269, 1909.
[71a] Gomez: Riforma Medica, Jan. 23, 1900.
[71b] Chvostek: Deut. med. Woch., May 20, 1909.

ing atrophy of the thyroid. These facts led both Möbius and Lundborg to connect the disease with the thyroid gland.

Various other phenomena, such as chronic rheumatism, arthritis, scleroderma, a brawny, or yellow-brown, pigmentation, hypothermia, etc., met with in cases of hypothyroidia, are also observed in paralysis agitans. In a case of mine the mask-like face of the latter disease recalled clearly that of an incipient case of myxœdema; Fraenkel had already observed myxœdematous areas. Parhon and Golstein[72] found in the thyroid proper of a woman who had died of paralysis agitans what they term "manifest macroscopical and microscopical lesions"; Castelvi[73] found marked atrophic lesions in the thyroid gland in two instances, though Pasquier found none.

Conversely, many cases of paralysis agitans may suffer from the sensations of heat with cutaneous rise of temperature, and the abundant sweating commonly observed in exophthalmic goiter. The most suggestive case in this connection, however, is one reported by A. Gordon,[74] in which the characteristic attitude of paralysis agitans, the stiffness and fixation, the mask face and absence of expression, the propulsive movement and the tremor, coincided with goiter, some degree of exophthalmus, tachycardia, dyspnœa, and Graefe's sign of exophthalmic goiter.

There is ground, therefore, for the hypothesis that the genesis of paralysis agitans is in some way related to the thyroid apparatus. Yet. a suggestive feature of the problem is, that thyroid preparations are useless in these cases, as many observers, including myself, have ascertained. Again, the fact that, while the main phenomena of exophthalmic goiter are distinguishable in certain cases, in others those of myxœdema occur, serves further to obscure the problem. Moreover, while R. L. Thompson[75] examined fruitlessly the parathyroid of 9 cases in which death had been due to paralysis agitans for lesions, others, including Berkeley[76] and Allen J. Smith, referred to in paper by Camp,[77] found lesions in these glandules. Indeed, Lund-

[72] Parhon and Golstein: "Les Sécrétions Internes," p. 218, 1909.
[73] Castelvi: Rivista de medicina y cirugia practicas, 1904.
[74] Gordon: Proceedings of the Philadelphia County Medical Society, Sept. 14, 1904.
[75] Thompson: Journal of Medical Research, Dec., 1906.
[76] Berkeley: Old Dominion Journal, April, 1909.
[77] Camp: Jour. of the Amer. Med. Assoc., April 13, 1907.

borg[78] suggested, in 1904, that paralysis agitans was specifically the syndrome of hyperparathyroidia, a view to which Berkeley[79] was also led independently, in so far as disease of the parathyroids is concerned.

That the latter view is based on good ground is suggested by the fact that, while, as stated above, thyroid preparations are useless in paralysis agitans, active preparations of parathyroid favorably influence the disease. Moreover, their favorable action harmonizes with two established facts: that the parathyroids produce a powerful antitoxic substance, and that the pathogenic element of the disease is a long-recognized toxæmia. That symptoms of exophthalmic goiter and of myxœdema occur, does not weaken this position if the thyroid and parathyroids are united functionally. Nor does the presence of these two antagonistic disorders militate against the parathyroid theory, since we have seen that exophthalmic goiter lapses, if the patient lives long enough, into a myxœdematous state. Nor need we even deem Thompson's failure to find lesions in the parathyroids as defeating the Lundborg-Berkeley theory, for the functions of the parathyroids may be inhibited precisely as are those of the adrenals and thyroid, by lesions along the paths of the nerves through which their functions are governed. Hence the cases on record in which the causative lesion was found in various parts of the cerebrospinal system.

Suggestive also is the beneficial action of parathyroid. Berkeley[80] first employed commercial preparations; while good results were obtained in some instances, they often proved unreliable. He then used properly identified gland rubbed up fresh with milk-sugar into a dry powder, but found this also unstable. Subsequently he used the nucleoproteid solution referred to under the preceding heading as prepared by Beebe's method, and preserved with a few drops in the bottom of the container. This raised the therapeutic value of the product, but it was found to precipitate readily, and that it failed to bear prolonged transportation. His latest process is the following: The nucleoproteid extraction process (Beebe's method)

[78] Lundborg: Deutsch. Zeitschrift für Nervenheilkunde, "27," 1904.
[79] Berkeley: Medical News, Dec., 1905.
[80] Berkeley: Medical Record, Dec. 17, 1910.

is adhered to generally, but all the preliminary steps are hurried, and the precipitated nucleoproteid is not redissolved, but quickly dried in a draught of cold air; so that within eight or ten hours after the warm glands leave the bullock a minute amount of smooth yellow powder is obtained which stands physiologic tests admirably, is stable, easily handled, and does not require a freezing temperature (though for safety's sake it is recommended to keep it on ice). The powder is rubbed up with milk-sugar as a menstruum, and is placed in sealed containers.

A large proportion of the patients slowly respond to the treatment, though in about 25 per cent. the response is only temporary and imperfect. The rest showed progressive benefit during the entire period of treatment. The dose of nucleoproteid, as previously stated, is about 20 drops (1.23 c.c.) per day, while that of the glandules proper is 5 to 8 per day. The preserved gland is also given in capsules containing each the equivalent of ½ grain (0.033 Gm.) of fresh gland, 5 to 7 of these being given daily. Parhon and Urechia[81] and Delille,[82] and others, have also reported considerable improvement, though the rigidity did not seem to be influenced.

ADRENAL OPOTHERAPY.

The prevailing view that adrenal preparations merely cause an ephemeral rise of blood-pressure and increase the vascular tone has greatly limited the intelligent use of these agents, though their empirical employment has somewhat compensated for this, and clinical applications have thus been discovered which the limited field of laboratory experimentation would never have brought to light. As we have seen, however, the adrenals are endowed with far more important functions, from my viewpoint: (1) their secretion takes up the oxygen of the air in the pulmonary alveoli and carries this gas to the tissue as constituent of the hæmoglobin; (2) it sustains, as such, oxidation, *i.e.*, metabolism, of the tissues (the latter having been sensitized for this purpose, we have seen, by the thyroiodase).

[81] Parhon and Urechia: Soc. de Neurol., Nov. 7, 1907.
[82] Delille: L'hypophyse et la médication hypophysaire, p. 186, 1909.

While this conception sustains the present interpretation, it accounts for clinical phenomena which had not previously been explained, witnessed in the use of adrenal preparations. It shows, we have seen, that the rise of temperature noted by Morel, Lépine and the concomitant rise of temperature and increased metabolism noted by Oliver and Schäfer are due to increased oxidation. It accounts also for the rise of blood-pressure, since increased metabolic activity—excited directly by the adrenal principle besides that due to general oxidation—of the muscular coats of vessels is manifested by contraction, and, therefore, by elevation of the blood-pressure. The increased power of the heart is the obvious outcome of increased metabolism in the myocardium, precisely as it is in the vascular muscles, while the slowing of its action is due to the greater diastolic expansion that attends increased functional vigor and the greater resistance the blood-column offers as a result of the increased blood-pressure.

The preparation most used is the *glandulæ suprarenales siccæ*, or dried adrenal gland, of the U. S. P. It is best given in capsules in doses of from 2 to 4 grains (0.13 to 0.26 Gm.).

Epinephrin, adrenalin, and other active principles of the gland are not reliable when given orally, being often oxidized in the stomach and intestines, and rendered inert. But they are absorbed from the colon.

They may, however, be injected subcutaneously in 10- to 20-minim (0.62 to 1.23 c.c.) doses in small (1 to 2 drachms—4 to 8 Gm.) or large (1 to 2 pints—500 to 1000 Gm.) quantities of warm saline solution, the smaller quantity of the latter being preferable when repeated doses are necessary, absorption being very slow. It causes pain and, sometimes, general pallor when the injections are repeated; this is due to the general effect of the drug on the arterioles, which are also contracted temporarily.

When prompt results must be obtained, as in the treatment of shock, cardiac failure, etc., the intravenous method is preferable, injecting slowly 10 to 20 drops (0.62 to 1.23 c.c.) in a pint or quart of hot (108° F.—42° C.) saline solution. Or, 5 to 10 minims (0.3 to 0.6 Gm.) in 2 drachms (8 Gm.) of saline solution may be injected drop by drop into a vein, using a hypodermic syringe in an emergency.

The local application of an adrenal principle, adrenalin, epinephrin, etc., causes such marked contraction of the vessels that their lumina, when applied over small vessels, may become obliterated, thus arresting totally the flow of blood. The tissues become very pale, therefore, and even blanched, owing to the active metabolic activity set up in the vascular walls, and particularly their muscular elements.

The disorders in which adrenal preparations are indicated are numerous; but the majority of those in which they are of greatest value have already been considered, viz., *Addison's disease* (page 97) and *terminal hypoadrenia* (page 109), which in itself includes practically all febrile infections. A few others, however, may be considered here.

Surgical Diseases.—Laboratory and clinical experience tend increasingly to show that man is more susceptible to the action of adrenalin than animals. While a subcutaneous injection of 1 drachm (4 c.c.) of a 1:1000 solution will hardly affect a rabbit, one-third of that quantity has produced untoward effects in normal as well as in tuberculous subjects (Souques and Morel), *e.g.*, vertigo, nausea, vomiting, severe pain under the sternum similar to that of angina pectoris, and a feeling of constriction about the chest, a rapid pulse, dyspnœa, cold sweats, and coldness of the extremities. Hypodermic doses of $^1/_{120}$ grain (0.00055 Gm.), however, are well borne. Intoxication may follow the use of adrenalin when injected into cavities such as the vagina, the rectum, the urethra, when the mucous membrane is abraded, lacerated, or denuded, thus rendering its absorption possible. The urethra seems to be particularly sensitive in this connection, the passage of bougies for stricture having caused poisoning in a number of cases. According to Braun,[83] the toxicity of epinephrin or other adrenal principles varies with the individual, but, in all, the danger lies in the use of concentrated solutions. He employs a solution of 0.64 Gm. (10 grains) of suprarenin borate in 100 c.c. (25 drachms) of 0.5 per cent. novocaine made up fresh from tablets for each operation; 125 c.c. (31 drachms) of this solution can be used without danger.

[83] Braun: Zeit. f. Gyn.; Amer. Jour. of Obstet., 1909.

Local applications may also be followed by untoward effects in the tissues to which adrenalin solutions are applied. Repeated applications, especially with the atomizer, of anything but weak solutions (1:10,000) to the nasal cavities or pharynx may give rise to œdema of the nasal mucosa, the uvula, tonsils, or pillars of the fauces. This is ascribed by most writers to "violent vasomotor constriction of the blood-vessels" and the resulting "venous stagnation," but it is in reality a secondary result of these effects, *i.e.*, paresis of the arterioles and œdema of the tissues. In some instances they cause persistent sneezing and acute coryza accompanied at times by severe pain in the upper portion of the nasal cavities. Some cases have been reported in which even sloughing and gangrene of the mucosa occurred. Elderly subjects are prone to this complication, according to Neugebauer. Post-operative hæmorrhages are not infrequently noticed after the use of adrenalin, owing to relaxation of the severed vessels. In the larynx, adrenalin solutions cause an uncomfortable dryness by interfering with the formation of lubricating mucus. This is especially distressing to singers. In the eye their use in scleritis and other disorders may be followed by severe iritis. Instillations of a 1:1000 solution in the Eustachian tubes have given rise to violent pain in the middle ear, which was renewed whenever the remedy was thus administered. The use of adrenalin solutions in the form of spray, at least, is contraindicated in infections, owing to the danger of facilitating the entrance of pathogenic germs into the sinuses.

The toxic effects produced, however, are readily accounted for by the functions in oxidation, metabolism, and nutrition I attribute to the adrenal secretion. Tracing the course of events from start to finish, we have at first the effects of excessive metabolism in all tissues: in the cerebro-spinal system, excitement; in the muscles, tremor; in the kidneys, polyuria; in the myocardium, violent contractions (palpitations); in the muscular coats of the vascular system, a marked rise of the blood-pressure. The latter in turn aggravates the process by causing congestion and engorgement of the capillaries (which are not, like the arteries, provided with a muscular coat) of all organs, including the lungs, causing œdema of these structures and dyspnœa. As the contraction of the arteries proceeds, the aorta has to bear the

brunt of the centrifugal pressure, giving rise to marked substernal pain. When it becomes such that the arterioles obstruct the circulation the lethal phenomena are initiated: the pulmonary circulation being impeded, oxygenation fails to occur; asphyxia follows, and, the myocardium receiving too little blood to sustain its contractile power, the heart, already hampered by the pulmonary congestion, ceases to beat.

After local applications the morbid effects are all the result of the action of the adrenal principle upon the vessels. The dryness caused by solutions sprayed into the larynx is due to deficiency of blood supplied to the acini and the resulting inhibition of their function. If this is kept up by repeated applications, the tissues, no longer nourished, may slough off, as has been noticed in the upper respiratory tract of aged subjects. The œdema observed in this location is not active, as it is in the lungs, but passive, *i.e.*, due to exaggerated relaxation of the vessels after the intense constriction to which the drug had subjected them. This applies equally well to post-operative hæmorrhage, and to the severe pain (due to passive congestion) in the middle ear after instillations in the Eustachian orifice.

Shock and Collapse.—The familiar influence of adrenal preparations on the blood-pressure and the rôle in tissue oxygenation I ascribe to them afford a self-evident explanation of the excellent action they have shown in the treatment of this condition, since they meet at once the two main morbid factors: low cardio-vascular tension and depression of the vital process. The latter effect is shown by the increase of body heat noted by Reichert, Lépine, Morel, and others.

Kinnaman, in a comprehensive study of the temperature relationship to shock, concluded that as shock increased in severity the most uniform and progressive factor was the fall in temperature. He states that "in one series [of cases] the fall in temperature was the sole cause of shock." The results of Crile with adrenalin in salt solution given very slowly and gradually for a considerable time thus find a normal explanation in my interpretation of the rôle of the adrenal secretion. He resuscitated animals in this manner—with simultaneous artificial respiration—fifteen minutes after all signs of life had ceased, and was able to keep a decapitated

dog alive over ten hours by this same procedure. That it was because the adrenal secretion is able to incite and sustain tissue metabolism, *i.e.*, the vital process itself, that such results were obtained seems obvious.

This applies not only to shock, but also to *surgical heart-failure, collapse* from hæmorrhage, *asphyxia,* and *submersion.* The adrenal principle (suprarenalin, adrenalin, etc.) promotes energetically, as a catalyzer and constituent of the hæmoglobin, the intake of oxygen and its utilization by the tissue-cells, including the muscular elements of the cardio-vascular system, and thus causes them to resume their vital activity. It should be very slowly administered intravenously, 5 minims (0.31 c.c.) of the 1000-solution to the pint of warm (105° F.—40.5° C.) saline solution. In urgent cases, 10 drops (0.62 c.c.) of supracapsulin or adrenalin in 1 drachm of saline solution can be used instead, and repeated at intervals until the heart responds. Artificial respiration hastens its effects.

The same remarks apply to the untoward effects of chloroform, which are also due to circulatory failure, with partial suspension of the vital process in the tissue-cells. Here a relatively large dose must be used, 30 minims (2 Gm.) of epinephrin, supracapsulin, or adrenalin in a pint of warm (108° F.—42.5° C.) saline solution intravenously. If injected very gradually it will excite the cardiac muscle by a direct action upon it before reaching the lungs, and cause it to resume its contractions. Kothe[84] has used this method successfully in 5 cases of cardiac failure following spinal anæsthesia. Too rapid injection causes cramp of the cardiac muscle and holds it in systole. Straub[84a] found that a weak solution kept up the blood-pressure if injected slowly intravenously.

The simultaneous use of $^1/_{100}$ grain (0.00066 Gm.) of atropine, hypodermically, aids materially the resuscitation by causing the arterioles to resume their functional tone, and thus to re-establish the *vis-a-tergo* motion of the blood in the capillary system. The physical methods, rhythmical traction of the tongue, suspension, etc., must, of course, not be neglected.

Hæmorrhage.—In hæmorrhage from the pharyngeal,

[84] Kothe: Therapie der Gegenwart, p. 95, 1907.
[84a] Straub: Münch. med. Woch., June 27, 1911.

œsophageal, gastric, or intestinal mucous membrane, the mastication of adrenal substance, or the use of powdered adrenal substance in 5-grain (0.33 Gm.) capsules, arrests the flow, by causing active metabolism in the muscular elements of the arterioles of the mucosa and constriction of these vessels—the characteristic local action of the adrenal principle.

Its use in intestinal hæmorrhage was studied with considerable care recently by C. J. Wiggers.[85] His conclusions were as follows: 1. Large doses of adrenalin (0.05 to 0.1 mg.) cause a short preliminary increase in hæmorrhage, followed quickly by a decrease or cessation of bleeding. On account of the great preliminary loss of blood they are always contraindicated. 2. Small doses of adrenalin (0.01 to 0.025 mg.) cause little or no preliminary increase, but shorten the course of hæmorrhage. As they save the red blood-cells in every way they are therapeutically desirable. 3. The method of introducing adrenalin determines the effect of blood-pressure and hæmorrhage. No results are obtained by subcutaneous administration. By continuous intravenous injection of weak solutions a slight elevation of pressure can be maintained and hæmorrhage simultaneously checked. This can also be accomplished by intramuscular injection. 4. Adrenalin is not indicated in all intestinal hæmorrhages. The condition of the blood-pressure is the criterion for its use. In hæmorrhages of short duration when the pressure has not fallen to any extent, a judicious use of nitrites proves of more benefit than adrenalin. When the bleeding has been profuse, however, and a low pressure already exists, it becomes vital that hæmorrhage should be checked without further reduction of pressure. Adrenalin finds its use in this field. 5. The use of adrenalin should always be closely followed by blood-pressure observations. A dose sure to be below the safety limit should first be tried, and the pressure carefully estimated. If no rise occurs, gradually increasing doses may be injected until a slight elevation of pressure is present.

Toxæmias.—It was noted long ago by Abelous and Langlois, Charrin, Oppenheim, and others, that adrenal extracts antagonized certain toxins and other poisons. This is due to the

[85] Wiggers: Archives of Internal Medicine, March 15, 1909.

participation of the adrenals in general immunity which I pointed out as far back as 1903, the specific action carried on by their secretion being that of amboceptor. Goldsieher[85a] noted a marked diminution of adrenalin in the adrenals of subjects in which death had been due to an infection: pneumonia, puerperal meningitis, etc., thus showing that in all such processes there is abnormal activity of the organs, *i.e.*, an extraordinary output of adrenal secretion. Many clinicians are now using adrenal preparations to compensate for this loss. (See Terminal Hypoadrenia, page 109).

Cancer.—In both rats and mice, carcinomatous and sarcomatous neoplasms have been caused to disappear by injections of adrenin, while they also prevented the growth of cancerous grafts. Reicher[85b] tried the same treatment in man. A sarcoma was reduced to one-third of its size, which third with the aid of X-rays and the high-frequency current was caused to disappear. Malignant lymphomata and a case of melanosarcoma were also favorably influenced. Injections of adrenalin around a tongue cancer also proved beneficial.[85c 85d]

In personal inoperable cases adrenal gland seemed to prolong life by delaying the cachexia, especially when given with iron. Suggestive in this connection is that, in Reicher's words: "It is remarkable that during the treatments the patients increased much in weight—up to 14 pounds. There must be a constant anomaly of metabolism somewhere." I may recall in this connection that eight years earlier I had pointed out that the function of the adrenal secretion was to take up the oxygen of the air in the lungs and to sustain tissue oxidation, metabolism, and nutrition—thus accounting for the gain in weight Reicher noted. Ritchie[85e] recently reported the disappearance of a skin carcinoma under local applications of the 1:1000 solution of adrenin.

The desensitizing action of adrenalin by cataphoresis has been found by Reicher and Lenz[85f] to permit the use of nearly double the dose of X-rays.

[85a] Goldsieher: Wiener klin. Wochenschrift, June 2, 1910.
[85b] Reicher: Deut. med. Woch., Nu. 22, 1910, and Berliner klin. Woch., Nu. 20, 1911.
[85c] Echtermeyer: Berliner med. Woch., Aug. 21, 1911.
[85d] Holscher: Ann. des méd. de l'oreille, du larynx, etc., No. 7, 1912.
[85e] Ritchie: London Lancet, June 29, 1912.
[85f] Reicher and Lenz: Deut. med. Woch., Jan. 4, 1912.