

abundant nervous structures in the immediate neighborhood of the adrenals or through dilatation of these organs when the general blood-pressure, from any intercurrent cause, becomes high. The intense congestion attending or preceding adrenal hæmorrhage, which often terminates Addison's disease, suggests that a temporary exacerbation of the local hyperæmia incident upon the local lesion is the main cause of this symptom.

Tendency to Syncope, Impairment of Vision, and Hearing.—The tendency to syncope is such in some cases that elevation of the head sometimes suffices to cause death. Not only is this accounted for by the low blood-pressure and the resulting cerebral ischæmia, but also by the poverty of the blood in adrenoxidase, its oxidizing principle. The extremely small, soft, compressible, and sometimes imperceptible pulse bespeaks a third factor in the pathogenesis of this symptom: great systolic weakness of the heart, owing to loss of the direct support received from the adrenal secretion in transit through its right auricle and ventricle, and deficient metabolism in the left myocardium.

The same cerebral ischæmia and anæmia which predispose to syncope and vertigo also affect the organs of special sense; hence the impaired vision and hearing.

Headache, Irritability, Hallucinations, Delirium, Convulsions.—We have seen that, as shown by Abelous and Langlois, the adrenal secretion is endowed with antitoxic functions. It follows, therefore, that any adrenal disorder capable of materially reducing the supply of this secretion must lead to accumulation of the tissue poisons it is known to destroy. It is these poisons that give rise to headache, irritability, muscular twitching, rigidity, delirium, and convulsions similar to those witnessed in puerperal eclampsia, also due to endogenous poisons.

Coma, Sudden Death.—Gradual decline with profound asthenia, or some intercurrent disorder and coma often terminates the case, but not infrequently death occurs in the midst of a convulsion, or suddenly without such, owing to adrenal hæmorrhage. This is due to the accumulation of poisons referred to under the preceding heading. By irritating or exciting the vasomotor center, these poisons cause a rise of blood-pressure and even fever. The remnant of medulla in the adrenals and their intrinsic sinusoidal vessels, medullar and cortical, being

subjected to inordinate pressure, suddenly rupture, constituting what Arnaud has very aptly termed "adrenal apoplexy."

TREATMENT.—The only curative measure worthy of any confidence is one calculated to replace the destroyed glands or, at least, to supply the organism with the adrenal product in some form.

The grafting of adrenals into the tissue has led to such unfortunate results that Courmont, after a personal experience in the use of this procedure, declared it formally contraindicated. Indeed, Bra,¹⁸¹ after grafting the suprarenals of a dog into the cellular tissue of the abdomen in a child of 14 years, witnessed its death in three days. Jaboulay,¹⁸² having resorted to the same method in two cases, lost both within twenty-four hours, owing, he honestly admits, to the operation. The same result followed in Courmont's case. If this question is closely analyzed, however, it becomes apparent that it is not the method proper, or the operators, that are responsible for the untoward results, but rather the fact that the functions of the adrenals were still too obscure, at the time the operations were performed, to afford the indications necessary for a judicious adjustment of the quantity of adrenal tissue grafted to the needs of each particular case.

The cause of death in such cases is made clear by my interpretation of the functions of the adrenals. Thus Courmont, referring to the three cases in which dog's adrenals had been grafted in cases of Addison's disease, writes: "In the three cases the results were disastrous. In my own case the patient died in twenty-four hours with a *formidable hyperthermia* and cardiac collapse," while specifying that there was no infection of the wound. With the adrenals as the source of a secretion whose mission is to sustain oxidation, the cause of the excessive temperature is self-evident. The grafted adrenal tissues furnished adrenal substance far in excess of the needs of the organism, and the phenomena produced were those of the physiological function carried out by the secretion, but "formidably" exaggerated.

If grafting is resorted to, the proportion of tissue employed

¹⁸¹ Bra: Cited by E. X. Adams, Practitioner, Oct., 1903.

¹⁸² Jaboulay: Lyon Médical, Mar. 21, 1897.

should be adjusted to the needs of each case, always beginning with a small quantity of tissue and adding small grafts until distinct improvement is noted. It must be said, however, that the experimental use of small grafts has not, so far, been attended with much success.

Indeed, it has not been possible to obtain successful grafts in a sufficiently large proportion of experimental animals so far to warrant grafting in man. Dominicis,¹⁸³ Boinet, Imbert,¹⁸⁴ Coenen,¹⁸⁵ Taddei and Torrini,¹⁸⁶ and others had unsuccessfully attempted to introduce grafts in various parts of the body. Abelous,¹⁸⁷ however, succeeded in preserving life in animals from which the adrenals had been removed by means of grafts; but subsequent degeneration of the latter caused death. Gourfein met with similar results. Haberer,¹⁸⁸ after partly detaching one adrenal in such a way as to provide a pedicle which would continue to supply the organ with blood, inserted the free segment in a slit in the kidney. This operation, tried in 86 animals, proved successful in 50 per cent. But to replace a diseased organ, transplantation of a normal organ obtained from another subject or lower animal is necessary. The nearest approach to this result was that obtained by Busch, Leonard, and Wright,¹⁸⁹ who succeeded in transplanting the adrenal of one rabbit into the kidney of another which had also been deprived of one adrenal. On removing the remaining adrenal thirty-six days later, the animal recovered, showing that the implanted adrenal was functionally active. On removing the kidney containing the grafted adrenal twenty-nine days later, however, the animal died in forty-three hours. On the whole, it has become apparent that the kidney is the best structure for the implantation of adrenal grafts, and that it is in this direction that our attempts at grafting should be directed. Recalling the experience of Jaboulay, Courmont, and others to the effect that the dog's adrenal produces fatal hyperthermia, the organs of smaller animals might be used, adding one or more subsequently if need be.

¹⁸³ Dominicis: *Gazetta degli Osp. e. d. Clin.*, Nov. 22, 1896.

¹⁸⁴ Imbert: *Le Bulletin Médical*, Nov. 8, 1899.

¹⁸⁵ Coenen: *Arch. f. klin. Chir.*, B. lxxxii, Hft. 2, 1907.

¹⁸⁶ Taddei and Torrini: *Lo Sperimentale*, July-Aug., 1907.

¹⁸⁷ Abelous: *C. R. de la Soc. de Biol.*, Nov., 1892.

¹⁸⁸ Haberer: *Arch. für klin. Chir.*, B. lxxviii, No. 2, 1908.

¹⁸⁹ Busch, Leonard, and Wright: *Jour. Amer. Med. Assoc.*, Aug. 22, 1908.

As to the general results of adrenal preparations and grafting, a series of 120 cases collected from literature within my reach, including 97 previously collected by E. W. Adams,¹⁹⁰ in all of which adrenal preparations had been used in some form, gave the following results:—

1. Cases in which death can be ascribed to grafting or adrenal preparations	8
2. Cases in which the benefit was slight or nil	51
3. Cases in which marked improvement occurred	36
4. Cases in which permanent benefit was obtained ..	25

120

The unfavorable results obtained with adrenal preparations given orally are doubtless due, in a great measure, to their empirical use, and regardless of the dose indicated in each case. E. W. Adams¹⁹¹ refers to a group of 7 cases, "in which alarming or fatal results were presumably or possibly due to the treatment." He mentions, for instance, 2 cases reported by Affleck¹⁹² treated with "suprarenal gland extract." The chart notes include the words: "Alarming collapse. One of the cases began to improve markedly when the extract was stopped." In the original paper, reference is made to another case treated by suprarenal extract in which "similar collapse was noted." The dose was not mentioned. Such cases are apt to be regarded as examples of the sudden death observed in Addison's disease, to which Addison himself, Dieulafoy, Anderson, Bradbury, and others have called attention. Guiol,¹⁹³ having observed similar signs of intoxication and collapse, tried the remedy in a normal subject and obtained the same morbid phenomena. The essential feature in carrying out this mode of treatment is to *adjust the amount administered to the needs of each case*. Addison's disease being due, from my viewpoint, to inadequate oxygenation and metabolic activity, the results in turn of a deficient production of the adrenal secretion, it follows that *the temperature and blood-pressure indicate the*

¹⁹⁰ Adams: *Practitioner*, Oct., 1903.

¹⁹¹ Adams: *Loc. cit.*

¹⁹² Affleck: *Lancet*, Dec. 31, 1898.

¹⁹³ Guiol: *Bull. de la Soc. médico-chi. du Var*, Dec., 1906.

degree to which the adrenals are still performing their functions. It is plain, therefore, that our aim should be to supply only just enough adrenal extractive to compensate for the deficiency of adrenal secretion produced.

This may be illustrated by the history of 25 cases of Addison's disease in which, out of the 120, permanent benefit occurred. In 1 of these, treated by Bate,¹⁹⁴ but $\frac{1}{12}$ grain (0.005 Gm.) of adrenal extract three times daily caused very great and lasting improvement with marked lessening of the bronzing. When the remedy could not be obtained temporarily, which occurred twice, the case relapsed. Conversely, Suckling¹⁹⁵ began with 10 grains daily in another case and gradually increased until 175 grains were given each day; he also obtained favorable results. That in Bate's case the adrenals were still able almost to carry on their function is self-evident, while in Suckling's the remedy practically compensated for the adrenals; the local morbid process in them was still active, and such as to paralyze their functions—a fact which was well shown by the severity of the case when the use of the extract was begun. The average dose is probably that used by Weigall¹⁹⁶ in a very severe case—5 grains, increased to 10 grains, of the extract three times a day. The patient increased 6 pounds in two weeks, and after about three months 56 pounds. In other words, in the 25 cases of permanent benefit, although the remedy was used empirically, it so happened in all probability that the doses employed coincided with the needs of the organism. In the 51 cases in which no benefit was obtained several occur in which failure was evidently due to inadequate dosage or to too early cessation of the treatment, while in others excessive doses—practically in every instance a too rapid or excessive increase of the dose—as clearly prevented a successful issue.

Excessive doses may not only raise the temperature beyond normal, as we have seen, but they may also, by increasing general oxidation and metabolism, so increase the functions of the thyroid that we may have, besides, symptoms of exophthalmic goiter. Boinet¹⁹⁷ reported such a case in a patient who had

¹⁹⁴ Bate: Amer. Pract. and News, Aug. 1, 1899.

¹⁹⁵ Suckling: Brit. Med. Jour., May 28, 1898.

¹⁹⁶ Weigall: Australasian Med. Gaz., Oct. 20, 1905.

¹⁹⁷ Boinet: C. R. de la société de biol., n. 891, 1889.

increased the dose of his own accord. The same clinician¹⁹⁸ observed sudden death in 2 cases after injecting $\frac{1}{180}$ grain of adrenalin, the rise of pressure having produced, doubtless, hæmorrhagic destruction of what remained of adrenal medulla.

Adrenalin or any active principle of the epinephrin group should not be used in the disease owing to the suddenness with which they elevate the blood-pressure. They prove effective, sometimes, when given by the mouth, 7 to 8 drops of the 1:1000 solution being given daily. Boinet¹⁹⁹ recently reported 3 such cases, while in 4 cases the same treatment proved useless. Supracapsulin (Cudahy) might prove more efficient than adrenalin owing to the claim that it is not oxidizable because it contains 0.5 per cent. of chloral. The dried gland (the *glandula suprarenales sicca* of the U. S. P.) is available in tablet form, 1 grain representing about 5 grains of the fresh gland. If the blood-pressure and the temperature are considerably below normal, 3 grains (0.2 Gm.) may be given to an adult twice daily during meals, from the start and kept up and increased if need be until they become normal, regulating the dose thereafter so as to maintain this level. Smaller doses are indicated if the blood-pressure and temperature do not depart much from the normal. The powder is sometimes to be preferred in the same doses, owing to the possibility of administering it in capsules which conceal the rather unpleasant odor of adrenal gland. Unfortunately no very reliable preparation is yet available.

Glycerin extract of fresh gland may be prepared where the desiccated gland cannot be obtained; or the fresh mutton or beef gland may be given twice daily, in doses of 5 to 15 grains, with the food. The glycerin extract is also used hypodermically, but the injections are painful and are no more effective than the dried gland.

As previously stated, I ascribe the therapeutic effects of pituitary extract to the adrenal principle it contains. It is indicated, therefore, in Addison's disease. The best way to administer it is by intramuscular injections, using 15 minims (1 c.c.) of the preparation termed "vaporole" by Burroughs Well-

¹⁹⁸ Boinet: Arch. générales de méd., Feb. 9, 1904.

¹⁹⁹ Boinet: Bulletin de l'Acad. de Med., Oct. 5, 1909.

come and Co. and supplied in small vials containing the above quantity. The dose should be renewed as frequently as needed to raise the temperature to normal and keep it there.

Pitres and Gautrelet²⁰⁰ found recently that the use of glucose, to compensate for the deficient formation of glycogen (due to inadequate conversion of starches into this substance), caused the intense adynamia and sensation of fatigue to improve materially, especially when given simultaneously with adrenal preparations.

Iron in the form of Bland's mass is of advantage to counteract the anæmia. The adrenal product, by increasing the albuminous hæmoglobin, requires the iron to build up hæmatin and the complete hæmoglobin. It is indicated even when the blood-count, which may be very low, as noted by Hayem, shows but little diminution of red corpuscles. One grain of iron can be given with desiccated adrenal powder in capsules. Other drugs should be used with great circumspection, especially in advanced cases. Strychnine, digitalis, and other drugs which raise the blood-pressure expose the patient to adrenal hæmorrhage.

The intense, asthenia, the tendency to syncope on exertion, and the weakness of the heart impose the need of remaining as quiet as possible. When the case is advanced, rest in bed is indicated. Nutritious, but readily digested food tends to delay the morbid process, meats and milk contributing their own adrenal substance to compensate in a measure for the patient's inadequate supply. Lavage of the stomach affords considerable relief in cases in which there is gastroptosis and retention of food materials as a result of relaxation of the muscular coat of the stomach, in keeping with the adynamia of all muscular elements. Bismuth is the safest agent to use for the diarrhoea in conjunction with the adrenal preparation employed.

When Addison's disease is due to tuberculosis of the adrenals, as is usually the case, the carbonate of creosote 5 grains (0.3 Gm.) three times daily may advantageously be given with the adrenal preparation. The iodides, which do not raise the blood-pressure, have been used with advantage.

²⁰⁰ Pitres and Gautrelet: *Revue de Thérap. Médico-Chir.*, Aug. 15, 1910.

TERMINAL HYPOADRENIA.

For reasons given on page 80, the term "hypoadrenia" was introduced in lieu of those at present in vogue, which are either incorrect or cumbersome. Interpreted from my viewpoint,

Terminal hypoadrenia is that form of adrenal insufficiency which occurs late in the course of an acute febrile disease, as a result of the exhausting secretory activity, probably aggravated by temporary local lesions to which the adrenals are subjected, as defensive organs, during the febrile period of the disease. It should be clearly differentiated from intercurrent *hyperadrenia*, a more dangerous type, considered beyond, which may appear at any time in the course of an acute infection or toxæmia.

The adrenals being admittedly concerned in the protection of the organism during infections and intoxications by contributing an excess of their secretion during the febrile stage of the disease (sometimes considerably prolonged), it follows that after this stage is over the adrenals should lapse into a condition of more or less temporary insufficiency through fatigue or exhaustion. This effect is well exemplified by the recent observation of Carl^{201a} that the adrenals of frogs after strychnine convulsion and also of a bicyclist who had died of extreme exertion no longer gave the chromaffin reaction.

In lobar pneumonia and bronchopneumonia, for instance, resolution may be considerably delayed and convalescence likewise. There is, late in the case, extreme adynamia and a low blood-pressure, the temperature is below normal, the pulse weak and more or less rapid, and death from heart-failure is not infrequent. In typhoid fever, hypoadrenia is commonly observed. The disease assumes what is now known as the cardiac type, with weak pulse, prostration, a tendency to fainting. A case of this class, and which shows clearly the adrenal involvement, was recently described by Josué.²⁰¹ Here, again, we find, late in the case, extreme prostration, a rapid, weak and sometimes irregular pulse, hypothermia, and a marked tendency to vertigo, fainting, and cardiac failure. Are these phenomena due, in keeping with the effects of poisons on the adrenals

²⁰¹ Josué: *Société Médicale des Hôpitaux*, May 21, 1909.

^{201a} Berliner klin. Wochenschrift, June 12, 1911.

already described in these pages, to vascular lesions of these organs? Sicard²⁰² reported the case of a young woman in whom the foregoing symptoms appeared on the ninth day of a bronchopneumonia. Extreme muscular weakness, marked hypothermia and low blood-pressure, diarrhoea, and Sergent's white line were present. On the fifteenth day the blood-pressure fell to 70 or 80 (7 or 8 per cent. Potain) and death followed three days later. At the autopsy the adrenals were found hæmorrhagic. This suggests that adrenal lesions may be present in all such cases. Yet, Ribadeau-Dumas and Bing²⁰³ have witnessed the same symptoms in cases of measles which recovered, while Bossuet²⁰⁴ refers to 8 cases in various febrile disorders in which typical symptoms of adrenal insufficiency, asthenia, low blood-pressure, etc., developed suddenly and disappeared spontaneously, aided perhaps by adrenal extract which had been administered. What organic lesions occur in such cases, therefore, are not necessarily fatal, as emphasized by the areas of fibrosis (old healed lesions) often found at autopsies.²⁰⁵

As stated recently by Morichau-Beauchant,²⁰⁶ the adrenals seem to show a special predilection for certain infections. Diphtheria easily leads them all in this connection. So seriously do these organs suffer in these cases that Sevestre and Marfan have termed the type "secondary syndrome of malignant diphtheria." Hutinel ascribes the fulminating cases of scarlatina to this cause. Tetanus, erysipelas, mumps, certain forms of tonsillitis, and certain streptococcal infections are occasionally witnessed which also present the typical syndrome of hypoadrenia. Goldzicher²⁰⁷ was led by his researches to conclude that in the various forms of septicæmia the appearance of lower blood-pressure was to be ascribed to insufficiency of the adrenals. Finally, Comessatti^{207a} found that in diseases of long duration, the adrenalin contained in the adrenals was far less than in those of subjects in which death had occurred suddenly.

PATHOGENESIS AND SYMPTOMATOLOGY.—These two features of terminal hypoadrenia have been partially covered in the

²⁰² Sicard: Bulletin de la Soc. Médicale, July 21, 1904.

²⁰³ Ribadeau-Dumas and Bing: Bull. de la Soc. Anat., June 3, 1904.

²⁰⁴ Bossuet: Gazette hebdomadaire de Sc. méd. de Bordeaux, Oct. 30, 1904.

²⁰⁵ Loeper and Oppenheim, in Malad. des Reins et des Caps. Sur., by Debove, etc., p. 738, 1906.

²⁰⁶ Morichau-Beauchant: Le progrès médical, Oct. 9, 1909.

²⁰⁷ Goldzicher: Wiener klin. Woch., June 10, 1910.

^{207a} Comessatti: La Clinica med. Italiana, Nov., 1910.

foregoing lines. Briefly, if at the end of an infectious disease the case, instead of proceeding to convalescence, remains in a condition of asthenia, with low blood-pressure and temperature, there is good ground for the conclusion that this form of hypoadrenia has occurred. Exhaustion of the adrenals during the acute process having inhibited their secretory activity, the above symptoms result from inadequate oxidation of, and metabolic activity in, the tissues. Sergent's white line, already described, may be obtained in the majority of these cases. The patient complains of chilliness, the surface is pale owing to the poverty of the blood in cellular elements and hæmoglobin, and to recession of the blood-mass from the surface to the deeper vascular trunks. The vascular tension being low the pulse is rapid and the heart-beat weak. Anorexia due to deficient metabolism and diminished nutritional needs, nausea, the result of relaxation of the gastric muscular coat, and diarrhoea due to a similar condition of the muscular coat of the (already passively engorged) intestine, more or less frequent fainting spells may all be witnessed in such cases, which are always greatly exposed to relapse or to sudden demise from heart-failure.

Complications of various kinds may occur. The immunizing processes being greatly weakened through the deficiency of adrenal secretion, one of its important factors, septic infection, abscesses, bone lesions, tuberculosis of a rapid type, and other infections may more or less rapidly develop. Disorders of nutrition, cholelithiasis, and occasionally Addison's disease may also appear. In acute pulmonary infections, pneumonia, for example, tissues in the neighborhood of the focus of infection, the pleura, the heart, etc., inadequately protected by the blood or its phagocytic cells become infected. Briefly, the body is rendered vulnerable to the attacks of almost any pathogenic organism.

PATHOLOGY.—In the special type in question no adrenal lesion may be discernible. In the majority of instances, however, the organs are enlarged and congested, and may show here and there a limited hæmorrhagic area. Their appearance suggests not only the conditions incident upon functional exhaustion, but the presence of a *passive* congestion (see page 34) resulting from loss of resiliency of their sinusoidal vessels, thus

impeding the circulation through them. Occasionally they are the seat of suppuration, a complication which is apt to be observed when the causative disease is, or includes, a streptococcic infection, pneumonia or meningitis.

The pathological picture of the more severe form of adrenal complication, *i.e.*, intercurrent hyperadrenia, considered beyond, shows far more distinct lesions of the adrenal parenchyma. Hence the typical lethal phenomena that attend many of these cases.

TREATMENT.—In these particular cases opotherapy, or rather the use of adrenal gland, or of pituitary body, which acts very similarly, but with less violence and more lasting effects, sometimes gives surprising results. The adrenal product—which from my viewpoint is also the main active agent in the neural lobe of the pituitary, as shown by the chromaffin test—supplies precisely what the body needs, *e.g.*, the resumption of all oxidation processes, which means general metabolism and nutrition, and the resulting rise of blood-pressure, which causes the blood to circulate normally in all organs, including the skin, and in the adrenals themselves. Indirect effects are also obtained: its action on the heart increases the contractile power of this organ, and, being thus rendered capable of projecting the blood with more vigor through the lungs, oxygenation of the blood becomes more perfect—a process materially aided by the rise of blood-pressure, which, as stated, drives the blood from the splanchnic area toward the peripheral organs, including the lungs and the brain. From these features alone, considerable benefit is derived. If we recall, moreover, the participation of the adrenal secretion (which the adrenal preparation administered represents) in the immunizing process, we have the added factors of ridding the blood of any intermediate—and therefore toxic—wastes, bacterial toxins, etc., it may contain, and of increasing phagocytic activity, thus antagonizing efficiently any pathogenic organism that may remain to compromise the issue. Thus explained, we can understand the phrase “little short of marvelous” applied to the results obtained by some clinicians. We can also understand the marked reduction in the mortality obtained by Hod-

dick²⁰⁸ in cases of peritonitis following appendicitis accompanied by uncontrollable decline of the blood-pressure, cyanosis, and other evidences of collapse, and also in puerperal toxæmias, by the slow intravenous use of adrenalin in saline solution. Hoddick ascribes the lowering of the blood-pressure to paralysis of the vasomotor center; but as the toxæmia is the cause of this condition, an agent capable of counteracting both cause and effect is necessary. This is met by the adrenal principle. Josué,²⁰⁹ in typhoid fever, likewise relieved threatening symptoms by injecting 15 minims (1 c.c.) of adrenalin (1:1000 sol.) in $\frac{1}{2}$ to 1 pint (250 to 500 c.c.) of physiological saline solution subcutaneously. The influence of the saline solution in these cases must not be overlooked, however. Seven years ago, I urged that death was often due, in infectious and septic diseases, to deficient circulatory osmosis, and advised the use of saline solution *from the onset* in all febrile diseases. Netter²¹⁰ has used large doses of the adrenal active principle with profit. Marran and Darré²¹¹ found it of great value in the collapse of diphtheria with marked asthenia, low blood-pressure, and subnormal temperature. Moizard²¹² recommended adrenal opotherapy as soon as asthenia and low blood-pressure occur in any infection. He gives daily two fresh adrenals from the sheep, finely divided and mixed with powdered sugar, or, better, the use of the active principle, adrenalin, supracapsulin, etc., 10 to 20 drops daily divided in five or six doses. Kirchheimer²¹³ has found large doses (10 to 24 minims) safe hypodermically in the collapse of pneumonia, diphtheria, and scarlet fever. Letulle, Lemoine, Grysez, and Dupuich^{213a} have found it of great value in the latter disease. Lesné, Gérard, and Francon^{213b} noted that the sudden death in erysipelas showed the characteristic symptoms of adrenal inhibition and obtained good results from the internal use of adrenalin and digitalis. The better plan, from my viewpoint, is to inject adrenalin with saline solution (at 108° F.) intravenously.

²⁰⁸ Hoddick: *Centralbl. f. Chir.*, Oct. 12, 1907.

²⁰⁹ Josué: *Loc. cit.*

²¹⁰ Netter: *Soc. Médicale des Hôpitaux*, May 7, 1909.

²¹¹ Marran and Darré: *Journal des praticiens*, May 15, 1909.

²¹² Moizard: *Revue de thérapeutique*, Jan. 1, 1910.

²¹³ Kirchheimer: *Münch. med. Woch.*, Dec. 20, 1910.

^{213a} Lemoine, Grysez, and Dupuich: *Bulletin médical*, Jan. 17, 1912.

^{213b} Lesné, Gérard, and Francon: *Presse médicale*, Nov. 15, 1911.