These measures are only indicated in emergency cases, however. In the average case the *glandulæ suprarenales siccæ* of the U. S. P. administered by the mouth is fully as effective if a good preparation is obtained as soon as asthenia and low blood-pressure appear. The powder in 3-grain (0.2-Gm.) doses three times daily in capsules, gradually increased until 5 grains are given at each dose, usually suffices. When the cardiac adynamia disappears, a small dose of thyroid, the desiccated gland, also ½ grain (0.03 Gm.) strychnine 1/60 grain (0.001 Gm.) and Blaud's pill, 1 grain (0.06 Gm.) added to each capsule greatly hastens convalescence. The iron and the adrenal product serve jointly to build up the hæmoglobin molecule, a slow process when left to itself.

For our knowledge of the action of the use of pituitary extracts in infectious diseases we are mainly indebted to L. Rénon and Delille,[214] who began their use in 1907. In a recent work in which the observations of both observers are recorded, Delille,[215] referring to grave cases of typhoid fever, states that they showed "arterial hypotension, irregularity of the pulse (especially the grave forms), oliguria, insomnia; while convalescents showed asthenia, hypotension, or at least effort hypotension (Oddo and M. Achard), paroxysmal or continuous tachycardia"—all, we have seen, symptoms of hypoadrenia. They found 1½ grains of pituitary extract (of both lobes), at noon daily, extremely efficient; it counteracted at once the depressed arterial tension, produced diuresis, relieved the insomnia, and greatly improved the general condition. Similar effects were observed in diphtheria and erysipelas. The use of the pituitary extract "vaporole," as described under the preceding heading, is also indicated in these cases. The results in pneumonia do not appear to me to warrant the use of any adrenal or pituitary preparations early in the case, the first few days of the disease, when the blood-pressure and the fever are high. They should be used *only when a low blood-pressure and other symptoms of hypoadrenia are present.* The results reported by Delille strengthen this opinion. In advanced tuberculosis no beneficial effect was observed.

[214] Rénon and Delille: Bulletin de thérapeutique, Feb. 8, 1907.
[215] Delille: "L'Hypophyse et la Médication Hypophysaire," 1909.

HYPERADRENIA.

Just as "hypoadrenia" has seemed to me to replace advantageously both "adrenal insufficiency" and "hypoadrenalism," so does "hyperadrenia" appear to convey a more exact meaning of excessive adrenal activity than "hyperadrenalism," which suggests the presence of habitual overactivity, and to be less cumbersome than the phrase "excessive secretory activity" and others habitually used.

To recall briefly the effects of large doses of adrenal extract, is all that is necessary in the present connection. Textbooks merely refer to the fact that it causes marked slowing of the heart, marked constriction of the blood-vessels, and a decided rise of blood-pressure; but we would not proceed far with these archaic limitations were we to attempt to explain with them the phenomena included under hyperadrenia. I shall, therefore, continue to have the interpretation of the phenomena witnessed upon the conception of adrenal functions I have advanced, viz., that the adrenals supply a secretion which becomes converted in the lungs into the oxygenizing albuminous constituent of the hæmoglobin molecule, and that as such it governs metabolism and nutrition, the action on the heart and blood-vessels being but an incidental result of this function. We have seen also that the adrenal secretion took part in the immunizing processes of the body at large. We shall now find that these functions account for those of hypoadrenia, as they did under the preceding heading.

Were we to identify a "functional" type, as I did in the opposite condition, hypoadrenia, we should find it necessary to include the many conditions in which overactivity of the adrenals takes an important part. When we recall, however, that, from my viewpoint, these organs play a leading rôle in all febrile affections, that an excess of adrenal secretion in the blood means hyperoxidation and hyperactivity of all organs, and that as a result we may have glycosuria, psychoses, pulmonary œdema, and many other symptoms, it will become apparent that no such a "functional" type could well be proposed without endowing the adrenals with a great part of the whole field of pathology. It was deemed far preferable, therefore, to treat

known diseases in the usual way and to illustrate the rôle played in their history by the adrenals. This has been carried out in the second volume, beginning with page 1389, reserving for the present chapter what disorders could strictly be associated with the adrenals *per se* or due essentially to an excess of adrenal tissue, as in the various forms of hypernephroma.

In point of frequency, subdivision of the subject is not difficult to establish, the first condition, treated below, being one which the general practitioner is liable to meet at any moment and continuously in the course of his everyday work.

ACUTE HYPERADRENIA AND ADRENAL HÆMORRHAGE.

By the term "acute hyperadrenia," I mean excessive functional activity of the adrenals or "hyperadrenalism," brought on by the presence in the blood of the system at large of any poison capable of exciting the adrenal center.

We have seen that various toxics, pneumobacillus cultures, diphtheria and other toxins, drugs, vegetable poisons, etc., caused, when injected experimentally, congestion of the adrenals, so marked in some instances as to provoke rupture of the congested vessels, or necrosis of the adrenal cellular elements compressed by them. To the confirmatory investigations already mentioned may be added those of Bernard and Bigart,[216] who studied the effects of arsenic, mercury, and lead, mainly in respect to the histological changes produced in the cellular elements of the adrenals, and who found that in the *less profound* intoxications there occur, instead of destructive lesions, the histological signs of *functional hyperactivity*. My own investigations have not only sustained this conclusion, but they have served to explain the manner in which this functional hyperactivity is brought about, viz., by excitation of the adrenal center, which, as already stated, I traced to the pituitary body.

As previously shown, we are dealing with the manifestation of an immunizing function in which the adrenals take part. Important to recall in the present connection, however, is that, when the intoxication becomes excessive, it may entail grave consequences. The intra-adrenal vascular channels, abnormally

[216] Bernard and Bigart: Jour. de physiol. et de pathol. générales, No. 6, p. 1014, 1902.

engorged through the marked back pressure induced by the high blood-pressure caused by the excess of adrenal secretion, are exposed to rupture. This hyperactivity of the adrenals (acting in conjunction with the thyroid) constitutes the phenomenon, so far unexplained by pathologists, of *fever*, while the excessive activity which exposes the adrenal vessels to rupture coincides with that of *hyperpyrexia* in these acute infections. In other words, the hyperadrenia which occurs in the course of acute febrile infections or intoxications is the expression of an immunizing process, but this assumes dangerous proportions and involves the danger of fatal adrenal hæmorrhage when excessive, *i.e.*, when the immunizing process exceeds certain limits.

Acute hyperadrenia, therefore, *is that condition of the adrenals which precedes adrenal hæmorrhage in any febrile infection or intoxication, and the danger-signal of which is hyperpyrexia.*

This does not mean that febrile infections and intoxications alone expose the adrenals to hæmorrhage; we have seen that many poisons and drugs even may do so by raising or depressing unduly the blood-pressure through a direct action on the vasomotor center. This process has been reviewed in sufficient detail. We shall now deal only with diseases due to toxins and endogenous poisons, toxic wastes, etc., that are capable of enhancing the adrenal functions to awaken a defensive process and, as a complication, adrenal hæmorrhage, and treat both conditions jointly, the better to emphasize their close clinical relationship.

Adrenal hæmorrhage first described as a disease by Rayer[217] early last century, and cases of which have been reported by Addison, is of common occurrence pathologically. Besides the evidence previously submitted illustrating the frequency with which this morbid process is observed may be mentioned the fact that, in 150 random autopsies, Loeper and Oppenheim[218] found, aside from instances of simple congestion, which were very numerous, 5 true hæmorrhages visible to the naked eye and 8 discernible microscopically. The proportion was much greater when infectious diseases had been the cause of death; and they hold that a large number of similar lesions are masked by

[217] Rayer: L'Expérience, May 10 and Nov. 10, 1837.
[218] Loeper and Oppenheim: *Loc. cit.*, p. 722.

cadaveric changes: adrenal congestion and necrosis being frequently present together. The newborn showed a special predisposition to this complication, the proportion of 250 autopsies being 45 per cent. That we are dealing with a frequent, though generally overlooked, cause of death, is evident.

While disorders of respiration predominate as cause in the newborn, infections do so in children and adolescents. Then come, in order, and, apparently, as the most frequent causes in adults: pulmonary disorders, especially tuberculosis and pneumonia; nervous diseases, particularly meningitis and epilepsy; chronic renal diseases, arteriosclerosis, cancer, abscess, burns, and general paralysis of the insane. Purpura is often regarded as a cause, but this should be considered, from my viewpoint, as a precursor or danger-signal of adrenal hæmorrhage, though the purpuric spots, which are in reality cutaneous hæmorrhages, persist after the adrenal hæmorrhage has occurred.

From the facts submitted below, I would define adrenal hæmorrhage as *an extravasation of blood into one or both adrenals due to rupture of some of their blood-vessels when, as a result of high blood-pressure throughout the body from any cause: toxins, toxic wastes, etc., these vessels are subjected to centrifugal pressure exceeding the resistance of their walls.*

Pathogenesis and Symptomatology.—Although adrenal hæmorrhage is due to the rupture of the vascular elements when the congestion of hyperadrenia exceeds safe limits in all cases, the pathogenesis of adrenal hæmorrhage varies considerably in its general lines according to the age at which it occurs. This applies also, to a limited extent, to the symptomatology. It becomes necessary therefore to divide the cases into three general groups, viz.: (1) the newborn, *i.e.,* during the first days of life; (2) children, up to puberty, and (3) adults, *i.e.,* beyond puberty.

Adrenal Hæmorrhage in the Newborn.—In these, adrenal hæmorrhage occurs within a few moments or days after birth. In a small proportion of cases, death ensues, without premonitory symptoms, shortly after birth. Delay or injuries in the course of delivery or interference therewith by malpositions, or any of the causes which are apt to render artificial respiration necessary, predispose to it. In another class of cases the infant,

having shown perhaps some slight difficulty in breathing or a tendency toward cyanosis, suddenly ceases to nurse; reddish-purple or bright-red spots of purpura appear on the face, neck, buttocks, or extremities; a convulsion follows, with death in its wake. Or again, patches of purpura appear, the infant refuses the breast and becomes somnolent, then suffers from colic, diarrhœa, vomiting, and fever and becomes rapidly emaciated. Convulsions usually precede death.

All such cases are due, from my viewpoint, to the inadequacy of the defensive resources of the infant, *i.e.,* its inability to counteract an endogenous toxæmia. As previously stated and as will be emphasized later, the adrenal system (consisting of the adrenals, thyroid, and pituitary, and to which I attribute a leading rôle in all immunizing functions) is not sufficiently developed in the nursling to protect it adequately against toxics of various kinds; the maternal milk provides the immunizing constituents derived from her own adrenals and thyroid to compensate for this function. My opinion has been recently sustained by Fassin, Stepanoff, and Marbé,[219] and also by Concetti[220] as to the influence of the thyroid in the process, while the immunizing property of maternal milk as a compensating factor for the deficiency of the suckling has been sustained by Ehrlich and Brieger, Abraham Jacobi, Welch, and others. Now, at birth, any condition which diminishes materially the immunizing activity of the maternal milk, or which, in the nursling, interferes with the utilization of the maternal immunizing bodies, such as a deficient intake of oxygen, asphyxia, hypocatabolism, etc., correspondingly impairs the power of the infant to break down its waste products, thus allowing these poisons to accumulate in the blood. Precisely as they are known to do in epilepsy, eclampsia, and other convulsive disorders, these endogenous intermediate wastes cause a violent elevation of the blood-pressure,—sufficient to cause rupture of the delicate but rich vascular network of the adrenal medulla, localized capillary hæmorrhages in the skin, *i.e.,* the purpura, melæna, hæmoptysis, epistaxis, and other forms of hæmorrhage witnessed. Vomiting and diarrhœa occur as results of the marked congestion in the

[219] Léopold Lévi and de Rothschild: Physio-pathologie du corps thyroïde, p. 20, Paris, 1911.
[220] Concetti: Revue d'hygiène et médecine infantiles, No. 3, 1910.

alimentary canal, while convulsions are produced by a corresponding hyperæmia of the cerebrospinal axis.

This accounts for the fact that these cases cannot be traced to infection or ascribed to the presence of any pathogenic organism (though we shall see presently that infection often causes adrenal hæmorrhage in older children), and also for the frequency of adrenal hæmorrhage the first few days after birth, especially where there is any indication of deficient respiration, or, as in the cases witnessed by Northrup, an incomplete septum lucidum.

The cortex is sometimes greatly distended by the hæmorrhage, and the friable medulla of the organ completely disorganized and replaced by a black blood-clot.

Adrenal Hæmorrhage in Children.—This is due to an entirely different class of causes, though the morbid effects and the symptomatology are very similar. Here again death occurs sometimes more or less suddenly in the course of the causative disorder, or, in fact, sometimes before its exact nature has been determined, though in most cases the lethal collapse is preceded by purpuric spots. If the causative disorder be an exanthema, varicella, for example, the eruption may itself show a change, each patch assuming a bluish or cyanotic tinge, soon followed by collapse. In most cases, however, there occurs two, three, or more of the following symptoms: vomiting, fever, marked prostration, a more or less extensive petechia or a purplish purpuric eruption, dyspnœa or at least rapid respiration, diarrhœa with perhaps abdominal pain radiating into the loins, due to pressure of the dilated adrenals upon the adjoining sympathetic plexuses, and convulsions, cyanosis, and collapse—forming an incomplete and variable syndrome which is characterized by a feature common to all—its rapid termination in death, *i.e.*, within a period varying from a few to forty-eight hours.

That a toxæmia underlies all cases, as in the newborn, is also evident: but its source is entirely different. Adrenal apoplexy has been met in the course of several of the exanthemata, varicella, variola in the unvaccinated, diphtheria, and scarlatina especially; during convulsions or as a complication of abscesses, pyæmia, septicæmia, hydatid cysts, bronchopneumonia, ptomaine poisoning, or after extensive burns and severe injuries.

It has also been attributed to the staphylococcus pyogenes aureus and albus (Riesman, Dudgeon), the streptococcus (Drysdale), the pneumococcus and bacillus coli communis (Rivière), the meningococcus (Candler), and to other micro-organisms. On the whole, it may be due to many morbid conditions; but the one striking feature of all these causative disorders is that they are all of such a nature (febrile diseases, convulsions, etc.) as to provoke a rise of blood-pressure. Just as we have seen the latter to be the cause of adrenal hæmorrhage in the newborn, so is it in children. Dudgeon[221] states that "any disease which is known to produce stagnation of the blood in the veins or a marked increase of the blood-pressure may be associated with adrenal hæmorrhage"; I would say instead that such a condition of the circulation tends to *produce* the latter as a complication.

Here again we are likely to find one or both glands more or less filled with a black coagulum with, occasionally, extravasation, or here and there hæmorrhages into the medulla or under the cortex, raising the corresponding portion of the latter.

Adrenal Hæmorrhage in Adults.—Adrenal hæmorrhage in adults is now thought to be rare, but this is probably due to the fact that it is seldom recognized. Although sudden death may occur without premonitory symptoms of the hæmorrhage in the adrenals, there is usually more or less sudden pain—sometimes excruciating—in the abdomen, radiating toward the back, under the costal margin; tympanites, vomiting, prostration, great weakness, copious and stubborn diarrhœa. Hæmorrhagic purpura and cutaneous hæmorrhages may also appear, but purpura is much less common than in children; anæmia, with a yellowish tinge of the skin ranging from sepia or light brown to the bronzing of Addison's disease in which adrenal apoplexy is not uncommonly observed. When it occurs in the midst of a convulsion, during an epileptic fit, for example, the patient may either die on the spot or show, on recovery, unusual asthenia, with, perhaps, uncontrollable diarrhœa. Gradually the pulse and respiration become weak, more or less cyanosis appears, followed by coma and death. Unusual physical exertion has also been known to cause adrenal apoplexy and sudden death. Acute

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[221] Dudgeon: Amer. Jour. Med. Sci., Jan., 1904.

nephritis is an occasional cause, death occurring suddenly with, perhaps, symptoms of pulmonary œdema.

The prevailing feature of adrenal hæmorrhage in adults is the presence of lesions in the adrenals themselves which cause these organs to yield with abnormal facility when a general rise of blood-pressure is brought on by any one of many causes. In adrenal apoplexy occurring in the course of Addison's disease, for example, the tissue-wastes which accumulate in the blood as a result of the diminished antitoxic power of the diseased adrenals excite, we have seen, the vasomotor center, and increase in proportion the vascular tension and blood-pressure. In the course of an epileptic fit the same exciting cause prevails, since, as is well known, the vascular tension is always marked. Over-exertion may produce adrenal hæmorrhage through the same mechanism, owing to the accumulation in the blood of an excess of tissue-wastes. Acute nephritis also produces it by raising the vascular tension; in a case of this kind reported by Loederich[222] this feature of the case is specifically noted. The production of adrenal apoplexy in Addison's disease by injections of adrenalin has also been reported in 2 cases (Boinet) —owing obviously to the rise of blood-pressure which this agent produces. Common to adults also is the form due to arteriosclerosis, the adrenal intrinsic arteries yielding here, as they do in the brain, owing to atheromatous degeneration, when from any cause the blood-pressure exceeds certain limits.

On the whole, it is apparent that adrenal hæmorrhage presents many features in common with cerebral hæmorrhage in which the gradually weakened vessel, particularly where, in the case of adults, arteriosclerosis prevails, can no longer sustain anything beyond the minimum blood-pressure.

Many auxiliary factors tend greatly, however, to impair the resistance of the adrenal vessels and tissues. As shown by Claude Bernard, hyperæmia is a cardinal feature of function. The adrenal vessels are already congested and under stress, therefore, when they are submitted to the excessive centrifugal tension which a marked rise of blood-pressure entails. Again, in the light of modern researches, and as will be demonstrated later in this work, the blood contains, during the febrile stage

[222] Loederich: Le Bulletin Médical, July 8, 1908.

of infections and intoxications, bactericidal and antitoxic bodies to which autolysis, under certain conditions, is ascribed. That the rich vascular elements of the adrenals and even the delicate adrenal medulla are probably subjected to such a process and thus rendered more vulnerable, in the course of acute febrile infections, is suggested by the areas of necrosis in these structures which many autopsies reveal. I must state, however, that I am not inclined to accept the conclusion that these necrotic areas are due to post-mortem changes, and that I regard them as due more to a process of autodigestion similar to that known to exist in the gastric mucosa. This subject cannot, however, be considered here.

Diagnosis.—The most important feature in this connection is to differentiate clearly the prehæmorrhagic from the post-hæmorrhagic phenomena. Careful attention in this particular makes it possible to save life, since the prehæmorrhagic symptoms include several which may be regarded as danger-signals to the effect that the blood-pressure is dangerously high, and that the adrenals are threatened.

In the *infant,* imperfect respiration following delayed delivery, purpura with or without fever points clearly to impending hæmorrhage: The course of events then, if no prophylactic measures are taken, will be the appearance in a few hours of the posthæmorrhagic state: abdominal pain, diarrhœa, vomiting, soon followed by a gradual decline of the temperature, coldness of the extremities with convulsions or cardiac collapse as terminal phenomena.

In the *child,* the presence of fever and high blood-pressure in the course of any infection entail the possibility of adrenal hæmorrhage, especially when any eruption that may be present tends to spread, or where purpuric spots are present. Here again, if not avoided by appropriate treatment, the posthæmorrhagic phenomena appear, likewise ending in death in a few hours.

In the *adult,* the great variety of disorders which, besides the acute infections, adrenal hæmorrhage may suddenly complicate would seem to preclude the possibility of preventive measures, but if it is remembered that the adrenals are exposed to hæmorrhage *whenever the blood-pressure is high from any cause,* as suggested by venous engorgement, venous pulse, facial

congestion, and a hard pulse, with the sphygmomanometer as control, the danger can as readily be forestalled as in the young. We must also, in the adult, take into account the possibility of adrenal hæmorrhage in all asthenic diseases of the adrenals themselves, particularly the tubercular lesions of Addison's disease in which death frequently occurs suddenly. In all of these, the symptoms of hypoadrenia are present, particularly muscular asthenia, emaciation, hypothermia, hypotonia or low blood-pressure, and feeble pulse.

The onset of adrenal hæmorrhage in adults is characteristic in its abruptness, the severity of the abdominal pain, and the rapidity with which it is followed by general collapse. The incoercible vomiting and diarrhœa (either one or both), the hypothermia, the cold sweats, the feeble pulse and heart action, the coma or convulsions with sudden death in their trail are unmistakable signs of sudden arrest of the adrenal functions.

The absence of all reference to adrenal hæmorrhage in text-books has caused it to be mistaken for arsenic poisoning and other intoxications, cholera morbus, appendicitis, cerebral apoplexy, and other acute disorders.

Prognosis.—As will be shown presently, adrenal hæmorrhage may be followed by the development of hæmatomata in the adrenals proper, proof evident that not all cases are necessarily fatal, particularly small hæmorrhages located in the depths of the organ. It is probable, therefore, that when the likelihood of this complication will be borne in mind by the practitioner when treating any one of its many causes, and its main cause, excessive vascular tension, generally recognized and counteracted, its present high mortality will be greatly reduced.

Treatment.—The multiplicity of pathogenic factors and of symptoms, sufficient to have suggested many clinical types to various authors, has, so far, prevented the elaboration of any treatment calculated to prevent or arrest adrenal hæmorrhage and its rapidly fatal course. With excessive blood-pressure as the direct cause of the disruptive congestion of the adrenal vessels, however, a general line of treatment calculated to relieve it obviously imposes itself.

In a threatened case, antipyrin or other coal-tar products suggest themselves; but their use cannot but prove pernicious,

owing to the primary action on the vasomotor center. By exciting this center and raising the blood-pressure they increase the likelihood of adrenal hæmorrhage, a fact which probably accounts for the many instances of fatal collapse observed under their use in acute febrile diseases. The physiological saline solution offers, on the other hand, all desirable qualities. It does not, as argued theoretically by some authors, increase the vascular tension, even if injected intravenously; as shown by the experiments of Sollmann,[223] Briggs,[224] and others, any excess of fluid leaves the vessels at once. By reducing the viscidity of the blood, saline solution tends to relax the blood-vessels; by increasing its osmotic properties, it facilitates greatly the penetration of the plasma into the lymphatic channels, thus further reducing the vascular tension. The bactericidal and antitoxic properties of the blood are not reduced in the least by this procedure; there is considerable evidence available to show, in fact, that they are enhanced (see p. 1367). Saline solution, therefore, should be used intravenously in emergency cases; subcutaneously in threatening cases, and per rectum in all cases in which there is any likelihood whatever that adrenal hæmorrhage might occur. If employed from the onset of all infections, as I suggested in 1903, the blood-pressure would probably never be raised sufficiently to endanger the adrenals.

As to drugs, we have several at our disposal which lower the blood-pressure. In emergency cases, nitrite of amyl by inhalation, with nitroglycerin (or in children the sweet spirit of niter) to sustain the effect, appears indicated. Chloral hydrate has been used advantageously by J. C. Wilson in certain exanthemata, to subdue the cutaneous discomfort and as a sedative; as it is also a vasomotor depressor, it might also serve advantageously in all but infants in whom the respiratory mechanism is defective. Veratrum viride suggests itself as another useful agent of this class. Of all measures, however, the saline solution is much to be preferred.

When the hæmorrhage has occurred, the lethal phenomena are of such short duration in most cases as to have suggested, we have seen, the term "adrenal apoplexy." In a fair proportion

[223] Sollmann: Archiv f. exp. Path. u. Pharm., Bd. xlvi, S. i, 1901.
[224] Briggs: Johns Hopkins Hosp. Bull., Feb., 1903.