

but regard them as abnormal in the sense that we deem adynamia abnormal and, therefore, susceptible to remedial measures. Indeed, there is much that can be done in each of the three forms of functional hypoadrenia described.

In *infants*, we should by every possible means prevent infection or intoxication to preserve the integrity of their adrenals and other auto-protective organs. The key of the whole situation lies in the fact that, as Ruhräh states, "nearly all the cases and nearly all the deaths are in bottle-fed babies." Physicians are, as a rule, entirely too ready to yield to the demands of social and other claims put forth by mothers who do not wish to nurse their offsprings. The responsibility assumed by both mother and physician under these circumstances is overlooked. I cannot but hope that if this continues, and the sacrifice of countless infants proceeds, laws may be enacted to prevent it by imposing upon the physician the duty of submitting to the State authorities a certificate in which sound reasons shall alone account for his consent to a departure from Nature's methods which entails deaths untold. J. Lewis Smith states that the death rate among foundlings in New York City reached almost 100 per cent. until wet-nurses were provided. Men such as Jacobi, Winters, and many French authorities have written forcibly upon this subject, but seemingly to no avail. The holocaust continues.

Experimental research in the same direction has only served to emphasize the all-important prophylactic value of maternal milk. As L. T. de M. Sajous<sup>165</sup> states: "That milk is capable of conveying antitoxic substances after these have been injected into the mother has been known for a number of years. In 1892 Ehrlich and Brieger demonstrated this fact in their experiments on mice. The offspring of non-immune mice were suckled by other mice which had been immunized against the actions of certain poisons. It was found that the young were thereby rendered immune to the poisons employed, viz., ricin, abrin, and tetanus toxin. This immunity steadily increased during the period of lactation, persisted for some time after, and then gradually disappeared. Ehrlich thus showed that a passive immunity was created in the young by the absorption of milk

<sup>165</sup> L. T. de M. Sajous: Univ. of Penna. Med. Bull., June, 1909.

from an immune adult, and even went so far as to assert that all so-called hereditary immunity was in reality of the passive variety, being transmitted during lactation and not inherent in the offspring itself.

"This transmitted immunity has been shown to occur in various other animals. Thus, in 1893, Popoff showed that immunity against cholera could be transmitted through cows' milk. He injected bouillon cultures into the peritoneal cavity of a cow and later injected into guinea-pigs from 2 to 10 c.c. of the cow's milk. The guinea-pigs became immune against cholera. The same observer noted also that when the milk was boiled before injecting it no immunity was produced. Kraus showed that the milk of goats immunized by injections of "typhus-coli bacilli" and cholera organisms had protective and agglutinating properties. He also ascertained that the relative proportion of agglutinating substance present in milk to that contained in the serum was as 1 is to 10. Taking up the subject from the standpoint of tuberculosis, Figari showed in 1905 that the agglutinins and antitoxins of this disease appeared in the milk of cows and goats that had been actively immunized against it. In another series of experiments he fed the milk of immune cows to a number of rabbits, and in others injected it subcutaneously. In both cases these animals, thus passively immunized, were found to transmit to their young, by their milk, the agglutinins and antitoxins of tuberculosis.

"Evidence is not lacking of the transmission of antitoxic substances through human milk. It has long been known that infants below one year of age were but slightly susceptible to certain infectious diseases, and in particular scarlet fever, diphtheria, measles, and mumps. In fact, it was in an attempt to throw some light on this subject that Ehrlich performed his classic experiments on mice in 1892. Four years later Schmid and Pflanz performed some interesting experiments on guinea-pigs. Into some of the animals they injected blood-serum derived from human blood which was taken, at the time of delivery of her child, from a woman to whom had been administered diphtheria antitoxin. Into other guinea-pigs they injected milk from the same woman. The animals were then

given injections of the ordinarily fatal dose of diphtheria toxin. From the results obtained the investigators concluded (1) that antitoxic substances found in the blood of parturient women exist also in the milk; (2) that the quantity of antitoxic substances excreted with the milk is much less than that found in the blood. Similarly, in 1905, la Torre injected diphtheria antitoxin in several wet-nurses, and noted the antitoxic power resulting in the blood of the nurslings by injecting measured amounts of this blood mixed with diphtheria toxin into guinea-pigs. He was able to satisfy himself that a passage of the antibodies occurred in small amounts into the blood of the infants.

"These experiments show, then, that antibodies injected into the mother are transmitted to the offspring. This being the case, it is but reasonable to expect that some of the protective substances ordinarily present in the normal mother's blood should likewise reach the child through the milk. Experiments have shown this also to occur. Moro found that the bactericidal power of the blood-serum in breast-fed children was distinctly greater than in those artificially fed. Further confirmation was afforded by the fact that this difference rapidly disappeared when the bottle-fed infants were put back to the breast."

The prevention of disease in the infant is raised to its highest standard by maternal lactation. The organisms of its gastrointestinal canal are kept under control; the barriers to infection that the respiratory tract and pulmonary alveoli offer are well armed with antitoxic bodies; the blood itself is destructive to pathogenic organisms, and the infant is thus protected against those diseases which, even if recovered from, we have seen, leave enfeebling lesions, fatty and fibrous degeneration, in those organs upon which his health in after years and the duration of his life depend.

In the *child* beyond the nursling period the problem is more difficult. The fatal "second summer" recalls the sins of the milkman, the filth of the cowshed, and of the vessels in which the milk is transported and kept—amply long enough to favor the growth of the oft-present Shiga bacillus, the virulent bacillus coli, and even at times the streptococcus. The correction of these and many other factors replete with danger

to the child, and which surround it on all sides, offers the only resources to diminish not only the mortality of children's diseases, but also their occurrence, besides safeguarding health and longevity in after years. The good already done by our profession in this direction is incalculable. Briefly, public, home, and school hygiene, in the light of the facts I have submitted, not only serves to protect life for the moment when the child is concerned, but its entire career as a healthful individual, while enhancing greatly its chances for a long life.

It now becomes a question whether our resources are such as to enable us to raise, where functional hypoadrenia exists, the autoprotective resources of the child, sufficiently, perhaps, to enable it to resist infection successfully. The influence of many toxins and drugs on the adrenals points clearly to overactivity under their influence. In the first edition of this book, I referred to mercury as occupying "a high position among the stimulants of the adrenal system." Now, C. R. Illingworth<sup>106</sup> and others have found the biniodide of mercury extremely efficient in aborting scarlatina, diphtheria, measles, variola, varicella, pertussis, parotitis, and many other infections. The great vogue of calomel among the physicians of the past generation may have found its *raison d'être* precisely in just such an action—which I have myself observed. Arsenic is a familiar agent in the abortive treatment of malaria in Africa, and, as Surgeon-General Boudin states, in many other diseases. The remarkable results of Petresco with large doses of infusion of digitalis in pneumonia have only been tentatively explained. But if we realize that division of the path to the adrenals arrests and prevents the effects of digitalis, as we shall see elsewhere, there is good ground for the belief that the prevailing conception of the action of this drug is erroneous, and that it is by stimulating the adrenals that it acts, at least in part. In view of the immunizing action of the adrenals, therefore, we can realize how digitalis could be of use in this infectious disease, and how it might prove useful in aborting any pulmonary disorder due to pathogenic organisms. These few examples are submitted merely to show that there is ground for the elaboration of a system of immunizing medication. Its use has served me well.

<sup>106</sup> Illingworth: "The Abortive Treatment of Specific Febrile Disorders," etc., London, 1888.

Very remarkable in this connection is the action of thyroid gland 1 grain (0.06 Gm.), adrenal gland 2 grains (0.12 Gm.), and Blaud's pill 1 grain (0.06 Gm.) in a capsule three times daily, previously referred to. Given during meals to a debilitated child of 10 or 12 years it seems promptly to start the vital machinery on a new lease of life—where, of course, the demands of hygiene are adequately met. Meat is of value here, while milk, the fluid portion of which gives the test for oxidase, and which, as shown in the second volume, depends upon the adrenal secretion for its ferment (adrenoxidase), is also of great value. Digitalin or strychnine in small doses is added if the heart is weak or to increase the oxygen intake. All these agents tend, by keeping up a slight hyperæmia of the adrenals (and of the other organs acting in conjunction with it), to augment the efficiency of the child's defensive resources.

In the *adult* functional hypoadrenia may have persisted from childhood. Here the measures just suggested for children apply as well not only as preventives where infection threatens, or as abortive treatment, but also to raise the efficiency of the adrenals and the general health of the individual to the normal plane. It is probable that most tonics exert their beneficial influence through the adrenals. That "tonic" doses of mercury, *i.e.*, minute doses, are efficient is well known; we have seen that it is a powerful adrenal stimulant. In toxic doses in fact, as observed by Molinié,<sup>167</sup> it causes intense congestion and even hæmorrhage of the adrenals.

While there is no doubt that meat in excess is harmful, as we shall see under Functional Hyperadrenia, it is no doubt true that, as Lorand<sup>168</sup> states, undernutrition through lack of the necessary proteids in the diet increases the liability to infection, as I urged several years ago in this work. Lorand refers to personal cases of tuberculosis arising from a purely vegetarian diet. On the other hand, Richet and Héricourt<sup>169</sup> obtained remarkable effects from a diet of raw meat in enabling animals to resist tubercle infection by inoculation, and raw meat has become an important factor in the treatment of this disease.

<sup>167</sup> Molinié: Bulletin général de thérapeutique, Apr. 8, 1906.

<sup>168</sup> Lorand: *Loc. cit.*, p. 313.

<sup>169</sup> Héricourt: Lancet, Jan. 7, 1911.

Grawitz<sup>170</sup> also found that a purely vegetarian diet predisposed to anæmia. We have seen that the adrenals supply the blood its albuminous hæmoglobin, a deficiency of which is an important feature of anæmia. Did we live where pathogenic bacteria do not flourish, we might safely undertake to adopt vegetarian principles; but a reasonable amount of meat, by keeping our autoprotective organs, and particularly the adrenals, active, serves a very useful purpose.

The influence of excessive fatigue on the adrenals, we have seen, is such as to weaken greatly their functional activity and, therefore, their oxygenizing and immunizing functions of the blood. The main harmful feature in this connection is the *relative* deficiency of rest, which means, from my viewpoint, inadequate opportunity afforded the adrenals to recuperate. This, of course, should be proportionate to the amount of strain imposed upon these organs, and the resistance of which they are capable. It is probably owing to lack of this that apparently strong men are often the first to "give out" in forced marches. The physical examination being based mainly upon the *status præsens*, and the adrenals being necessarily (for we are now dealing with a new line of thought) overlooked as factors, there is marked inequality in the resistance of the men to strain. This applies as well to the pathogenesis of chronic disorders. In a personal analysis of 40 cases of hay fever, for instance, the severity of the disease corresponded to a considerable degree with the number of children's diseases the patient had had, the worst cases having had six of these diseases in comparatively quick succession.

This suggests the need of ascertaining the number and severity of children's and other diseases to which the recruit has been subjected and to add this factor to others in deciding upon his admission to the service or the arm to which he is to be assigned. The mounted man suffers less from actual fatigue than the infantryman who must carry his accoutrements, arms, cartridges, etc., aggregating in some armies as much as 70 pounds. When, besides, defective or poor food, impure water, exposure, etc., and other frequent accompaniments of a campaign

<sup>170</sup> Grawitz: Klinische Pathologie des Blutes, 3d ed., 1906.

are taken into account, one need not wonder that disease is a far greater factor as a cause of debility and death than wounds.

Briefly, fatigue should be considered, owing to its inhibiting influence on the adrenals and the immunizing process in which they take part, as an important predisposing cause of disease. The periods of rest should be so adjusted, therefore, as to counteract this by far the most destructive factor of active warfare. In civil life, such hardships are seldom endured, but here likewise much could be done to prevent infection by means calculated to insure the functional integrity of the adrenals.

To stimulate the adrenal functions when marked fatigue prevails would of course only aggravate the hypoadrenia after perhaps a period of temporary betterment. The powdered adrenal substance should, on the other hand, judging from the effects of injections of adrenal extracts in experimentally fatigued animals, serve a useful purpose.

In *old age* the ductless glands assume such importance, that a valuable work has been written by Lorand<sup>171</sup> to indicate how the functional activity of these organs could be preserved in order to retard the ravages of age beyond the fifth decade, while prolonging life. The reader is therefore referred to Dr. Lorand's volume for a mass of information which cannot be considered here.

The adrenals, as shown by the plate opposite page 88, are deficient in circulatory activity, and, therefore, unable to sustain functional activity of all organs up to its former standard. It becomes a question whether, realizing this fact, we should by artificial means excite the adrenals to greater activity. That such a step might shorten life instead of prolonging it is probable. In the first place, the frequent presence of arteriosclerosis in the aged counsels prudence; in the second place, to activate the adrenals would only hasten their degeneration by imposing a greater wear and tear upon them. Drugs capable of enhancing adrenal activity had, therefore, better be avoided in the aged.

Far better is it to *compensate* for the loss of efficiency of the adrenals by supplying to the blood, through a suitable diet, substances which contain the adrenal principle. If my opinion

<sup>171</sup> A. Lorand: "Old Age Deferred," F. A. Davis Co., Phila., 1910.

that spermin owes its virtues to the adrenal principle it contains is warranted we can understand why Brown-Séquard rejuvenated himself by means of testicular juice injections (I saw him at the time and can testify to its wonderful effects upon him), since he enriched his blood with the *pabulum* of oxidation, metabolism, and general nutrition, without impairing his adrenals. With advanced knowledge we need not follow his example. We have seen that milk contains the adrenal principle, and that all animal tissues owe their functional activity to its presence. In milk, buttermilk especially (since it is almost pure plasma), we have a ready and inexpensive means to compensate for deficient adrenal activity. If debility and other signs of functional hypoadrenia prevail, I advocate the daily addition to the plain, though varied diet to which elderly people should restrict themselves of the expressed juice (uncooked) of one pound of *fresh* beef daily taken in soup, if distasteful otherwise, and salted to taste. This is a powerful agent for good which is well borne by the stomach, and which more than compensates for the weakened adrenals, since it rapidly restores strength and vigor—provided, of course, harmful influences in other directions are avoided, and a hygienic mode of life, with reasonable out-of-door exercise, prevails.

In matters sexual, aged men should be extremely reserved, since the waste of seminal fluid to them means waste of life substance replaced with difficulty and never in abundance.

#### ADDISON'S DISEASE, OR CHRONIC PROGRESSIVE HYPOADRENIA.

That new lines of thought concerning this disease are not untimely is suggested by Anders's previously quoted statement in a recent edition of his textbook that "the pathologic connection between the symptomatic phenomena of Addison's disease and the anatomic lesions has not been made out."

Of major importance in this connection are the facts that advanced lesions have been found in the adrenals post-mortem, though the subject had during life presented no signs of the Addison syndrome, and that, as Davis<sup>172</sup> states, "in the majority of cases the patients have complained of asthenia for a consider-

<sup>172</sup> Davis: *Sajous's Cyclopædia of Prac. Med.*, vol. i, p. 133, 3d ed., 1900.

able time prior to the appearance of noticeable pigmentation on the surface." Many cases die, in fact, before the pigmentation appears. Under these circumstances it is evident that the prevailing teaching that bronzing is the characteristic sign of Addison's disease—raised to the dignity of a *sine qua non* in some works by the dictum "without bronzing, no Addison's disease"—is an unfortunate one for the patient's welfare, since, as shown elsewhere in this work, bronzing is a symptom denoting advanced lesions of the adrenals or in the course of their secretory nerves, whether in the ganglia or the splanchnic, or even the spinal cord from which the adrenal paths originate. It is because of the presence of these nerves in the abdominal sympathetic (the greater splanchnic in particular, as demonstrated by Biedl<sup>173</sup> and Dreyer<sup>174</sup>), was not known to Martineau,<sup>175</sup> Jaccoud, Lancereaux,<sup>176</sup> von Kahlden,<sup>177</sup> and others that they denied that the adrenal insufficiency was always the underlying cause of the disease, as held by Addison himself, Gull, Trousseau, and many other of the older clinicians. It is apparent that a lesion anywhere in the course of these nerves must be capable of causing inhibition of the adrenal functions and Addison's disease, by interfering both with the secretory activity of the glands and the formation of their secretion. This is well exemplified by cases reported by Semmola and Brault in which bronzing was due to pressure upon the semilunar ganglia and the solar plexus; the flow of impulses through these structures to the adrenals being impeded, the functions of these organs were inhibited. Pressure or organic lesions may occur anywhere in the pituitary-adrenal nerve-path. Even the cachetic stage of acromegaly is often attended by a bronze pigment "strongly resembling that found in Addison's disease" we have seen. From my viewpoint, therefore,

*Addison's disease is the symptom-complex of progressive hypoadrenia, i.e., of insufficiency of the adrenals. It occurs when, owing to progressive organic lesions in these organs or in the course of their secretory nerves (the abdominal sympathetic and its ganglia, the spinal axis or the pituitary body), the*

<sup>173</sup> Biedl: *Loc. cit.*

<sup>174</sup> Dreyer: *Loc. cit.*

<sup>175</sup> Martineau: Thèse de Paris, 1864.

<sup>176</sup> Lancereaux: Archives de Médecine, Jan., 1890.

<sup>177</sup> Von Kahlden: Archiv f. Anat. u. Phys., Bd. cxiv.

*adrenal secretion produced is increasingly inadequate to sustain general oxygenation, metabolism and nutrition, and the cardiovascular tone.*

**PATHOGENESIS AND SYMPTOMATOLOGY.**—These will be considered together to indicate the intimate relationship between them when the functions of the adrenals are interpreted from my viewpoint. This will be further facilitated by analyzing the symptoms in their physiological sequence.

*Hypothermia, Coldness, and Dyspnoea.*—These symptoms are self-evident results of deficient oxygen intake, and of the correspondingly deficient oxidation and metabolism incident upon the deficiency of adrenal secretion. The sensation of cold is aggravated by the fact that the deficiency of the latter—or rather of the adrenoxidase it becomes—entails relaxation of the arteries and a low blood-pressure; the blood accumulating in the larger trunks of the splanchnic area, the peripheral vessels are partially depleted of theirs, and peripheral oxidation being thus diminished from two directions, the patient complains of chilliness. The dyspnoea is due to the same two factors: inadequacy of adrenal secretion to properly oxygenize the blood, and ischæmia of the lungs through retrocession of the blood into the deeper vessels. An aggravating factor is the intense muscular weakness which also, of course, affects the thoracic respiratory muscles.

*Progressive Asthenia, Weak Heart Action, and Vascular Hypotension.*—Oliver and Schäfer and, later, Cybulsky and Szymonowicz having found, we have seen, that the adrenal secretion sustained the tone of the cardiovascular and skeletal muscles by a direct action upon them, a process supplemented, as I have shown, by its power to sustain oxidation and metabolism in these (as well as all other tissues), it is obvious that deficiency of this secretion should produce weakness of all muscular tissues, i.e., loss of contractile power. Asthenia, weak heart action, and relaxation of the arteries—the blood-pressure sometimes being as low as 50 mm.—are thus a direct result of the adrenal insufficiency. Here again, however, the low vascular tension aggravates the morbid process by causing retrogression of the blood toward the deeper channels of the splanchnic area. The cardiac and skeletal muscles receiving an unusually small volume of blood, their contractile power is weakened in proportion and their

resistance to fatigue reduced practically to *nil*. Sergent has proposed a diagnostic sign, "the white line," which I would explain by this peripheral ischæmia, is obtained by lightly rubbing the surface of the abdomen with the pulp of a finger. A broad, white streak soon appears, which gradually becomes more distinct, then after three or four minutes fades away.

*Emaciation, Anorexia, Vomiting, Diarrhœa.*—That deficient oxidation and metabolism, upon which nutrition depend, should entail emaciation is self-evident. Anorexia is but a consequence of this state of affairs, the utilization of less foodstuffs being a normal result of deficient demand for the same by the tissues. The vomiting is due mainly to the gastroptosis caused by relaxation of the muscular coat of the stomach, a condition similar to that present in all other muscles of the body. Vomiting occurs when imperfectly digested materials accumulate in the stomach, partly because of its dilatation and partly as a result of deficient peristaltic action from the same muscular incompetence. A corresponding degree of asthenia of intestinal muscles also entails constipation owing to deficient peristalsis in certain cases, while in others, or subsequently, there is diarrhœa owing to relaxation of the intestinal arterioles and the resulting passive congestion of the intestinal mucosa.

*Bronzing.*—Langlois, Gourfein, and others have found that one-eleventh of the adrenals sufficed to carry on their functions; this illustrates the small proportion of adrenal secretion required and the progress any local lesion may make before the organism at large is morbidly influenced. Vassale and Zanfrognini<sup>178</sup> found that if all but a small fraction of the medulla is left in experimental animals, all the typical signs other than pigmentation may appear. This illustrates the valuelessness of Nothnagel's observation that pigmentation did not occur in 153 animals from which he had removed both adrenals. Death occurred in all these animals long before bronzing had had time to occur. Boinet, who, on the other hand, utilized rats, which are known to survive the operation longer than any other animal—owing to the frequent presence of accessory organs—observed typical pigmentation in all animals which had had several months' postoperative life. Tizzoni noted

<sup>178</sup> Vassale and Zanfrognini: *Riforma Medica*, Oct. 31, 1902.

similar results after crushing the organs; Brown-Séquad, in fact, had long before noted that bronzing appeared in animals in which the operation did not prove fatal for some months, the other symptoms present being analogous to those of Addison's disease. It is because of these and other facts adduced in the earlier editions of this work that I concluded<sup>179</sup> that "*insufficiency of the adrenals only manifests itself by bronzing when, from any cause, all but a small proportion of the organs has been rendered physiologically inactive.*" Briefly, the bronzing of Addison's disease occurs only in advanced hypoadrenia.

We have seen that the pigment which gives the skin and the mucous membranes their bronze hue is mainly composed of the adrenal product, or adrenoxidase, which, from my viewpoint, is the oxidizing body of the hæmoglobin.<sup>180</sup> That the pigment was a product of the adrenals was first suggested by Brown-Séquad. But why should it, though a constituent of the circulating blood, accumulate in the tissues? Here, again, two factors prevail: the extremely weak blood-pressure in advanced cases, and the identity of the adrenal product as the albuminous constituent of hæmoglobin. The *vis a tergo* motion of the blood being slowed, the plasma circulating in the cutaneous capillaries is increasingly unable to traverse these minute vessels and is deposited in the rete mucosum. The adrenal constituent being freed, it resumes its original reducing power and undergoes the changes of color witnessed when fluid-extracts of adrenal substance are exposed to the air and light—a yellowish brown gradually turning to bronze and often to black. It is because of this that bronzing is not characteristic of Addison's disease, and that it occurs in other cachectic disorders.

This does not militate against the production of bronzing by other factors, local irritation, drugs, cutaneous or nervous disorders. It explains only its mode of production in Addison's disease, as I interpret it.

*Lumbar and abdominal pain* often occurs early in the disease, but may be absent through its entire course. The fact that it occurs suddenly in crises points to pressure upon the

<sup>179</sup> See 1st, 2d, or 3d ed., p. 86.

<sup>180</sup> This question is treated in full on p. 835.