

Calcium chloride has likewise given good results, owing to the well-known influence on coagulation, but its effect is only temporary. It is given in 10-grain (0.6 gm.) doses, three times daily. If given to prevent bleeding during a minor operation (it allows of no other than trifling ones, extraction of teeth, opening of small abscesses, etc.), the coagulation time should be taken, and if this does not reach below five minutes, thyroid extract should be given in addition. *Digitalin* in full therapeutic doses is also useful.

Sympson,⁵⁹ Wallace,⁶⁰ Parry⁶¹ and others have obtained good results with calcium chloride in hæmophilia. Ballantyne⁶² used it successfully as an antenatal remedy, *i.e.*, to prevent hæmophilia in the third child of a woman whose two first children were bleeders. I used tincture of digitalis and obtained a prompt recovery in the case of a boy whom recurrent hæmorrhages had almost exsanguinated.

The most valuable local hæmostatic is *adrenal chloride* (1 to 1000 solution), gauze saturated with it being applied directly to the wound. A thick layer of the powdered extract also arrests the bleeding promptly. The ordinary styptics, *perchloride of iron*, *ergot*, etc., have been used, but seldom with success in serious cases. *Fresh entire blood* may be transfused, a small quantity being sometimes sufficient to arrest a profuse flow.

Adrenalin has been used successfully in the above manner by W. Milligan,⁶³ E. Francis,⁶⁴ and the extract by W. T. Thomas⁶⁵ and others. The use of entire blood was recommended by Hayem,⁶⁶ who thought that his "hæmotoblasts" caused the formation of a clot. I have shown⁶⁷ that these hæmatoblasts or blood-platelets are droplets of adrenoxidase, *i.e.*, of fibrin-ferment.

⁵⁹ Sympson: *Lancet*, May 13, 1899.

⁶⁰ Wallace: *Brit. Med. Jour.*, May 10, 1902.

⁶¹ Parry: *Lancet*, Feb. 21, 1903.

⁶² Ballantyne: *Jour. Amer. Med. Assoc.*, Aug. 24, 1901.

⁶³ W. Milligan: *Brit. Med. Jour.*, Feb. 1, 1902.

⁶⁴ E. Francis: *Ibid.*, May 28, 1904.

⁶⁵ W. T. Thomas: *Ibid.*, Nov. 23, 1901.

⁶⁶ Hayem: *Le bull. méd.*, vol. ii, p. 1235, 1267, 1888.

⁶⁷ *Cf.* this vol., p. 829.

CHAPTER XXXII.

THE INTERNAL SECRETIONS IN THEIR RELATIONS
TO PATHOGENESIS AND THERAPEUTICS (*Continued*).THE ADRENAL SYSTEM IN INFECTIONS OF THE LYMPHATIC
SYSTEM.

We have already seen that in tuberculosis, infection occurs to a great extent through the lymphatic system. In the diseases reviewed in the present chapter, syphilis and bubonic plague, infection not only occurs by way of this system, but the lymphatic glands act as foci for the development of pathogenic organisms. Hence the occurrence of buboes and kindred complications. An important feature emphasized is the need of energetic measures, as represented by the value of mercury, the iodides, etc., in the treatment of such disorders. Toxæmias are readily antagonized by ordinary adrenal stimulants because it is in the blood that the bactericidal and antitoxic agents which these remedies evoke first appear. In the lymphatic system, however, the protective process is relatively deficient, owing to the absence of red corpuscles, and therefore of adrenoxidase, in the lymph, a fact which involves a deficiency of auto-antitoxin in this fluid. Hence the freedom with which bacteria multiply therein; hence also the presence in the lymphatic glands of a multitude of phagocytes, small and large, whose purpose is to rid them of pathogenic elements of all kinds. The aim, therefore, should be to increase the proteolytic power and the aggressiveness of the phagocytes by agents which cause their digestive vacuoles to be well supplied with auto-antitoxin (their digestive triad) and to sensitize actively the bacteria. These requirements are met by mercury, the iodides and thyroid extract, as suggested below.

SYPHILIS.

SYNONYMS.—*Lues*; *Pox*; *Lues Venerea*.

Definition.—A specific disease due to inoculation, probably by the *spirochæta pallida*, characterized by three stages: (1) the *primary* stage, in which the seat of inoculation is con-

(1795)

verted into a specific ulcer, the chancre, whence the pathogenic organism may invade the lymphatic system if the body's auto-protective functions as exercised through the lymphatic phagocytes are unable to prevent it; (2) the *secondary* stage, or stage of general infection, during which the toxins or endotoxins of the specific germ excite a general reaction of the adrenal system and eruptions of various kinds; and (3) the *tertiary* stage, or period of sequelæ, provoked by the pathogenic organism or its toxins or endotoxins in various tissues during the secondary stage, characterized by a specific lesion, the gumma, and by marked debility or quasi-paresis of the adrenal system, which may be transmitted to offspring. *Congenital syphilis* is the expression, therefore, of inherited inadequacy or quasi-paresis of the adrenal system.**

Symptoms.—The *initial* lesion or "primary syphilis" occurs, as a rule, from two to three weeks after infection. Beginning as a small papule or abraded spot, it gradually develops into the chancre, which softens in the center, constituting an ulcer surrounded by a hard ridge—the "hard" or "indurated" chancre. This ultimately breaks down, leaving a scar. The appearance of the initial lesion is soon followed by enlargement of the adjacent lymph glands, forming the bubo or buboes. All these lesions are the seat of an active defensive process.

After a period varying from a few days to two weeks, the *second* stage appears. This is evidently due to a general reaction,* for it is attended with fever ranging from about 100° F. (37.8° C.) to as high as 105° F. (40.5° C.), characterized by irregular exacerbations and often by headache and insomnia. When the febrile process is high, hæmolysis may occur, as shown by the anæmic appearance of the patient. Cutaneous lesions of various kinds, none of which cause pruritis, are peculiar to this stage, viz., roseolar, squamous, papular, and even pustular, the pustules recalling those of variola and other eruptions, some of which often leave copper-colored pigmented patches. Syphilitic warts, which usually conjoin to form condylomata, may appear at the mucocutaneous junctions, while the

* Author's conclusion.

** Author's definition.

mucous membranes of the tongue, nose, vulva, etc., often show similar lesions, *i.e.*, grayish, somewhat raised erosions: mucous patches. The second stage is a very active one—so active, indeed, that all organs, including the bones, the liver, the kidneys, the eyes, the ears, the hair, the nails, etc., may become the seat of inflammatory processes, *i.e.*, of local defensive reactions.*

This stage—a period in which the infectious principle is fought at every step wherever met*—usually lasts from one year to eighteen months, when the disease either disappears—vanquished by the body's auto-protective resources*—or proceeds on its fell way, *i.e.*, to "tertiary syphilis," the third stage.

The *third stage* has been very appropriately defined as the "stage of sequelæ." Owing to the vascular lesions that are started during the second stage* and the formation in various structures of gummatous growths, morbid phenomena may appear in any organ through local pressure, distortion, denutrition and pressure-absorption. In the *respiratory tract*, for example, there may occur necrosis of the nasal cartilages and bones, causing the saddle-nose, perforation of the soft palate, and cicatricial adhesion of the latter to the pharynx; ulceration and gummata of the larynx and epiglottis, causing hoarseness, aphonia, cough, etc. The *lungs* may also be involved, especially in children. In the *brain*, pressure of gummata is a frequent source of paralysis, facial, ocular, etc. Syphilis is also a recognized cause of general paralysis. Areas of softening in the brain itself, or its vessels, with formation of miliary aneurisms leading to hæmorrhages, may occur; symptoms of brain tumor may also appear. The pressure may be such as to cause passive congestion of the brain and the pia; violent headache, excitement, even epileptic convulsions, sometimes of the Jacksonian type, may be caused. In the *spinal cord*, symptoms of myelitis or of tumor, paralysis, such as hemiplegia, paraplegia and monoplegia, and locomotor ataxia, are relatively frequent results of spinal lesions. In the testicles the gummata may form hard, painless masses; suppurative orchitis may also occur and be followed by atrophy. Corresponding disorders of the ovaries may occur and provoke miscarriage. The *liver* may be the seat of gummatous enlarge-

* Author's conclusion.

ments and later show areas of cirrhosis or fibrous cicatrices; ascites and jaundice may also be caused. The *cardio-vascular system* is not exempt; endocarditis, arteriosclerosis, gummata of the adventitia, etc., being not infrequently observed. On the whole, all tissues are exposed to the ravages of this terrible disease, each organ attacked giving rise to symptoms denoting perversion or arrest of its functions.

In *congenital syphilis*, symptoms may be present at birth, which usually develop later—roseola, excoriations at the mouth and anus (the latter appearing also as if scalded) readily developing into mucous patches and condylomata. An eruption of ulcerative bullæ around the wrists, pemphigus neonatorum, a typical sign of syphilis, is also frequently observed. The viscera, and particularly the liver, spleen and kidneys, are pre-eminently the seat of connective tissue lesions similar in every respect to those observed in the adult. Syphilitic rhinitis, the “snuffles,” which obstructs the nasal cavities, and may be followed later by necrosis of the nasal cartilage, contributes greatly to the general wasting or marasmus, by interfering with oxygenation. The special senses, especially the eyes—interstitial keratitis being commonly observed—and ears are always threatened. The cerebro-spinal system, especially at birth, may be the seat of apoplectic effusions owing to lesions of the arteries. The osseous system and particularly the diaphyso-epiphyseal junction of long bones is often involved, the rosary at the costocartilaginous junctures observed in rickets and nodular thickenings on the tibia and other bones, being readily discernible in most instances. When the second dentition is reached, the permanent teeth appear notched, irregular and “pegged,” the two upper incisors being particularly deformed in this manner, *i.e.*, the Hutchinson teeth.

This brief résumé of the symptomatology of syphilis contains but the most salient features, but it suffices to suggest that if from the beginning of the first or second stage of the disease, an active defensive process is in operation, it would, when raised to its highest efficiency by remedial measures, prevent the ravages which constitute the third stage.

Etiology and Pathogenesis.—The pathogenic organism of syphilis, found in the primary and secondary cutaneous and glandular lesions, and in some of the tertiary lesions, is probably Schaudinn and Hoffmann's recently discovered *spirochæta pal-*

lida, a slender, corkscrew-like spirillum. Inoculation experiments have given rise to typical ulcers containing this parasite; but it has not so far been possible to cultivate it in artificial media.

The initial lesion, the chancre, is from the start the seat of a defensive process. It is at once invaded by various phagocytic leucocytes, lymphocytes and epithelioid macrophages, which accumulate *in situ* along with connective-tissue and other cells connected with the process of repair.*

That the *spirochæta pallida* is the specific germ of syphilis is sustained by considerable evidence. It must not be forgotten, however, that Lustgarten's bacillus was also found in all lesions. That the initial sore is invaded at least by scavenger cells is now generally recognized. Thus, Ohlmacher¹ states that, “like other allied infections, syphilis seems to irritate principally the elements of the connective tissue, and in consequence we find in both *early* and *late* lesions, a proliferation of endothelioid cells, small round (lymphoid) cells, and giant cells. As in most other infections, the endothelioid cells, giant cells, and certain migrated leucocytes engage in phagocytic activity in the effort to rid the body of the noxious invaders or to remove the detritus of cellular necrosis.” The defensive process is essentially local, however. Thus, Hallopeau² found that “the pathogenic action of the toxins is *nil* during the periods of incubation and latency of the disease,” a fact which shows, from my viewpoint, that these toxins do not evoke a protective reaction from the start. I regard this as a very important fact from the standpoint of prophylaxis, for such being the case, the immediate use of remedies such as thyroid, iodine, etc., which powerfully stimulate the thyro-adrenal functions must tend to prevent general infection even when the chancre is feebly developed.

The germ-laden leucocytes, epithelioid cells and giant-cells—all phagocytes—are the “syphilitized cells” of Besiadecki, Otis and others, which become infectious through the fact that either as micro- or macrophages, they ingest the specific organism.* In some cases they succeed in preventing infection. If, however, the vital functions of the patient be at all depraved, either through alcoholism, antecedent disease, starvation, etc., the production of adrenoxidase, trypsin, nucleo-proteid and thyroidase, the constituents of auto-antitoxin, be deficient, these defensive cells, inadequately supplied with this bacteriolytic substance, fail to destroy the germs.* On leaving the seat of infection to enter the lymphatic vessels, therefore, they are laden with these pathogenic organisms and infect the lymphatic glands of the groin, giving rise to the “buboes,” and finally infect the body at large.

* Author's conclusion.

¹ Ohlmacher: “*Amer. T. B. of Physiol.*,” p. 259, 1901.

² Hallopeau: *Annales de dermat.*, 4 série, vol. v, p. 736, 1904.

That, as I suggest, general infection is influenced by debility of the adrenal system's protective power, owing to general adynamia, and as manifested through the leucocytes, harmonizes with established facts. The debilitating influence of alcohol and squalor is well known. Thus Prof. Neumann³ recently emphasized the fact that syphilis "is more common in ill-nourished persons and in hospital patients than in those seen in private practice" and that "alcohol diminishes the resistance of the tissues to specific infection." The "resistance of the tissues" means, in the light of the evidence I have adduced, a deficiency of auto-antitoxin in the blood and cells: Applying this principle to the prevailing conception, the rôle of the leucocytes, as I have depicted it, will suggest itself. G. Frank Lydston⁴ in an able review of the whole subject, says, for instance: "The first effect of the syphilitic infection is a gradually increasing accumulation of leucocytes—i.e., white blood-cells or lymph-cells—at the site of inoculation, produced by a modification of the normal leucocytes and connective tissue elements through the influence of the syphilitic infection." "The previously normal accumulated cells (the syphilized cells of Besiadecki, Otis, et al.) contain the germ of syphilitic infection. They become larger, more granular and contain numerous nuclei [giant cells] and possess exaggerated powers of proliferation and amoeboid movement." "This much is certain, however, that just as the leucocyte is the primordial cell in the normal physiological processes of growth, so is it the basis of all so-called pathological processes, and particularly those of syphilis, when modified in the manner peculiar to the particular disease."

Interpreted from my standpoint, however, the normal phagocytic leucocyte is fully able to digest the pathogenic germs and to convert them into granulations that are more or less useful to the body at large, while the leucocyte, deficient in bacteriolytic bodies and moving in blood deficient in thyroidase (opsonin), is not, and acts as infecting agent.

Some of the germ-laden leucocytes carried along by the torpid lymphatic current, finally reach the receptaculum chyli, along with quantities of specific germs produced through multiplication in the lymph and lymphatic glands, and are finally emptied into the blood-stream. When the germs and their toxins have accumulated sufficiently in the blood, the *second stage* begins; which means a reaction of the body to protect itself, through the adrenal system, against infection.*

The "syphilitic fever," marked in proportion as the reaction is severe, is accompanied by a marked rise of the blood-pressure due, as in arteriosclerosis, to hypermetabolism in the vessel-walls. So marked is the vascular tension that the blood is driven by the deeper vessels into the peripheral capillaries, which become intensely congested. As the specific germs and their toxins, waste-products of the prevailing hypermetabolism (including various acids), detritus, broken-down cells, etc., are

* Author's conclusion.

³ Neumann: Wiener klin. Woch., Bd. xvii, S. 551, 1904.

⁴ Lydston: Sajous's "Analyt. Cyclo. of Pract. Med.," Art. on Syphilis, vol. vi, 1898.

inadequately removed from the cutaneous capillaries, owing to the torpor of the blood-stream in the vessels,* many kinds of eruption may appear, one of which, the syphilitic roseola, usually leaves copper-colored spots.

The fever, which, we have seen, may attain 105° F. (40.5° C.), is of course, as elsewhere, due to excitation of the test-organ and adrenal center—or thermogenic center—by the poison. So marked is the excess of auto-antitoxin in the blood, in fact, that a slight increase of this protective compound suffices to produce hæmolysis. This explains the phenomenon known as "Justus's test" in which one large dose of mercury is sufficient to produce a sharp hæmolysis. This destruction of red corpuscles (10 to 15 per cent.), according to Justus,⁵ "is a specific phenomenon, and is not observed in the blood of healthy persons." This is accounted for from my standpoint by the fact that the mercury, by suddenly exciting the test-organ, increases the proportion of auto-antitoxin in the blood sufficiently—in addition to the excess already present in the latter—to render it hæmolytic. All this proves that an intense protective process is going on in the blood.

The capillary hyperæmia is well shown by the leucoderma. That it is at least closely related with the second stage is suggested by Fiveisky's⁶ statement that "these pigmentations may remain for several years and can be regarded as among the best signs of the secondary period"—though as observed by Lewin,⁷ it is also met with in subjects who have never had syphilis. It has been ascribed by some writers to "a transient congestion of adrenals," according to Frattalli.⁸ This conclusion is warranted—since, as we have seen, the adrenal system is overactive—but only in the sense that the blood is thus caused to contain an excess of the adrenal active principle which, as I have shown in the thirteenth chapter, is the main factor, when oxidized, in bronzing and kindred pigmentations.

The relationship between this cutaneous hyperæmia and the eruptions of all kinds observed during the second stage is generally recognized. Thus, Lydston⁹ states that "the syphilitic roseola is due to dilation of the cutaneous capillaries and subsequent stasis, and the exudation of leucocytes [which, we have seen, contain the germs] and red corpuscles into the implicated integumentary area." L. S. Schmitt,¹⁰ referring to the fact that Veillon and Girard¹¹ "found the spirochæta pallida in sections of syphilitic roseolæ of four days' duration" and that "the sections showed intense capillary and beginning perivascular infiltration," states that "the organisms were found in the terminal subpapillary capillaries and in some of the subpapillary vessels" and that "a few were found in the perivascular nodules." Schmitt concludes from this "that the roseolæ are not of toxic origin, that they are due to a true parasitic embolus lodged in the terminal capillaries of the skin and producing a perivascular infiltration."

The *third stage*, as already stated, is not a manifestation of the syphilitic infection, but of a variety of disorders which occur as sequelæ of the lesions that the presence of the patho-

* Author's conclusion.

⁵ Justus: Virchow's Archiv, Bd. cxl, S. 91, 1895.

⁶ Fiveisky: Annales de dermat. et syph., 3 série, vol. ii, p. 418, 1891.

⁷ Lewin: Charité Annalen, Bd. xviii, S. 614, 1893.

⁸ Frattalli: Clinica dermosifil della R. Univ. di Roma, Oct., 1895.

⁹ Lydston: Loc. cit.

¹⁰ L. S. Schmitt: Cal. State Med. Jour., Mar., 1906.

¹¹ Veillon and Girard: C. r. de la Soc. de biol., vol. lix, p. 652, 1905.

genic organism in various organs has provoked, directly or indirectly, during the second stage.

The arterial lesions are in part due to a process similar to that which prevails in arteriosclerosis,* viz., to excessive metabolic activity in the vessel-walls, and particularly in those of the vasa vasorum.* These minute nutrient vessels becoming occluded, the areas they nourish become necrosed and, ultimately, fibrous and calcareous.* This morbid process is greatly aggravated by vascular lesions provoked by the presence of the germs, the reparative process which follows entailing likewise local sclerosis. Any or all vessels may thus be affected, the lesions being either of the inflammatory type: endo- or periarteritis, and endo- or periphlebitis; or secondary thereto: thickening or fibrosis of their walls, entailing partial or complete obstruction. Thrombosis may also occur.

The only lesion that may be considered as truly syphilitic is the gumma, a gelatinous mass varying greatly in size, and containing at first endothelioid and mononuclear cells (both phagocytic), then a cheesy mass. Their microscopical resemblance to tubercles is such as to indicate that they fulfill a rôle similar to that carried on by these masses in tuberculosis (*q.v.*) viz., to enclose colonies of pathogenic bacteria and cellular detritus* and thus arrest dissemination of the germs. They may become hard and dense, and are traversed by fibrous bands forming meshes which enclose their caseous contents, however, and being liable to form anywhere, particularly in the liver, testis, spleen and brain, and in the bones, which they may soften and destroy; they add a formidable pathogenic factor to the already formidable vascular lesions, through the pressure which they exert. They often break down, but this either leaves an open lesion or a mass of cicatricial tissue which is in itself a menace in certain regions, the central nervous system, for example.

That syphilitic infection is absent when the third stage is reached is shown by the absence of the pathogenic organism during this stage. Sobernheim and Tomaszewski,¹² for instance, having examined 58 cases of syphilis for the spirochæta, found it in all with the exception of the only 8 cases of tertiary syphilis. This fact, which has been confirmed by other observers, accounts for non-communicability of tertiary lesions.

* Author's conclusion.

¹² Sobernheim and Tomaszewski: Münch. med. Woch., Bd. lii, S. 1857, 1905.

This should not be considered as a law, however, for, as is well known, relapses of the disease may occur years, even decades, after apparent exhaustion of the infection, a fact ascribed by Virchow to retention in the lymph-nodes of the pathogenic agent.

The prevailing view is that the arteriosclerosis of syphilis is an independent process. Thus, Neumann¹³ stated recently in one of his lectures that "arteriosclerosis favors tertiary lesions." As I show above, however, it can clearly be caused by syphilis, *i.e.*, through the prolonged hypermetabolism to which the vessel walls are submitted during the secondary period. This further emphasizes the need of curative measures as early as possible in the second stage. That lesions can be caused in the walls of vessels is emphasized by the fact that Buschke and Fischer¹⁴ found the spirochæta pallida attached to the vascular endothelial cells and traced them into, and even through, the vessel walls.

A cardinal feature of the third stage is the depressed condition of the adrenal system.* Although lesions of the adrenals themselves are rarely observed in syphilis, they are sufficient in some instances to cause bronzing and other manifestations of Addison's disease. This bronzing is due to the exhausting stimulation to which the test-organ, and through it, the adreno-thyroid center, is submitted during the secondary period.*

That physical degeneration is a paramount factor of tertiary syphilis is generally acknowledged. The connection with the adrenal system is emphasized by the general adynamia and the pigmentation occasionally observed both in acquired and congenital syphilis and also by the fact that Addison's disease may develop as a result of syphilitic infection, as in cases reported by Sacaze,¹⁵ Chauveau, and others. The adynamia can hardly be always ascribed to disease of the adrenals *per se*, for in a study of 100 autopsies of syphilitic children, Hecker¹⁶ found the adrenals rarely involved, though Guleke¹⁷ found the adrenals of three cases out of eight of *bona fide* inherited syphilis, the seat of necrotic foci. Engel-Reimers,¹⁸ Fürst,¹⁹ Wermann²⁰ and others have reported instances in which the thyroid was enlarged, thus indicating impairment of the functions of this organ. It is thus apparent that the two secreting structures of the adrenal system, the adrenals and thyroid, may, either directly or indirectly, be compromised by syphilitic infection.

The relationship of cancer to syphilis is very interesting in this connection. The prevailing view is that syphilitics are proof against cancer. Indeed, Roger Williams²¹ in an examination of 165 breast-cancer patients, did not find undoubted signs of syphilis in a single instance, while in 160 uterine-cancer cases similarly examined, only one presented signs of having had syphilis. This is accounted for in some cases, from my standpoint, by the fact that during the secondary period, the blood is so rich in auto-antitoxin that the initial lesion of

* Author's conclusion.

¹³ Neumann: *Loc. cit.*

¹⁴ Buschke and Fischer: Berl. klin. Woch., Bd. xliii, S. 6, 1906.

¹⁵ Sacaze: Gaz. des hôpitaux, vol. lxxviii, p. 58, 1895.

¹⁶ Hecker: Deut. Archiv f. klin. Med., Bd. lxi, S. 1, 1898.

¹⁷ Guleke: Virchow's Archiv, Bd. clxxiii, S. 19, 1903.

¹⁸ Engel-Reimers: Jahrb. der Hamburgischen Stadtkrankenanstalten iii; Therap. Monatshefte, Bd. ix, S. 267, 1895.

¹⁹ Fürst: Berl. klin. Woch., Bd. xxxv, S. 1016, 1898.

²⁰ Wermann: Berl. klin. Woch., Bd. xxxvii, S. 122, 1900.

²¹ Roger Williams: Edinburgh Med. Jour., Oct., 1898.

cancer is promptly counteracted, while during the tertiary period and the resulting adynamia, the blood is too poor in auto-antitoxin to sustain the process of cellular growth to which the tumor is due. Various recorded instances seem to have proved that cancer can be grafted on syphilis; but examined in the light of my views, their number is subject to reduction. Thus, A. Patterson²² reported a case of scrotal epithelioma in which, notwithstanding repeated removal of neoplastic tissue, the wound refused to heal. On learning that the patient had been in the army, iodide of potassium was administered. The wound healed rapidly and the patient was still in good health when last seen, 10 years later. Now, this case is ascribed to syphilis, but inasmuch as I have shown that the iodides are also capable of stimulating the adrenal system and thus curing cancer, syphilis may be eliminated in Patterson's case—as it could in all cases in which the diagnosis of syphilis is based on the results of antisyphilitic treatment. On the other hand, there are many cases recorded in which cancer will develop upon syphilitic leucoplakia, syphilitic scars, etc.—a sufficient number, in fact, to indicate that the supposed protection afforded by syphilis (aside from the secondary stage) is a myth.

Treatment.—Syphilis is essentially a disease in which the adrenal system can be utilized advantageously by the physician, since the local primary sore and the general infection it entails, the secondary reaction, and even the typical expression of the third stage, the gumma, and to a certain extent the vascular lesions, can be influenced through this system.* The manner in which *mercury* and the *iodides* produce their curative effects in this disease suggests itself in view of their powerful stimulating action on the test-organ, and through it on the adreno-thyroid center.* This applies as well to *thyroid extract*,* which not only increases the functional activity of the adrenal system, but also, by adding thyroiodase (opsonin) to the blood, sensitizes the germs for the phagocytes.*

In the first volume²³ I urged "that simultaneous impairment of the functions of both the anterior and posterior pituitary bodies accounts for the ravages of syphilis," and that it was through this system that iodine and mercury produced their beneficial effects. Thyroid extract was used by Menzies²⁴ as an adjuvant to other methods and is recommended by him. Gouladsé²⁵ used it in a very severe case, in which the *alæ nasi* and one ear were destroyed by ulceration, besides marked adynamia and emaciation. The usual measures having failed, thyroid gland was tried. On the third day improvement began; the ulcers healed promptly, all morbid phenomena ultimately disappearing. Champlin²⁶ states that where other remedies fail "thyroid gland, 2 grains (0.13 gm.) three times daily with sodium bicarbonate, brings about results truly marvelous," his report being based on 20 cases.

* Author's conclusion.

²² A. Patterson: Scottish Med. and Surg. Jour., Aug., 1899.

²³ Cf. vol. i, p. 777.

²⁴ Menzies: Brit. Med. Jour., July 7, 1894.

²⁵ Gouladsé: Vratch, No. 30, p. 854, 1895.

²⁶ Champlin: Amer. Jour. Clin. Med., Apr., 1906.

During the *primary stage*, the use of *thyroid extract*, 3 grains (0.2 gm.) every three hours, the first day, then after meals, is indicated as a prophylactic to increase the opsonic properties of the blood and thereby render the pathogenic organism more vulnerable to the phagocytes.* Mercurials alone are not protective at this stage.

During the initial stage, the phagocytes are alone entrusted with the protection of the body. Although mercury excites the adreno-thyroid center, the thyroiodase produced is inadequate to raise materially the sensitizing properties of the blood. Neisser,²⁷ in fact, found that injections of sublimate one hour after inoculation of the syphilitic virus did not prevent development of a chancre near the seat of inoculation nor general infection. Nor does washing with a solution of sublimate (1:4000 or 5000) proposed by Guinard²⁸ protect, a fact ascertained by Roux and Metchnikoff.²⁹ I only suggest thyroid extract, owing to the physiological action I attribute to it; but I know of no instance in which it has been tried.

The *second stage* is essentially the stage for *mercury*, since this drug excites violently the test-organ and correspondingly increases the proportion of auto-antitoxin in the bloodstream.* The simultaneous use of *thyroid gland* is also indicated, however, to increase the vulnerability of the specific germs to the phagocytes, practically the only protective agents in the lymphatic system.*

The effect of mercury—of stimulation of the adrenal system, from my standpoint—on the *Spirochæta pallida* was shown recently by Freund.³⁰ As soon as the patients were given this remedy, these parasites gradually became less numerous, until, after a course of injections, they completely disappeared from the blood. Lydston³¹ holds that "the slow, continuous and moderate use of mercury" "without at any time producing its full physiological effects will generally bring about a cure that can be accomplished in no other way." This harmonizes perfectly with the interpretation I have offered of the action of mercury, viz., that salivation marks the beginning of *excessive* and *destructive mercurialism*.

The *third stage*, though not a direct manifestation of the infection, affords three morbid processes of far-reaching pathogenic influence which can be antagonized by adrenal stimulants,* particularly *thyroid gland* and the *iodides*. These are (1) the general adynamia, which is offset by the greatly augmented oxygenation and general nutrition; (2) the pressure symptoms

* Author's conclusion.

²⁷ Neisser: Deut. med. Woch., Bd. xxxii, S. 52, 1906.

²⁸ Guinard: Annales de dermat. et syphil., 4 série, vol. ii, p. 1037, 1901.

²⁹ Roux and Metchnikoff: Cited by Metchnikoff: "The New Hygiene," p. 99, 1906.

³⁰ Freund: Münch. med. Woch., Bd. lii, S. 1819, 1905.

³¹ Lydston: *Loc. cit.*

(which may cause various forms of paralysis) due to gummata, absorption being enforced through the fact that these agents promote leucocytosis, and therefore phagocytosis—a process which applies likewise to the production of the proteolytic triad (auto-antitoxin) which breaks down these masses; and (3) the mechanical constriction of arteries to which denutrition and atrophy of many structures are due, by increasing the general pressure (lowered during the third stage) and thus causing a greater volume of blood to circulate in all capillaries, including those of the cerebro-spinal system, the neuroglia, the neuro-fibrils, the neurons themselves and their axis-cylinders, which are all adrenoxidase-laden plasma channels.*

That the conditions referred to are benefited by the iodides is so well known, that I deem it unnecessary to submit evidence.

During the second and third stages, the alkalinity of the blood is often greatly reduced, a fact which suffices to thwart the beneficial effects of the remedies used.* This lowered alkalinity is shown by a noticeable increase of blood-plates.* The use of *alkaline waters* and an increase of sodium chloride in the food,* all supplemented, if necessary, by large warm enemas of *saline solution*, aids the curative process materially by enhancing the osmotic and antitoxic power of the body fluids and facilitating the migration of leucocytes, including the phagocytes, where their aggressive, protective and reparative work is needed.*

Losdorfer, Vörner³² and others have observed a large increase of blood-plates in the blood of syphilitics, irrespective of the stage. In the first volume³³ I pointed out that these blood-plates were droplets of adrenoxidase derived from the red corpuscles, which were visible only when the alkalinity of the blood was greatly reduced.

As to the use of normal saline solution, Heineck³⁴ states that it has been found valuable "in malignant forms of syphilis that fail to respond to the anti-syphilitic treatment." Gastou and Quinton³⁵ found that isotonic injections of sea-water added to the medicinal treatment greatly enhance the curative process.

Of course, the introduction of *salvarsan* on the scene has relegated all other methods of treatment to the rear.

CONGENITAL SYPHILIS.—In the definition I specified that the transmission of "syphilis" to offspring was in reality

* Author's conclusion.

³² Vörner: Deut. med. Woch., Bd. xxviii, S. 897, 1902.

³³ Cf. vol. i, p. 715.

³⁴ Heineck: Surgical Clinic, Apr., 1912.

³⁵ Gastou and Quinton: Presse médicale, vol. xii, p. 453, 1905.

the transmission of a debilitated or quasi-paresis of the adrenal system. I would suggest, as an efficient agent in these cases, *thyroid gland*.

I append hereto the methods employed by T. W. Kilmer,³⁶ by mercurials and iodides. Both these agents being powerful stimulants of the adrenal system, the results obtained are readily accounted for. "Having employed the various forms of mercury in the treatment of congenital syphilis," writes Dr. Kilmer, "I have discarded practically all of them except the employment of *bichloride of mercury*, administered by the mouth. This has been, in my experience, the best method in which to use this drug. Ointment soils the clothing, and is soon discarded by the parents as being too dirty and troublesome. In using the bichloride of mercury I usually administer it in plain water to infants, or in some simple vehicle to older children. Each teaspoonful contains the desired dose of mercury. To an infant I begin by giving $\frac{1}{200}$ of a grain [0.00033 gm.] morning and night; to a child one to two years old, commence with $\frac{1}{100}$ of a grain, [0.00065 gm.] morning and night, keeping this up for a few days, and then give him the same dose three times a day; then, after a day or two increase the dose to $\frac{1}{100}$ of a grain [0.00065 gm.] to an infant of six months; or $\frac{1}{50}$ of a grain [0.0013 gm.] to a child one or two years old. If no symptoms of mercurialization are seen, which in infants occur in the form of loose, greenish stools, increase the dose slightly up to the abatement of the symptoms or the occurrence of loose, greenish stools. It is impossible to salivate an infant, and the physiological limit to the administration of mercury is manifested by the presence of loose, greenish stools in nearly every case.

"Infants bear the mercurials well. When the dose is reached which causes either a diminution of the symptoms of syphilis or loose, greenish stools, hold the patient at this dose until the symptoms of syphilis disappear.

"It is oftentimes of advantage in older children to combine *iodide of potash* in the form of the saturated solution, two or three drops three times a day up to a diminution of symptoms or the production of an iodide rash. It is best to give separate prescriptions for the mercury and for the iodide of potash. The iodide is generally well borne by young children.

"After the subsidence of all symptoms the child should be examined monthly for six months, and then every two months for a while, and then every six months until puberty. It is always necessary, to my mind, to give these syphilitic children a one to two weeks' course of antisyphilitic treatment out of every six months until adolescence is reached, and then caution them to be examined twice a year for the remainder of their life. It is quite an easy matter to cure a patient with syphilis, but to *keep him cured* is a far more difficult proposition! Aside from the medicinal antisyphilitic treatment, of course, a régime of proper diet and hygiene should be instituted."

PLAGUE.

SYNONYMS.—*Bubonic Plague; Black Death; Malignant Adenitis.*

Definition.—Plague—a virulent infectious disease characterized by the formation of buboes and the development in some

³⁶ T. W. Kilmer: Monthly Cyclo. of Pract. Med., May, 1907.

cases of pneumonia—is due to the Kitasato-Yersin bacillus. On penetrating the lymphatic system, this germ multiplies therein, causing the characteristic lesion of the disease, the bubo, and secretes a toxin which tends to paralyze the sympathetic center in the pituitary body, and to inhibit the function it governs, general nutrition. It is to the resulting adynamia that the development of pneumonia is due, through the agency of the ever-present pneumococcus.*

I cannot do more in this connection, owing to want of space, than to submit the conclusions to which a study of the relationship between the ductless glands and bubonic plague has led me, reserving the evidence itself for another article to be published elsewhere. This section is only published here, in fact, for the benefit of those colleagues who are fighting this terrible disease in the East, and in the hope that the new ideas advanced as to treatment may be of some slight use to them.

Symptoms.—The true symptoms of the disease are usually preceded by a period of incubation varying from two days to a week, characterized by increasing weakness, and toward the end of the period by nausea and perhaps vomiting and vertigo. The acute stage is ushered in by rigors or a chill, the temperature rising somewhere between 101° and 105° F. (38.3° to 40.5° C.). The patient reels like a drunkard, owing to marked vertigo, and complains of violent headache and great lassitude. This sudden and early exhaustion is apparent in the features, the drooping eyelids, the apathetic air, and the evident indifference to surroundings constituting the *facies pestica* characteristic of the disease. The respiration is usually rapid, the pulse also; the conjunctivæ are congested, and keratitis, iritis, or panophthalmia is sometimes observed. The tongue is swollen, shows the impression of the teeth, and is covered with a whitish fur resembling mother-of-pearl (Bulard).

In the bubonic form, the bubo appears during the first hours of the malady and is usually unique. In the order of frequency, it presents itself in the groin, the axilla, or the neck. It develops with rapidity, and is well advanced as early as the beginning of the second day, and is always very sensitive to the touch almost from the start. The neighboring tissues are tumefied and œdematous, especially in the parotid region. When this locality is invaded, œdema of the larynx is to be feared.

* Author's definition.

On the second day, the bubo is about the size of a pigeon's egg, and there is aggravation of all the constitutional symptoms, the pulse reaching sometimes 140. Delirium now appears and the stage of apathy is replaced by one of excitement, during which the patient may try to get up. Physical disorders become manifest, fixed ideas predominating. Functional disturbances of speech are also frequently observed. On the third day, all the symptoms become still further aggravated, the pulse reaching 140 or beyond, and the bubo attains perhaps the size of a hen's egg, and suppurates. Occasionally it becomes gangrenous. Carbuncles may develop in different parts of the organism. Extensive petechiæ are usual: the "plague-spots" of older writers. Hæmorrhages from mucous membranes, the nose, the lungs, etc., are frequently observed. In some epidemics hæmorrhages are witnessed in all cases, the buboes assuming an hæmorrhagic type.

Death, in the majority of fatal cases, generally occurs about the fourth day, either from toxic paralysis of the respiratory or cardiac centers or from collapse. If the first four or five days—the acute stage—are passed safely, the chances of recovery are favorable. On the other hand, a stage of marasmus or profound depression may appear on the fifth day and the patient succumb on the sixth. Much depends upon the condition of the heart. Some cases, especially in children, are very benign, showing but an insignificant rise in temperature, slight inguinal or axillary pain, general depression and ephemeral torpor. Such cases, however, are apt to occur early in the course of an epidemic. On the whole, the disease shows a very high rate of mortality.

In the pneumonic or septic variety there is profound septicæmia. The pulmonary inflammation closely resembles commencing influenza (Lewin) and does not show clear physical signs. It is a form of confluent lobar pneumonia without apparent or noticeable implication of the lymphatic system. It begins also with a chill, severe pain in the side, and more or less severe cough with rusty expectoration. The plague bacillus is always found in the latter. In this variety death may occur within twenty-four hours.

Some epidemics exhibit symptoms representing both varieties.

Etiology and Pathogenesis.—The disease is due to a bacillus discovered by Kitasato, in 1894, and which is probably communicated to men through the bites of insects, fleas especially, themselves contaminated by the blood of contaminated animals, especially the rat. Filth and bodily neglect are predisposing causes. When the infection has occurred, the germ invades the lymphatic system and gives rise, as in syphilis, to buboes, the characteristic objective symptom of the disease.

The relationship of the disease with the ductless glands is shown by various phenomena which the presence of the buboes does not explain, viz., the toxæmia.* The combination of marked exhaustion and weakness at the commencement of the disease, the moist non-tremulous mother-of-pearl tongue of Bulard and the delirium and excitement on the second or third day, indicate the identity of the center affected, viz., the sympathetic center, and the character of the morbid process: intense depression or paresis of this center.* The tendency to capillary hæmorrhages in the viscera and subcutaneous tissues points from a different direction to the nature of the peripheral disorder: paresis of the arteries, a fact further shown by the impaired nutrition of the peripheral tissues and bones,* which in some cases may even undergo necrosis. The intense muscular weakness is a normal outcome of this condition and to it also is due the development of pneumonia,* owing to the ubiquitous presence in the respiratory channels of the pneumococcus and its readiness to multiply when the vital functions are torpid.

Fortunately, the test-organ is not influenced in the same way and soon reacts,* as shown by the rise of temperature, which may reach 105° F. (40.5° C.). In many cases, however, its reaction is inadequate* and the temperature does not exceed 101° F. (38.3° C.). Under these conditions the case, if at all a severe one, rapidly assumes a lethal trend, the body's defenses being unable to save it.*

Treatment.—The main indications, in the light of my views, are three in number. The first of these is to raise the functional activity of the adrenal system to its highest possible

* Author's conclusion.

potential, to check the multiplication of the bacillus in the lymph and the blood.* As its toxin is very sensitive to heat, both pathogenic elements are thus antagonized.* *Mercury*, of all agents, does this most promptly and should be injected intravenously. The best agent for this purpose is the *biniodide*, $\frac{1}{8}$ to $\frac{1}{2}$ grain (0.01 to 0.03 gm.) dissolved in 15 minims (1 gm.) of water every four hours, until the first signs of mercurialism appear. It is painless when injected—preferably in the veins of the elbow. The test-organ being promptly stimulated, the blood is soon rendered richer in auto-antitoxin, and the phagocytes which penetrate into the lymph-channels and glands likewise.* This salt does not contain enough iodine to increase adequately the proportion of thyroidase (opsonin) and the bactericidal activity of the phagocytes.* *Sodium iodide*, 15 grains (1 gm.) in a large glass of water, should be given orally with each dose of mercury and continued every four hours after the use of the latter drug is stopped.

Pending the action of these agents, *adrenalin chloride*, 1-1000 solution freely diluted, may be given hypodermically, remembering, however, that its effect can only be ephemeral, since it is promptly converted into adrenoxidase.*

Far more efficient, however, is *Yersin and Roux's serum*, which corresponds, in composition, with the auto-antitoxin that accumulates in the blood under the influence of the above-mentioned drugs.* The failure of this serum in a large proportion of cases is due to the fact that it only increases the blood's asset in auto-antitoxin, without exciting the adrenal mechanism.* As an adjunct to adrenal stimulants, mercury, for example, should prove invaluable.*

The main indication is to consider those remedies as sheet-anchor which will evoke the strongest weapons that the body can muster. Mercury has been used extensively in plague, but either as a purgative, or combined, or given simultaneously with agents which counteract its beneficial effects. H. Lorans³⁷ states that patients "show toleration for large doses of sublimate, taking as much as $\frac{1}{2}$ grains (0.1 gm.) in twenty-four hours without signs of salivation or stomatitis. They improve under the action of the drug." This applies likewise to iodine, which has been found of great value by a large number of practitioners. Gujjar, of Bombay,³⁸ for example, gives the following report of the results obtained with iodine tetrachloride:—

* Author's conclusion.

³⁷ H. Lorans: *Med. News*, Dec. 30, 1899.

³⁸ Gujjar: *Indian Med. Record*, May 1, 1906.

For February.

STATIONS.	NO. OF CASES.		RECOVERIES.		DEATHS.		PERCENTAGE OF RECOVERIES.	
	With buboes.	Without buboes.	With buboes.	Without buboes.	With buboes.	Without buboes.	With buboes.	Without buboes.
Girgaum.....	41	45	23	45	18	0	56.09	100.
Pydhoni.....	23	64	9	60	14	4	39.1	93.7
Bazargate....	15	26	12	26	3	0	80	100
Total.....	79	135	44	131	35	4	55.6	97.03
		214		175		39		

For March.

Girgaum.....	110	258	58	252	52	6	52.7	97.6
Pydhoni.....	49	209	26	206	23	3	53.06	98.5
Total.....	159	467	84	458	75	9	52.8	98.07
		626		542		84		

Although this report seems extraordinary and makes one wonder why the mortality of plague is so great, the fact remains that it shows at least that iodine is not harmful in the disease and that the indications which I submit are warranted.

The use of adrenalin chloride has been extolled by Choksy, of Bombay,³⁹ for cardiac failure in plague. He states that "a marked change for the better was soon apparent in the condition of the patients after they were put under adrenalin." I have shown under "Antitoxin" that all sera were in reality the auto-antitoxin of the animal from which the "antitoxin" is obtained. The value of Yersin and Roux's serum suggests itself under these conditions.

The second indication is to restore the normal caliber of the arterioles by stimulating powerfully the sympathetic center. A careful selection of drugs is necessary here. Excessive constriction of these vessels would greatly diminish the volume of blood admitted to the capillaries. It is advisable, therefore, to avoid opium, the coal-tar products, and all analgesics in fact, as these agents reduce pain by causing marked constriction of the arterioles, which would mean added torpor of the lymph-stream and freedom to the plague bacilli to pullulate.* The aim should be to employ an agent capable of compensating for the reduced caliber by an augmentation of the propulsive activity of the vessel.* We have precisely such an agent in *atropine*, which, besides, is capable of stimulating the test-organ and therefore of increasing the volume of auto-anti-

* Author's conclusion.

³⁹ Choksy: Indian Med. Gazette, Apr., 1905.

toxin in the blood.* A dose of $\frac{1}{100}$ grain (0.00065 gm.) with each dose of sodium iodide suggests itself, but much larger doses would probably be necessary to overcome the torpor of the sympathetic center due to the toxin.*

Atropine has likewise been used in plague, but practically always with drugs capable of counteracting its action. Where such has not been the case, however, it has shown distinctly its value. Thus, R. Row⁴⁰ says that in August and September, 1899, he tested atropine in the treatment of 97 cases of plague. To these he adds the 291 cases of Major R. J. Windle, and 78 cases treated by Dr. A. Turkhud in November and December. The most prominent feature observed in the treatment was the condition of the bubo, which either subsided completely or remained as a hard nodule, which, in some cases when cut into, showed a mass of slough with hardly any pus. Personal cases gave scarcely 14 per cent. of suppurations, and it was interesting to note that the smaller the dose of atropine administered, the more frequently suppurations were found. Some cases not treated with atropine showed 84 per cent. of suppurations. The localization of the bubo indicated a favorable termination of the disease. As to the size of the dose, Dr. Row states 6 drops of the liquor atropinæ sulph. failed in some instances to cause contraction of the pupil, and that such cases, as a rule, fared badly. From my viewpoint, the sympathetic center had been paralyzed by the toxin, and reacted no more to atropine than to any other agent—except, perhaps, mercury.

The third feature of the treatment is to maintain the fluidity of the blood and lymph, *i.e.*, their osmotic properties.* This factor is of especial importance in all diseases in which, as in plague, the lymphatic system is primarily involved, since any degree of abnormal viscosity of the lymph, by slowing the speed of the current, retards transmission of the pathogenic germs to the blood, where they are most readily destroyed.* The indications outlined on page 1367 are eminently applicable in the present connection.

Prophylaxis.—In the light of the above facts, to protect the body against plague infection, the protective activity of the adrenal system should be increased by remedies able to excite the test-organ.* Haffkine's prophylactic fluid owes its properties to such an action,* while the serum of Yersin and Roux is the antitoxin itself. *Thyroid gland*, 2 grains (0.13 gm.) after meals, suffices to increase markedly the auto-antitoxin in the blood;* the *iodides of mercury* and also *iodine* and its preparations are both, we have seen, capable of enhancing powerfully the efficiency of the body's auto-protective mechanism.*

* Author's conclusion.

⁴⁰ R. Row: Lancet, May 19, 1900.