

very strongly that the acid-fast bacilli in verruca tissue described by various writers are really tubercle bacilli, and that those who have merely examined tissue without seeing the autopsy, and who have described necroses in verruca tissue, which very closely resemble those of tuberculosis, have been describing tuberculosis of various viscera which has existed as a complication of verruca and which do not represent any specific change due to verruca *per se*.

#### PROPHYLAXIS

As the disease is limited to certain endemic regions, and is generally contracted at night, it may be prevented, of course, by keeping out of the danger zone. During 1909 an American bridge company undertook the construction of several bridges on the Oroya Railroad. The engineers and workmen engaged in putting up the first of these structures encamped within a verruca zone, and suffered much from the disease. At the suggestion of Dr. Barton, it was arranged that the men should sleep in a place a few kilometers distant, out of the endemic district, while they continued their work in the day time as usual. From that date there were no new cases. Peruvian physicians are quite alive to the economic importance of this disease and we may expect them to determine in due time the mode of infection, the true pathogenic agent, and thus establish a means of preventing the ravages of this tropical scourge.

In conclusion it should be stated that whatever the final opinion with regard to the  $\alpha$ -bodies may be, the disease in all its aspects will amply repay careful study and research into the mode of transmission, relation of the  $\alpha$ -bodies to the different clinical phases of the disease, the pathology and treatment.

I am under special obligations to Dr. A. L. Barton of Lima, Peru, for his kindness in furnishing me with clinical notes and consecutive blood-films from several cases of verruca.

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### VERRUCA PERUANA OR CARRION'S DISEASE \*

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#### HISTORY AND DISTRIBUTION

Verruca peruana, or Carrion's disease, is an infectious disease endemic in certain districts in Peru. It is characterized by fever, rheumatoid pains, anemia and an eruption which develops into bleeding, warty tumors. Verrugas, to use the Spanish term, caused many deaths among the ancient Peruvians and among the followers of Pizarro during the conquest of Peru.

Various writers of that country, since 1730, have described the disease, but it was brought into greatest prominence in 1870 during the construction of the Oroya Railroad over the Andes mountains. Many of the foreign laborers were attacked by a strange and fatal disease which was given the name of Oroya fever and the connection of this fever with the external eruption, previously known as "verrugas," was established during this period. Their unity was illustrated by the case of Wilson, a mining engineer, who after an attack of Oroya fever returned to the United States and afterward developed a typical case of verrugas.

Carrion, a Peruvian medical student, inoculated himself, Aug. 27, 1885, on each arm with blood from a tumor of a case of verrugas; initial symptoms appeared September 17 and his death occurred October 5, the thirtieth day after inoculation, having passed through all the stages of Oroya fever. This experiment established still more fully the relation of Oroya fever and verruca and showed the infectious nature of the disease.

While verruca was formerly endemic in several countries of South America, it is now limited to Peru, being found in three departments, Ancachs, Libertad and Lima; and the infected areas are confined to certain deep river valleys of high altitude. Any person is liable to infection, regardless of age or sex, although organic debility seems to be a predisposing cause. Natives of the infected districts are immune, but all others are liable to contract the disease, even when merely passing through the country. Intra-uterine infection occurs, children being born with the disease.

The lower animals are liable to infection and present the same symptoms as human beings, but the external lesions grow much larger.

No authentic case of infection by personal contact has been known to occur outside of infected districts. Verruca, in common with many other diseases, has been confused with malaria, to which the character of the fever bears a close resemblance. In many ways it closely resembles yaws, but there are so many distinctive points of difference that it hardly seems probable that it is a form of that disease, as is claimed by some authorities.

#### BACTERIOLOGY AND PATHOLOGY

But little animal experimentation has been done, consequently the etiology has not been shown conclusively and the method of transmission is unknown, but it is very probable that it is conveyed by some form of insect life. An organism, apparently a bacillus, is found in the red blood-cells during the febrile period and in the tissues of the local lesions. It presents two forms, found in different stages of the disease, one closely resembling, morphologically, the tubercle bacillus, the other much thicker and apparently an involution form. This organism is 2 to 6 microns in length, has rounded ends, is motile, contains two or three granules resembling spores and is gram-negative, but stains well with methylene-blue. It grows readily on bouillon at a temperature of 98.6 F., cloudiness appearing on the second day. The organism from this culture is from 10 to 12 microns in length, and stains well with gram and carbol-fuchsin. Much careful investigation will be necessary to prove definitely whether this organism is really the specific cause of verruca as it now appears to be.

On autopsy, all organs are found pale and bloodless, the liver and spleen are frequently enlarged and there is constant enlargement of the lymphatic glands—a diagnostic point. There is hyperplasia of Peyer's patches and congestion of the intestinal mucous membrane.

#### SYMPTOMS

The period of incubation is not sharply defined; in Carrion's case transmitted by inoculation, it was twenty-one days, but if contracted in the natural way it may be from fifteen to forty days. The invasion is slow, beginning with headache, pains in the lower extremities, chills followed by fever, thirst, anorexia and insomnia. The digestive system presents the symptoms of an acute fever, the liver, spleen and lymphatics are engorged and petechiae frequently appear.

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The fever follows a remittent or intermittent type and during the fastigium varies from 100 F. in the morning to 104 F. or higher in the evening, extending over a period of twenty-five or thirty days.

Anemia is the predominating symptom, coming on very rapidly, and much resembles that following hemorrhage. The red blood-cells are reduced to 1,000,000 or 500,000 and there is marked leukocytosis with a great increase of polynuclears.

The skin is white and wax-like, the lips, tongue, gums and nostrils blanched and the nails discolored. Icterus is visible in the conjunctiva, the respiration is rapid, often with dyspnea, the pulse from 120 to 140 and systolic murmurs are heard at the base of the heart extending into the vessels of the neck, the latter symptom being very annoying to the patient. Epistaxis is frequent and serious, but hemorrhage from the bowels occurs less often. Edema is often present in the lower extremities, rarely becoming general.

Vertigo is so severe that the patient cannot sit up for fear of syncope. Mild delirium occurs in the evening and hiccough is frequent.

Many patients succumb within twenty-five or thirty days, but if the patient survives the febrile period the symptoms gradually decline until the appearance of the eruption, when they recur. In most instances the eruption is not noticed until after the decline of the fever, but in some cases it appears simultaneously, although in the former instance it is quite possible that the eruption escapes notice, or may be located internally.

It was formerly thought that Oroya fever was a distinct stage of verruca, but later studies show that no sharp line can be drawn between the fever and the eruption and the division is made only for convenience of study.

In some cases there is a sudden onset of high fever, all other symptoms are very severe, and death occurs in a few days showing the eruption on the skin, small, discrete and with no tendency to multiply, or the disease may prove fatal without the appearance of the external eruption.

In a majority of cases there is an intermediate period of from forty days to four or five months before the eruption is seen. When it does appear, the digestive and nervous symptoms are increased in severity, and the anemia is more marked, being identical with that of the initial fever, but it develops more slowly. The fever of the eruption also follows a remittent or intermittent type, rising to 104 F. or higher and varies with the amount and form of the eruption. Edema is more constant than during the early stages, it is often limited to the lower extremities and is due to the induration caused by the eruption with the consequent compression of the venous circulation. The muscular and articular pains recur, the joints being tender and often tumefied.

There are two distinct forms of the eruption, miliary and globular, often difficult to classify, as there are all grades between the two extremes. The miliary form, the smaller, occurs both externally and in the deeper tissues.

Externally, this form is located above the true skin and may originate in three ways: a petechia beneath the Malpighian layer, as a sort of rosy drop more or less transparent, or as a slight elevation of a dead white tint resembling hypertrophied papilla. In whatever manner it first appears it grows gradually and develops into an elevated papule, dark, glossy and slightly pointed. In this form the papule varies in size from the head of a pin to that of a small pea, the smaller ones sessile, the larger tending to pediculate.

Exfoliation and bleeding occur, the larger ones ulcerating and discharging a yellowish liquid which forms a crust. A retrograde process follows and the growth disappears, leaving a slight stained appearance of the skin, which is transient.

The miliary eruption may be localized or general, discrete or confluent, and is located especially on the extremities and about the face, the palms, soles and body being usually exempt. The lesions occur on all the mucous surfaces of the body, on the peritoneum, in the liver, spleen, kidneys, lungs, pancreas, testicles, periosteum, bones and brain. Those on the conjunctiva form small, flat elevations the size of a millet-seed; in the nose they are larger and are the cause of the epistaxis. The brain lesions are the size of a pin-head, and located at the base, in the chorioid plexus and on the arachnoid membrane. It is a notable fact that the eruption always begins in the connective tissues and never in the parenchyma.

The globular form is found only externally and consists at first of a small subcutaneous elevation, tender and resistant to the touch, and like the miliary has a predilection for the extremities, the face and especially the ears. As the tumor grows, the overlying skin becomes purple, painful on pressure and in appearance and consistency resembles a furuncle. It finally becomes conical, the skin grows thinner and is pierced by the growth, which now assumes a globular form and shows a tendency to pediculate. Fissures form and ulceration with hemorrhage are subsequent symptoms. This form varies from the size of a hazelnut to that of an orange.

In those of medium size, subinvolution begins, the growth becomes pale and shriveled, falls off and cicatrization takes place; but when they are large, gangrene, secondary infection and extensive suppuration are common. Both forms may be found in the same case, or they may alternate, the period of eruption being from six months to two years. In the section, a verruca tumor somewhat resembles a sarcoma, having a stroma similar to embryonic tissue, and a circumscribed adherent wall. It is highly vascular, the blood-vessels having the appearance of sinuses.

Pneumonia, enteritis and paratyphoid are common complications, and secondary infection of the eruptive lesions may result in septicemia.

#### DIAGNOSIS AND PROGNOSIS

The diagnosis is not always easy, but in a person who gives a history of having been in the infected districts, showing the symptoms of fever, anemia, vertigo, rheumatoid pains and enlargement of the lymphatic glands, verruca should be strongly suspected. When the eruption appears it is easily recognized.

The enlarged liver and spleen are not so constant as in malaria; in the latter the anemia comes on more slowly, prostration is not so severe, lymphatic enlargement is absent, the action of quinin is positive and the plasmodium is found in the blood.

Yaws, apparently a very similar disease, is not congenital; the yaws appear on the body as well as on the extremities, the general health is little affected, there are no visceral changes, the mortality is low, and the *Treponema pertenue* is found in the eruptive lesions.

The prognosis is grave, the mortality, according to some authorities, being as high as 90 per cent. Most of the deaths occur prior to the appearance of the eruption, and when it appears the outlook is more favorable, especially if it comes out rapidly and becomes general, but when it is partial or pale and atrophies without the general condition improving, it is not so good.

## PROPHYLAXIS AND TREATMENT

Until the manner of infection is known, the only prophylactic measure to be recommended is to remain outside the districts known to be infected.

It is not considered necessary to isolate the patient, as there is no danger from personal contact. The patients whom I have seen were being cared for in the medical wards of Dos de Mayo Hospital, Lima, where they are received and treated without fear of infection.

The therapeutic resources are limited and consist principally of symptomatic and supportive treatment. Quinin is indicated if malaria exists as a complication, but it has no effect on verruca itself. The digestive system should be put at rest, the food being light and digestible, and when vomiting is constant, rectal feeding is necessary. Tonics and reconstructives are very useful when they can be borne. Saline solution by rectum and intravenously is used to great advantage during the critical part of the febrile period.

In presenting this paper, I do not wish to be taken as an authority on verruca, but merely give the impressions gained by a rather limited study of the disease while on a recent visit to Peru, together with information gleaned from literature which it is believed is but little known to the profession of the United States.

Verruca has not been widely investigated as yet, and it is believed that a further study of this interesting disease will prove it to be insect-borne and perhaps throw some light on other diseases, the etiology and transmission of which are not yet understood.

It is desired to render proper credit to Dr. Ernesto Odriozola of Lima, Peru, whose excellent monograph on verruca has been freely consulted in the preparation of this paper, and to extend thanks to Dr. Julian Arce, Director of Health of Peru, for presenting me with a copy of this work. Finally, I would acknowledge my obligation to my wife for the translation from the French of the above monograph.

## THE RELATION OF PELVIC DISEASE TO EXOPHTHALMIC GOITER \*

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The exophthalmic syndrome is now generally conceded to be due to excessive secretion of the thyroid gland, and as a result of this view recent therapeutic measures have been directed toward removal of a portion of the secreting tissue. In connection with this I desire to express my suspicion that too much emphasis has been placed on a merely excessive secretion. The histopathology of the exophthalmic thyroid should make us suspect that the secretion is not only excessive, but also is changed in character, for the reason that whenever gland-cells depart from the usual as markedly as is indicated by tinctorial chemistry in these glands, there is likely to be some change in their product. I desire to question emphatically the entire correctness of the minor premise before beginning my argument.

From time to time inquiries as to the relation of the thyroid to other organs have been conducted. It is my purpose to offer a contribution to this phase of the subject, in so far as it relates to the genital organs. This paper will be confined to clinical observations, including the result of therapeutic tests in cases in which a relation of this kind was believed to exist.

There are a number of phenomena both physiologic and pathologic which call attention to the relation between the genital organs and the thyroid. The most familiar phenomenon, and one which is known even to the painters, is the slight congestive enlargement of the thyroid incident to menstruation. This enlargement when associated with menstruation is worthy of note, as it is often attended by a nervous irritability and a quickened pulse and a slight rise of temperature. Equally well known is the genital aplasia in cretins and the suspension of genital function in myxedematous patients, which returns, however, when the myxedema is relieved by thyroid therapy. Suggestive, also, is the disposition to obesity after the menopause or after ovarian atrophy and the temporary reduction of fat by the exhibition of thyroid extract. In vomiting of pregnancy Siegmund and others report beneficial results from the administration of thyroid extract. It has long been recognized that in exophthalmic goiter the uterine function is frequently disturbed. This has usually been considered as a secondary result, though the opinion that the sequence of events is direct, has existed without, however, any attempt at proof. Some exophthalmic patients are much benefited by pregnancy while others are made worse. These and many other phenomena show the relation between the thyroid and the genital organs.

Unfortunately, we have little information of the pathology of these coexistent conditions. I have sought to contribute something to this question by careful clinical observation together with examination of pathologic material whenever such became available. My plan has been to treat the associated lesion as if the goiter did not exist, whenever it was clear from the history that the former began before the goiter. I have operated on five patients who presented gross gynecologic lesions such as are amenable to ordinary surgical treatment, in whom the pelvic disease certainly existed many years before the first symptoms of thyroid intoxication. Only patients operated on more than three years ago will be reported.

**CASE 1.—History.**—Mrs. S. A., patient of exceptional intelligence, 36 years of age, has had no children; she gives a history of pelvic inflammation soon after marriage twelve years before, and has not been strong since, being subject to periodic pain and bladder irritation. Menstruation was variable, but not painful; in fact the pelvic disturbance was often less marked during this time. She was nervous and slept badly. Eighteen months before examination, while going past an excavation on a dark night, she fell into an incompletely celled. The bruises sustained were not severe but she suffered greatly from fright. She never overcame her nervousness and soon her heart became rapid and irritable. She noticed that her eyes were becoming prominent. This caused her to consult an oculist, who prescribed 5 grains of thyroid extract four times a day. She grew worse.

**Examination.**—The pulse was 136, quick and jerky. The thyroid gland was noticeably enlarged. Exophthalmos and von Graefe's sign were well marked. Tremor and irritability were especially prominent. Pelvic examination showed a uterus very tender and immovable with resistance on each side. No definite mass could be outlined.

**Operation.**—Laparotomy, done in 1904, showed chronic pus tubes, the tubes and ovaries being imbedded in masses of fibrous tissue. Both tubes and the left ovary were removed.

**Postoperative History.**—The operative recovery was uneventful. Three months after operation the pulse was 80 and soft, the thyroid enlargement much less and exophthalmos was still discernible. Two years later she writes that she is well and adds that her heart palpitates easily, particularly at the menstrual periods. The condition of the thyroid and exophthalmos could not be determined by correspondence. The results in this case are symptomatically very satisfactory.

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