

VERRUGA PERUVIANA AND ITS COMPARATIVE STUDY IN MAN AND THE APE*

HAROLD NEWTON COLE, M.D.
CLEVELAND, O.

The fact that the Panama Canal is to be opened shortly calls our attention to a disease that may be of more or less interest and importance to Americans in the next few years. Even before the Spanish occupation of South America a peculiar sickness was endemic over a certain inland portion of Peru. The Spaniards suffered terribly from its ravages, as have the natives since then, and the trouble is still present in this same region. At the time of the building of the Oroya Railroad through this country in 1871, the workmen were afflicted greatly with a severe fever termed Oroya fever, and from Verruga peruviana. Clinicians finally began to have the feeling that the two diseases were one and the same, though in a different type, and in 1885 a young medical student, Daniel Carrion, allowed himself to be inoculated with the blood of a patient suffering from the latter affection, and in thirty-nine days he was dead from a typical attack of Oroya fever.¹ The heroic young man apparently settled all doubt as to the entity of the two diseases; though, as I will mention later, the question is once more under discussion.

Through a peculiar happening the Berne Dermatology Clinic had what was probably the only case of this trouble ever seen in Europe in the person of a Swiss mountain guide from Zermatt. In 1909, along with a companion, he assisted Miss Annie E. Peck² in climbing Huascarán Mountain in Peru. Through misfortune on their way down they were forced to stop twelve days on the ice fields, and his companion had his hands and feet so badly swollen that the two guides were forced to remain some time in Peru before their return to Switzerland.

About one week after his arrival in Zermatt the patient began to notice fleeting symptoms of an uncomfortable feeling, followed by sweating, when in a hot room. They only lasted five or ten minutes, and he was not aware of any temperature disturbance. A little later he noticed a small growth on his left leg and shortly afterwards quite a few came

*From the Dermatology Clinic in Berne, Switzerland (Director, Professor Dr. Jadassohn).

1. For the history, clinical symptoms, etc., of this interesting disease, I have drawn largely from the complete and well written monograph of Prof. Ernesto Odriozola; "*La Maladie de Carrion*" ou "*La Verruga Peruvienne*." Paris, Georges Carré, et C., Naud, 1898.

2. Peck, Annie E.: Harper's Monthly Magazine, January, 1909.

out on his face, arms and hands, and the patient on advice consulted Prof. Jadassohn in the Berne Clinic. He had had no other symptoms, and on admittance to the hospital seemed to be perfectly well; except for the tumors. I will not go into detail of what has been already described,³ but suffice it to say that thorough physical examination showed absolutely nothing pathological outside of the cutaneous growths. The blood-picture was absolutely normal, the Wassermann reaction negative and the von Pirquet cutaneous test for tuberculosis and subcutaneous injections of tuberculin in varying amounts up to 1.0 mg. also showed nothing. Some of the tumors were excised for histological examination and inoculation experiments, others were treated with carbon dioxid snow, pyrogallic ointment, tincture of iodine, etc., and in about three weeks it was impossible to prevail on the patient to remain any longer in the hospital, as he was feeling perfectly well and the lesions had practically healed. And since his departure occasional reports show that, outside of a few rheumatic symptoms, he has been quite well.

ETIOLOGY

The mountain climbers on their trip had just touched the edge of the verruga territory, but it was apparently enough to transmit the infection. The disease is limited to an inland portion of Peru, from 28 to 60 kilometers from the seaboard. The country is quite mountainous in character, varying in altitude from 400 to 3,000 meters. Curiously enough, the present limits of the disease are somewhat smaller than at the time of the Spanish occupation. The valleys are deep and hot, while the streams are sluggish and many swamps abound. Odriozola thinks that the climate may have some etiological importance; while the water is blamed by others. However, cases have been known to occur in patients who have used nothing but potable water, and, moreover, in April,⁴ when the water recedes, the verruga cases augment. No race, age or sex is spared, and Odriozola says that the horses, mules, dogs, llamas, chickens, etc., have symptoms closely allied to those of the human beings. Cases have been cited where the patients have staid but one-half an hour or an hour in the verruga territory and there is at present a feeling that, as in many other tropical diseases, some insect may have something to do with the transmission of the disease. The affection is inoculable, though not contagious, and it is apparently transmissible by the placenta. The incubation period varies from fifteen to forty days, or even longer. In Carrion's case it was twenty-one days, perhaps due to the fact that he was inoculated intravenously; while in Jadassohn's patient it was at least sixty days. Apparently one attack gives immunity for the rest of life.

3. Jadassohn, J. and Seiffert, G.: Ein Fall von Verruga peruviana, gelungene Uebertragung auf Affen. *Ztschr. f. Hyg. u. Infektionskr.*, 1910, lxvi, 247.

4. Brault, J.: La Verruga du Pérou. *La Pratique Dermatologique*, iv, 832.

SYMPTOMS

In the severe type of the affection, the so-called Oroya fever, the disease is usually ushered in with a chill accompanied by a fever; after prodromal symptoms of headache, general malaise and pain in the joints and muscles.⁵ The fever may go up to 40 C. (104 F.), or even higher, and is accompanied by nausea, vomiting, rapid anemia, sleeplessness, vertigo, hemorrhages, coma and death. The glands are enlarged and the liver and spleen engorged. If the termination be good, the temperature gradually falls and the symptoms lessen. The fever is either remittent, intermittent or irregular in type and may accompany, precede or follow the appearance of the cutaneous manifestations. The pulse is frequent, soft, compressible and, even with a temperature of normal, it may be 120 to 140, or even higher. Among the types of hemorrhage, enterorrhagia is rare, and usually comes along towards the termination of the disease, being an unfavorable prognostic sign. Epistaxis is a very common symptom and petechiae are frequent. Sweating is profuse, especially in the fever of an intermittent type. Edema of the toes and legs is generally found, though it is rarely generalized except in the grave cases. Nervous symptoms of vertigo, syncope, cephalalgia, delirium, insomnia and hic-cough are sometimes seen.

Pneumonia, enteritis, enterocolitis and hemorrhages are among the complications most frequently encountered; though several cases of verruga meningitis have been reported. Occasionally malaria and verruga are seen in the same patient at the same time.

ERUPTION

The cutaneous eruption is of two general types: "*miliaire*"⁶ or tuberculous, and "*mulaire*" or nodular. Under the first a tubercular, a sud-aminal, a vesicular and a pustular efflorescence are noted. The eruption may be localized, generalized, discrete or confluent, and the favorite seats with the tubercular or "*miliaire*" efflorescence are the anterior regions of the legs, extensor surfaces of the forearms, antero-extensor surfaces of the arms, forehead, jaws, nose, eyebrows, knees and elbows. The mucous membranes of the eyes, mouth, digestive and genito-urinary tracts are also frequently involved. Moreover, verruga nodules have been found in the peritoneal coats, spleen, liver, pancreas, kidneys, lungs, muscles, and central nervous system. The "*mulaire*" or nodular lesions are subdermic, varying in size from a walnut to a small orange, and they may be sessile

5. Prof. Odriozola proposes to divide the disease into two types, according as the fever or as the cutaneous tumors predominate in the symptoms. The first type he would call "Oroya fever" or "*Fièvre de Carrion*," and the latter "*Eruption de Carrion*"—thus naming the disease after the young martyr.

6. The words "*miliaire*" meaning tubercular and "*mulaire*" meaning nodular have been taken over bodily from the Spanish by Prof. Odriozola.

or pedunculated. They are never internal and are found on the eyelids, cheek-bones, lobules of the ears, bridge of the nose and the knees. Jadassohn's patient had examples of both the "*miliaire*" and the "*Mul-
aire*" efflorescences—confined mostly to the face, arms and legs. The conjunctiva of one eye was affected, but otherwise the mucous membranes showed nothing. The patient also showed a macular eruption resembling a lupus and thus far not described in connection with verruga peruviana.

PATHOLOGY AND BACTERIOLOGY

In regard to the pathology and bacteriology of the disease, much still remains to be desired, because of the marked differences in the findings of investigators. The blood-picture is that of a rapid and marked anemia. Bassett-Smith⁷ found an abundance of nucleated red cells, and the erythrocytes were irregular in their size, shape and staining qualities. Many basophilic granulations were seen and a few myelocytes were present. The bone-marrow usually shows signs of proliferation. The liver and spleen are generally engorged and the latter organ occasionally extends down to the iliac fossa. It is soft and more or less friable, while the liver is slaty in color, as in malaria, due to the destruction of red cells. The lymphatic ganglia are greatly engorged; those of the mesentery occasionally reaching the size found in tuberculous peritonitis and leukocythemia. The urine is merely febrile. Histologically, Nicolle⁸ found small nodules of epithelioid cells in the liver and lungs, but no caseation. In the lymph-nodes he found true caseation in their centers, but no giant cells. Somewhat analogous though more marked lesions were noted in the spleen. DeVecchi⁹ found early hemorrhagic lesions in the spleen, lungs, liver, muscles and skin along with new tissue formation. In the liver there was a vacuolization of the elements and compression of the cells by the widening of the vessels and by the formation of verruga nodules. Pigment clumps were also noted and phagocytic leukocytes were noted in both the liver and spleen. He found giant cells in both these organs and in the lungs there were appearances of new tissue formation and small areas of bronchopneumonia. The cutaneous lesions have been studied by several men and it seems to be the consensus of opinion that they are granulomatous in type; made up of fibroblasts, mono- and polymorphonuclear leukocytes, plasma and red cells. The tumors are very vascular and later show signs of necrosis. Acid-fast bacilli have been found in the internal lesions by Nicolle,⁸ and also by

7. Bassett-Smith, P. W.: The Pathology of the Blood in Verruga. Brit. Med. Jour., Sept. 18, 1909.

8. Nicolle, C.: Note sur la bactériologie de la verruga du Pérou. Ann. d. l'Inst. Pasteur, 1898, xii, 591.

Letulle,¹⁰ Escomel,¹¹ Giltner¹² and Izquierdo,¹³ while just lately an organism closely related to the paratyphosus bacillus, type B, has been found by DeVecchi,⁹ Barton,¹⁴ Biffi¹⁵ and others. Cell inclusion-bodies have also been reported.

DIAGNOSIS

In diagnosis one must always keep malaria in mind, for in fact the two diseases have been very frequently confused, and they are occasionally found together in the same patient. Typhoid fever must also be ruled out. In a patient having the cutaneous tumors as the predominant symptom it would also be necessary to think of neurofibromatosis (von Recklinghausen's disease). The affection occurring in a tropical country, framboesia and *Bouton d'Orient* would likewise have to be considered in a differential diagnosis. In the former, suitable examination for the specific spirochete would be sufficient, while in the latter there would be the history of painless ulcers on the exposed parts, in which proper examination would reveal the Leishmann-Donovan bodies.

PROGNOSIS AND TREATMENT

The prognosis of verruga should always be guarded, though the cases having the cutaneous tumors as their main symptom usually do better than the ones with the high fever.

The treatment is symptomatic and apparently of little avail. Quinin and the salicylates have been the drugs mostly relied on and it will be interesting to see what will be the effect of our new drugs, salvarsan and neosalvarsan. Perhaps they will be as effectual as in framboesia, and their use is to be recommended—at least as an experiment. Despite all treatment the cutaneous lesions usually last from four to six months, and even up to two years. In the Berne case the growths were practically all gone in a space of three months.

9. DeVecchi, B.: Ueber die Verruga peruviana. Arch. f. Schiffs u. Tropenhyg., 1909, xiii, part 4, 143.

10. Letulle: Histological Study in Prof. Odriozola's monograph (Note 1).

11. Escomel, E.: Anatomie pathologique du verrucome de Carrion. Ann. d. derm et d. syph., 1902, iii, 961.

12. Giltner, H. A.: Verruca Peruana or Carrion's Disease. Jour. Am. Med. Assn., 1911, lvii, 2074, Abstr., München. med. Wehnschr., 1912, No. 8, p. 440.

13. Izquierdo, V.: Spaltpilze bei der Verruga peruviana. Virchow's Arch. f. path. Anat., 1884, xcix, 411.

14. Barton: Quoted by DeVecchi (Note 9).

15. Biffi y Carbajal: Verruga peruviana und schweres Fieber Carrion. Arch. f. Schiffs u. Tropenhyg., 1908, Part I. Quoted by DeVecchi (Note 9).

EXPERIMENTAL TRANSMISSION

Outside of one experiment mentioned by Odriozola¹ on page 175 of his book, no attempt has ever been made to transmit the disease to lower animals. In this case a bitch was inoculated with the blood from a large verruga tumor. Later she had several growths on the paws and ears, delivered two dead pups and died. The experiment was rather indefinite, and no autopsy was done. In Jadassohn's case several of the tumors were excised, ground up into a "brei" and many cultures made on different media, though in vain. Like success also attended experiments with rabbits, guinea-pigs, doves, chickens, rats and a dog. But in working with apes the results were better. The first animal (*Cercopithecus sabaeus*) was inoculated on the eyebrows with some of the "brei," and in forty-five days several growths appeared which eventually reached the size of small cherries. One of these was excised for further transmission to a *Rhesus*, and in fourteen days tumor growths were noted which finally reached a larger size than in the first animal. Lesions from the second ape were successfully transmitted to still a third animal (a *Rhesus*), where the incubation period was only seven days. This ape died suddenly, autopsy revealing nothing, so that further inoculations had to be made with the almost healed tumors from Ape 2, and they were unsuccessful, though done intravenously. Rabbits, guinea-pigs, rats, white and gray mice, chickens and doves were also further experimented on, but in vain. In all these apes the blood-picture was at all times normal, and neither in them nor in the man was it possible to find in the blood or in the red cells of the tissue fluids any of the inclusion-bodies that have been reported by Basett-Smith,⁷ Galli-Valerio,¹⁶ DeVecchi⁹ and others, though practically all known parasite stains were used. Moreover, in none of the apes did the autopsy show changes that could in any way have been due to *Verruga peruviana*. The cutaneous lesions from both the man and the apes showed the same characteristic histological picture, which will be taken up more in detail in a later paper.¹⁷ Here it will be enough to say that the growths showed a marked vascular proliferation along with the presence of many free red blood-cells in the tissues. Many mono- and polymorphonuclear leukocytes, plasma cells and fibroblasts were noted in the tissues and peculiar lymph-vessels inclusion-areas, thus far imperfectly noted and described, were also seen. By the use of no known tissue parasitic stain was it possible to find any of the acid fast bacilli, cell-inclusion parasites or other organisms that have been described by different men. Odriozola says he has made examinations in two types of patients. In the first class, where there is a cutaneous

16. Galli-Valerio, B.: Observations microscopiques sur la Verruga peruana ou maladie de Carrion; Centralbl. f. Bakteriöl., etc., 1911, lviii, Part 1. Orig. p. 228.

17. A histological study will appear later in the *Journal of Cutaneous Diseases*.

eruption and no temperature, he has always had negative results. In the second type, with eruption and temperature, he has always found a small bacillus. In such classes of patients Biffi, DeVecchi, Barton and others have also found an organism closely related to the paratyphosus bacillus, Type B, and it may be that the negative results are due in this case to the fact that the patient, at least to our knowledge, at no time had any temperature or other especial symptoms of the "*Fièvre grave de Carrion*." Is it possible that Carrion could have been inoculated from a *Verruga peruviana* patient suffering also from a different disease, Oroya fever or "*Fièvre grave de Carrion*," and that he succumbed to the latter before the "*Eruption de Carrion*" had an opportunity to make its appearance? This question and many others in regard to the advisability of separating the affection into two clinical and distinct entities can only be solved by future study with large amounts of material at hand. However, I feel safe in making at least the following conclusions:

CONCLUSIONS

1. In a case of *Verruga peruviana*, *Eruption de Carrion*, there was success in inoculating the disease into apes to the third generation, further transmissions being hindered only from want of material.
2. The lesions from the man and the apes resembled each other very closely histologically, were granulomatous in type and had peculiar lymph-vessel inclusion-areas.
3. None of the organisms mentioned as specific for the disease were found either in the lesions from the patient or from the animals.

2047 East Ninth Street.