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PHLEBOTOMUS AND OROYA FEVER AND VERRUGA PERUANA

HISTORIANS of the early seventeenth century, writing of the conquest of the Incas, refer to the Peruvian Indians as suffering from numerous warts ("verrugas"), varying in size from small red prominences to masses as large as eggs, and covering the face and limbs. Many of Pizarro's soldiers developed the warty condition and died of the fever sometimes attending it. In their ignorance they attributed death not to the peculiar disease but to fish or water supposed to have been poisoned. In earlier times the disease seems to have occurred in regions now in Ecuador, but at present it is confined to the provinces of Lima, Ancachs and Libertad in Peru, lying in south latitude 9° to 13°.

The distribution of the disease is curious. The districts at sea-level and 25 to 35 miles inland are free from it, but as the mountainous parts are approached the disease makes its appearance, and foci or endemic centers are encountered at altitudes of 9,000 feet and over. In certain narrow clefts, called "quebradas," the disease has prevailed in a severe form from early periods, and strangely enough a given village may be severely ridden and a neighboring one a few miles distant may escape entirely.

In 1870, during the construction of the trans-Andean railway, an acute, febrile and fatal disease carried off many thousand laborers in the region between Lima and Oroya. One feature of this destructive malady was an anemia so profound as to have blanched the color of the natives or, in local language, to have changed "blacks" into "whites." Another curious circumstance noted at this time was that the workmen escaped the disease so long as they avoided certain localities at night. A single night passed in these danger zones might be followed by fever and death. Finally, the laborers were removed from them before sunset, and after this was done the disease abated.

This severe disease of the Andes was called Oroya fever, and while it might run its fatal course without other symptoms than fever and anemia, yet at times it was attended by the warty skin affection previously mentioned; or, when recovery occurred, the "verrugas" might appear. Conversely, sometimes the warty disease arose attended only with mild fever and anemia. Because of their frequent association in the same individual and their common geographical distribution, the two conditions, Oroya fever and verruga, came to be regarded in the popular mind as one disease appearing in a malignant and in a benign form.

The identity of the two forms was, however, a controverted point, and to settle it a medical student, David Carrion, in 1885, inoculated himself on both arms with tissue juice taken from "verrugas." He developed Oroya fever and died. Since this self-sacrificing experiment the malady has often been called Carrion's disease. In 1905 a Peruvian physician, Barton, discovered in the red blood corpuscles of Oroya fever patients certain rod-shaped bodies resembling bacilli, and later similar rods were detected in small numbers in the blood of verruga patients. These bodies were named *Bartonella bacilliformis* by the Commission of the Harvard School of Tropical Medicine in 1913 and regarded by them not as bacterial but as protozoal organisms. Many attempts were made to develop the rods in artificial cultures but without success. Such bacteria as were cultivated proved to be either secondarily invading organisms (paratyphoid bacilli) or extraneous contaminants. That the verrucous disease can be transmitted by inoculation from man to monkey has been known since 1909, but the Harvard Commission was unable to detect any of the rod-shaped organisms either in the human warts or in those induced in animals.

In 1925 Dr. T. S. Battistini, a Peruvian fellow of the Rockefeller Foundation, brought to one of us (Noguchi) a specimen of blood taken from a case of Oroya fever. The red corpuscles of the blood contained the rods, and cultivation experiments were undertaken which resulted successfully (Noguchi). The microorganisms obtained in the cultures reproduced on inoculation into monkeys and apes experimental diseases agreeing with both Oroya fever and verruga. Subsequently the microorganism was isolated from the blood of two other cases of Oroya fever and seven of verruga peruana, and from the skin nodule in a case of verruga (Noguchi). The bacterial incitant of the disease was now isolated, and the important fact determined that, as grown outside the body, it was capable of infecting monkeys, in which could be induced the two characteristic manifestations of Carrion's disease.

The one essential point which remained to be established in order to account for the origin of the disease was the mode of infection. Indications pointing to direct transfer from person to person were wanting, while evidence implicating insects in the transmission existed. The strict limitation of the endemic zone of the disease and the nocturnal dangers pointed to an insect source of inoculation. This aspect of the subject had been investigated in 1913 with remarkable energy and penetration by Charles H. T. Townsend, an American entomologist. He gave consideration to all kinds of blood-sucking insects to be found in the verruga zone, and, after excluding one and another variety of insects, finally, in a brilliant manner, concentrated attention on certain blood-sucking gnats of the class Phlebotomus. By excluding all insects whose range extends outside the verruga zone, he reduced the possible carriers to buffalognats, horseflies and phlebotomi, and by excluding the insects which bite by day as well as by night, he reduced the possible verruga vectors to phlebotomi alone. So certain did he feel of his discovery that he called the gnat *"Phlebotomus verrucarum."* Townsend went one step further in attempting experimental induction of verruga in dogs and man by means of phlebotomi. It is doubtful whether he actually succeeded in this undertaking.

With the artificial cultivation of the rods, the mode of transmission was opened to rigid experimentation. One of us (Noguchi) discovered that *Bartonella bacilliformis* can be taken up by the wood tick from the blood of an infected monkey and be transferred to a healthy monkey through bites. Probably this is a purely mechanical process without significance so far as the natural insect vector of Carrion's disease is concerned. The next step was actually to test insects from the verruga zone in Peru. The International Health Division of the Rockefeller Foundation was invited by the Department of Health of Peru to send an entomologist to Peru, and one of us (Shannon) spent five months there studying insect life in the verruga zone and collecting and sending to the Rockefeller Institute insects for purposes of inoculation, according to a plan arranged by Dr. Noguchi before he sailed for Africa to study yellow fever. The phlebotomi collected and identified consisted of *Phlebotomus verrucarum* Townsend and two new species named respectively *P. noguchii* and *P. peruensis,* which are readily differentiated from each other and from *P. verrucarum* by the sex characters of the males. Only the females are blood-suckers, however, and those of *verrucarum* and *noguchii* are indistinguishable, hence some doubt must remain whether the females of both species carry *Bartonella bacilliformis.* We are confident that the females of *P. noguchii* are carriers, and we think that *P. peruensis* is probably not a carrier.

Other blood-sucking insects which were tested by inoculation are ticks (Argasidae), mites (Trombidium), midges, sheep lice, bird lice, bedbugs, mosquitoes (*Anopheles pseudopunctipennis* and *Culex fatigans*), buffalognats (*Simuliidae*), flies (*Stomoxys calcitrans*), "sheep ticks" (*Melophagus ovinus*), Streblidae of blood-sucking bats, and fleas of guinea-pig and dog. None of these was found to harbor *Bartonella bacilliformis.*

The plan followed was to inject saline suspensions of the crushed insects into the skin of *rhesus* monkeys. No verrucous nodules developed. At regular intervals thereafter cultures were made from the blood of the inoculated monkeys with a view to determining whether the Bartonella had entered the blood and multiplied in it. Four different lots of phlebotomi, as tested in this way, were proved to carry *Bartonella bacilliformis*. In the first instance the culture was obtained with blood withdrawn from the inoculated monkey on the 19th day, in the second on the 20th day, in the third on the 10th day, and in the fourth on the 42nd day. The inoculation of monkeys with the cultures thus obtained produced experimental verrucous nodules, with recovery of the Bartonella from the blood and the nodular tissue. The chain of evidence uniting Phlebotomus with Oroya fever and verruga peruana may be said to have been completed by these tests.

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THE RELATION OF RESEARCH TO WEALTH PRODUCTION[1]

WEALTH is produced by the performance of work upon the materials of nature as we find them on and in the earth's crust. In the term work is included not only the actual physical work done by men and machines, but also the work performed by capital, and this includes the use of money and of the facilities which money purchases. Wealth then represents an accumulation of something above actual requirements for maintenance and is usually represented by some form of money or negotiable exchange. The extent to which research contributes to wealth might, therefore, be discussed from the point of view of the increased possibility of producing from natural resources desirable commodities in excess of immediate requirements, and we at once think of the extent to which savings have been made in the physical labor required in carrying out the industrial program of the world.

While for the purposes of discussion wealth may be taken in this case as something measured by dollars, nevertheless the less tangible but equally important contributions of science to things cultural and even spiritual must not be overlooked, and because of these factors a complete evaluation of the contributions of science is well nigh impossible. To attempt to measure in terms of wealth as it is usually understood the value of a local anesthetic, the beauty of a synthetic color, the pleasure of a synthetic scent or the value of a medicinal produced from a coal-tar base becomes an absurdity. While statisticians have succeeded in arriving at figures which express the probable value of a life in terms of earning power or cost of development and education, we are still unable really to value a life in terms of money, and the close relationship between modern science and the life of our age makes it equally impossible really to measure the contributions of research to wealth, when considered in the broadest sense.

But to revert to the subject of eliminating drudgery, of doing by chemistry, physics and mathematics as applied to industry much of the work which formerly required endless hours of time. It is fairly well agreed that an enormous amount of human energy was expended in the construction of the pyramids and in beautifying ancient Greece and Rome, but it is doubtful whether any modern agency could afford to lavish the labor of hundreds of thousands of human beings on such an enterprise. It is only when the world is at war that such great blocks of labor are employed for a common end. In those ancient days slavery was held to be justified because slave labor enabled the patrician and the philosopher to have the necessary leisure to make their type of contribution to the welfare of the state. It is doubtless true that through the contributions of science the average individual to-day has an amount of leisure far beyond that experienced at any other period of the world's history, and an increase in leisure is almost directly in proportion to the contributions which science makes in the perfection of industrial processes and means for doing the world's work. Indeed, many hold that the vital problem of our times is the manner in which this additional leisure is to be invested, and we progress or retrogress as we employ this leisure constructively or destructively.

Our telephone companies carry some twenty billion communications a year, these messages covering more than fifty billion miles and involving work which if performed by messengers working nine hours a day, making a high average of ten miles per hour, would require seven million individuals at a cost of eleven billion dollars. The contributions of a long line of research workers enter and we see this labor performed by a few hundred thousand em-

[1] Read before the general session of the association devoted to the work of the Committee of One Hundred on Scientific Research at the Nashville meeting.