TEMPERATURE VARIATION AND LEPROSY DEFORMITY

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In its morbid histology, leprosy has much in common with tuberculosis and other granulomata. It is in the distribution of its lesions throughout the body that it is unique. Its predilection for the skin is so apparent that it is commonly treated in departments of dermatology. Its selective effect on peripheral nerves has earned it the title of a "disease of the nervous system" by Khanolkar and others. The freedom of the lungs, the gastrointestinal tract, the cardiovascular system, and the central nervous system from involvement by the disease is so striking that most observers have concluded that leprosy is a disease which attacks certain tissues only, and that other tissues of the body are immune from its destructive effects.

During the past few years I have had the opportunity of observing the exposed tissues of leprosy patients during the course of more than 2,000 reconstructive operations on their limbs and faces. The opportunity has been used to make numerous biopsies of all of the exposed tissues in the damaged and deformed areas, and also of tissues in undamaged parts of the body where we had to operate to obtain healthy tissue for grafting.

It soon became clear that, at least so far as the limbs and face were concerned, there was neither tissue specificity for nor tissue immunity to the damaging effects of the disease. Although certain tissues were more severely and perhaps more regularly damaged than others, all tissues showed damage from time to time, and the type of damage when present was remarkably uniform, no matter what the tissue might be. It was a low-grade inflammatory response in which the tissue was first invaded and later sometimes replaced.

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by a nonspecific type of chronic inflammatory, granulomatous infiltrate. The type and severity of the infiltration vary with the type of leprosy, especially in the subepidermal layers of skin, but in most tissues the changes vary in degree rather than in type. These changes have been seen in connective tissue, tendon sheath, tendon, joint capsule, synovial membrane, bone, cartilage, nerve and nerve sheath, skin, mucous membrane, testes and lymph nodes. Immunity seems to occur only with depth. In the deeper parts of a limb, we have never found any evidence of damage from leprosy. Conversely, in areas under the skin, e.g., underneath the skin of the knuckles on the back of the hand, all tissues seem to be particularly susceptible to damage.

Depending upon the type and severity of the disease, the zone of susceptibility to damage seems to extend down to anywhere from 5 mm. to 1 or 2 cm. from the surface of the skin. At first I attributed this phenomenon to the influence of trauma, on the assumption that leprosy itself might exist without damaging the tissues until the tissues were weakened by some form of traumatic injury. This trauma would naturally be more severe near the surface of the body than deeper. The inadequacy of this theory became apparent with more careful study. Many of the most severely damaged tissues were sheltered from obvious trauma, as for example the cartilage on the inside of the nose and the septum.

It was the study of the nose, and the nasopharynx and larynx, that suggested an alternative hypothesis. The lining of the nose and the upper respiratory passages are constantly cooled by evaporation as a stream of air is drawn across its moist surface. Temperature measurements with a thermocouple demonstrate that the lining of the nose is one of the most regularly cold parts of the body. It is also one of the most regularly damaged areas in a leprosy patient. The lower end of the alimentary canal is morphologically not dissimilar to the upper end. The epithelial linings of the mouth, nasopharynx and anus are histologically similar, but the anus does not have a stream of cool air drawn inwards over its surface. It is undamaged by leprosy. Might it not be true that it is variation in temperature that determines the susceptibility of a tissue to damage from leprosy?

Spermatogenesis is the one function of the human body which requires a temperature lower than normal body temperature. The testes are therefore so placed that the whole of their substance is sufficiently superficial to remain below normal body temperature. Is it coincidence that the testis is the only true gland in the body which is regularly damaged by leprosy?

One of the most interesting and baffling problems in the pathology of leprosy is set by the pattern of motor and sensory loss in the disease. There is a superficial and patchy anesthesia which may occur anywhere on the surface of the body and which is secondary to
the involvement of sensory nerve endings in an affected skin area. In addition to this haphazard superficial anesthesia, there is a more severe paralysis of larger nerve trunks causing total anesthesia and motor paralysis. This nerve paralysis is absolutely regular in its pattern, always affecting the same nerves and always in the same places.

Because, in the design of operations for reconstructive surgery in the limbs, these nerves were of importance I have had reasons to study them in detail. All of the nerves so affected are superficial, but not all superficial nerves are paralyzed. In order to account for the regularity of the pattern I first tried to invoke trauma as the deciding factor, but it became obvious that the pattern was far too regular to be determined by anything so unpredictable as trauma. Besides that, some of the most severely affected nerves were in positions where they would be unlikely to be exposed regularly to injury. Proximity to joints was another factor common to many but not to all of the nerves. A reasonable explanation suggested itself only after the mechanism of nerve paralysis in leprosy had been worked out.

The transmission of nerve impulses in affected nerves has been studied by stimulation of exposed nerves at operation. This study revealed that in its early stages the paralysis is a block to conduction unaccompanied by Wallerian degeneration, i.e., it is not caused by loss of continuity of the nerve fiber. As in the case of the nerves of the experimental animals investigated by Denny Brown, of Boston, these nerves are paralyzed by ischemia. The ischemia is secondary to edema and cellular infiltration. Edema and cellular infiltration do not cause ischemia of a nerve fiber if the latter is free in loose connective tissue. Severe ischemia, however, occurs in a nerve bundle in which a large number of fibers are bound together within one sheath.

Examination of autopsy specimens has demonstrated the fact that in a limb where the disease is widespread, every nerve within a certain critical distance of the surface of the skin is infiltrated, and that at equal depths from the skin thick nerve trunks suffer more damage than thin ones. Tests upon living patients have demonstrated that not all infiltrated nerves are paralyzed. Nerve bundles composed of only a few fibers may be near the skin, may be severely infiltrated, but may remain unparalyzed. Thicker nerves which are infiltrated are regularly paralyzed.

The peculiar pattern of paralysis in leprosy is due to the fact that two independent factors are operating. The infiltration of the nerves causing the swelling around the fibers is inversely proportional to the depth from the skin; and, given an equal degree of infiltration, the thinner the nerve trunk the less it is likely to be paralyzed.
It so happens that most nerves, by the time they become superficial, are divided into slender filaments. Conversely, most thick nerves are more deeply placed in the body. Thus the infiltrated nerves near the skin may escape paralysis because they are thin, and the thick nerves deeper down escape paralysis because they are not infiltrated. When a thick nerve trunk does approach near to the surface of the skin, as occurs in certain situations in the limbs, that nerve is regularly at risk from paralysis. Certain nerves, such as the ulnar and the posterior tibial, pursue a course in which they are superficial for a short distance in the proximal part of the limb, and then become deep beneath a muscle belly, subsequently again becoming superficial in the distal part of the limb. Such nerves on dissection show very beautifully the relationship between depth from the skin and the degree of abnormal swelling.

In the case of tendons, the most severely affected ones are those which are flattened over the surfaces of the knuckles of the fingers and lie within 2 or 3 mm. of the skin. Tendons on the back of the wrist are affected to a lesser degree, whereas tendons in the carpal tunnel are seldom damaged and those still more deeply placed in the limb are never affected. On the back of the wrist there is a point at which the extensor pollicis longus tendon crosses the radial extensors of the wrist. The extensor pollicis longus may be affected over the whole of its length, but the extensors of the wrist are infiltrated only proximally and distally to the point where they cross under the pollicis tendon. At that one point only, where they are slightly deeper than elsewhere, they are free from infiltration.

Bone is affected in leprosy by the infiltration of the medulla, and of the spaces between the trabeculae of cancellous bone. This infiltration gives rise to hyperemia and to absorption of the trabeculae. X-ray examination at this time will show osteoporosis and decalcification, and loss of some trabeculae. The decalcification and osteoporosis of leprosy are observed only in superficial bones, such as the phalanges and the bones of the wrist and of the tarsus.

It should be noted that the infiltration of bone by leprosy does not cause gross destruction of the bone, but increased fragility secondary to the osteoporosis and absorption of trabeculae. If affected hands and feet are carefully splinted while they are in this stage, they may be preserved without gross damage until recalcification takes place.

Cartilage seems to be affected by leprosy only when it is within 2 or 3 mm. of the skin. Joint cartilage is usually unaffected (apart from trophic change) except in the interphalangeal and metacarpophalangeal joints, where it is nearly subcutaneous. The only cartilages which are regularly destroyed are those which are intimately adherent to skin, as in the ear and in the lining of the nose and the nasal septum.

The hair follicles of the skin are attacked in leprosy. Soft downy hair which has very superficial roots is lost early. Hair which has
deeper follicles, such as eyebrow hair, is lost as the disease progresses. The hair of the scalp, which has very deep follicles indeed, is usually not lost in leprosy. In Japan, Korea, and China leprosy alopecia occurs in the scalp. I do not know whether this is associated with a more severe type of leprosy or with a more superficial placement of hair follicles in the Mongolian race, but it is interesting to note that even in cases where these deeper follicles are affected by the disease, there seems to be protection for those follicles which lie along the line of the major scalp arteries. The big arteries of the scalp are outlined by a growth of hair, rather as a river is marked by the growth of trees. This finding is consistent with the theory that there may be a sufficient temperature difference between the area immediately surrounding a great vessel and one that is further removed, to allow protection to some hair, and not to the rest.

The only tissue which seems to be affected by leprosy in the deeper parts of the body is the reticuloendothelial system. There is sometimes a toxic change in the liver which is concentrated in the reticuloendothelial areas. I was interested to note that Riddle in his studies on the liver has recently pointed out that the changes in the liver seem to coincide with destruction of *M. leprae* in the body, rather than with multiplication. He has suggested that the liver is concerned with the destruction of the bacilli, or at least with the removal of bacillary debris and toxins. Damage that may occur in the liver therefore is not a sign of the activity of the disease itself. I have discussed this matter with Riddle, and his conclusions seem to be so reasonable that they have removed the one difficulty which has up till now prevented me from publishing my conclusions with regard to the effect of temperature on the activity of the leprosy bacillus.

It has often been pointed out in discussion that if this theory is true, patients in cold countries should suffer much more severely than patients in hot countries. I do not suggest that leprosy deformity increases with cold, or that leprosy activity is greater when the temperature is lower. It seems to me that there is probably an optimal temperature for the growth and activity of the leprosy bacillus, and that this optimum is just below body temperature, perhaps only 2 or 3 degrees.

Ordinary mechanisms of heat control maintain the temperature of the body and the skin within certain limits. This occurs in hot climates by sweating from the surface of the skin, thus bringing superficial tissues down to the temperature which is optimal for the leprosy bacillus. It is doubtful whether a further lowering of the temperature due to external environmental conditions would make a very striking difference. In any case, the response of a human being to this type of environmental condition is to add clothing which tends to maintain the skin at a reasonable temperature. Spermatogenesis only occurs in the
human testes at temperatures below normal body temperatures. This does not mean that people in hot climates are sterile, nor that cold increases fertility.

Many of us have noticed, however, that deformity does seem to increase in cold weather. I have had patients who have developed claw hands in successive winters, recovering in the following summers. This association between cold and increased deformity is not a regular finding, but it happens frequently enough to be significant.

I put this theory forward at the present time in a preliminary and suggestive form so that it may be followed up by bacteriologists who are seeking to cultivate the bacillus. It may also have applications in therapy, because, although it would be impossible to maintain the whole of the surface of the body continuously at body temperature, which would be fatal, it may be possible to maintain certain critical parts of the body at a higher temperature so as to avoid certain serious deformities in especially susceptible parts.

**SUMMARY**

An explanation of the selective distribution of the lesions of leprosy is offered on the basis of observations on tissues studied at operation and at autopsy. Tissue damage is not selective with respect to the nature of the tissues affected, and changes themselves vary in degree rather than in kind, which primarily is chronic inflammatory.

Freedom from involvement depends on depth from the surface, and therefore on temperature. This explains, for example, why the lining of the nose is so regularly damaged in leprosy; and why the ulnar nerve is so much affected where shallow at the elbow and wrist but not in the forearm where it is covered by a muscle belly.

With special reference to nerves, the irregularity of their functional alterations is discussed. All nerves that are paralyzed are superficial, but not all superficial nerves are so affected. In its early stage paralysis is not due to Wallerian degeneration, but rather to block caused by ischemia, and the ischemia results from inflammatory infiltration. The occurrence and degree of infiltration depend on depth, and more damage occurs in large nerves than in small ones because the latter are apt to be looser and less liable to harmful compression from the swelling.

Similar considerations apply to affection of tendons, bones, cartilages, and hair follicles of skin and scalp. Possible effects of climate are discussed. This factor of temperature may be of importance in attempts to cultivate the leprosy bacillus. It may also have limited application in therapy.

**RESUMEN**

A base de las observaciones verificadas en tejidos estudiados al operar y en la autopsia, se ofrece una explicación de la distribución selectiva de las lesiones de la
lepra. El daño a los tejidos no es selectivo con respecto a la naturaleza de los tejidos afectados y las alteraciones mismas varían en intensidad más bien que en género, que es primariamente inflamatorio crónico.

La extensión de la invasión depende de la profundidad desde la superficie, y por consiguiente de la temperatura. Esto explica, por ejemplo, por qué el recubrimiento de la nariz es lesionado regularmente en la lepra; y por qué el nervio cubital se ve tan afectado donde es superficial como en el codo y la muñeca, pero no en el antebrazo donde lo protege el vientre de un músculo.

Con referencia particular a los nervios, se discute la irregularidad de sus alteraciones funcionales. Todos los nervios que se paralizan son superficiales, pero no se afectan así todos los superfi ciales. En su período inic平安, la parálisis no se debe a degeneración walleriana, sino más bien al bloqueo ocasionado por la isquemia y la isquemia proviene de la infiltración inflamatoria. La existencia y la intensidad de la infiltración dependen de la profundidad y se reviste más daño en los nervios grandes que en los pequeños, por ser los últimos más propensos a la laxitud y menos susceptibles a la compresión nociva derivada del edema.

Razon consideraciones semejantes con la afectación de los tendones, los huesos, los cartilágenos, y los folículos pilosos de la piel y del cuero cabelludo. Se discuten los posibles efectos del clima. Este factor de la temperatura puede revestir importancia en los esfuerzos dedicados a cultivar el bacilo leproso. Puede tener también aplicación limitada en la terapéutica.