# LETTERS TO THE EDITOR

30th April, 1963

(1) From DR. S. G. SPICKETT

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*on the 'Weddell Theory'.*

Dear Sir,

The recent paper of WEDDELL and PALMER[1] raises a number of important issues and although they have received some discussion elsewhere[2] I should like to comment on two problems relevant to my own work[3,4,5].

If the portal of entry of *Mycobacterium leprae* is not the skin, but rather the alimentary and respiratory tracts, then the site of the first cutaneous manifestation of leprosy can bear no relationship to the site that is most likely to come into contact with a lesion of an affected individual. The 'Weddell Theory' argues that the bacilli are distributed by way of the circulation to the sensory nerves and that the site of the first lesion is determined by neural turn-over and hence is very frequently induced by trauma. The problem as to whether the site of the initial lesion is random, associated with skin to skin contact or associated with areas of high neural turn-over might not be easy to solve unequivocally, but should be amenable to some degree of resolution by a careful analysis of the locations of intial lesions.

The widely held view, that the portal of entry is the skin and that the bacilli are acquired from skin to skin contact, is based on a great mass of observation to the effect that the initial lesion is very frequently at the site of skin to skin contact with an infected individual. Perhaps the clearest example of this is in the high frequency of forehead lesions in African infants as compared with Korean infants, where the mother is the infected contact. In the Africans the back of the mother is naked and in prolonged contact with the child's forehead whereas in the Korean mothers the back is clothed and there is no skin contact. Although these observations are not the result of carefully designed surveys they cannot be disregarded and the evidence they give is clearly in favour of the skin as the portal of entry.

WEDDELL and PALMER concede that the portal of entry may be the skin through cuts, abrasions, insect bites and the like, but it is implied that this is an exceptional circumstance. There have been many attempts to incriminate certain arthropod vectors. Transmission by arthropods is a persuasive hypothesis, and it may well be that many arthropods are capable of effecting transmission of the bacilli but here also there is the difficulty that some of them, e.g. the

mosquito, do not fit the observations consistent with skin to skin contact. One arthropod in particular (*Demodex folliculorum*) does satisfy all the criteria demanded of a transmitter and moreover there is the supporting evidence of bacilli having been seen in its gut at a time in its life cycle when it may penetrate to the dermis. Since this parasite is ubiquitous in man its role in the transmission of leprosy could be sufficient to explain the very large numbers of cases where the disease does appear to be acquired by skin to skin contact.

The evidence of WEDDELL and PALMER does appear to establish that *M. leprae* may be disseminated throughout the body by the circulation, and this being so one of the major problems connected with a respiratory or alimentary portal of entry is solved. However this does not in any sense provide evidence that such portals of entry are used and it is difficult to see how the type of evidence that WEDDELL and PALMER have produced can provide such evidence.

The second point I should like to raise relates to the problem of 'natural immunity'.

It is now apparent that resistance and susceptibility to leprosy are, in part, attributable to genetic variability in the human host[4,5]. It has been shown that a single irregularly dominant gene controls susceptibility to leprosy and that the penetrance of this gene varies between populations[6]. Although the main effect is due to a single gene, irregular dominance and variation in penetrance between populations implies a strong possibility of there being other genes influencing susceptibility. Furthermore, environmental variation may be of considerable importance in the determination of resistance and susceptibility. This then is one mechanism of 'natural immunity' but nothing is known as yet of the way in which the genes exert their effects. It may be that the gene controls the ability of the body to produce antibody to *M. leprae*; it may be that the control is over some aspect of the chemistry of the host cell that is essential to the pathogen. Moreover there is another genetic system influencing the course that the disease may take, e.g. whether it is lepromatous or non-lepromatous in expression, or whether there are severe reactions or not. The point at issue is that there are many genes in man affecting the relationship with *M. leprae*, and many of them affect what is loosely termed 'natural immunity'. It is therefore clear that natural immunity in man to *M. leprae* is a very heterogeneous phenomenon. Similar levels of 'natural immunity' may be gained through different mechanisms controlled by different genes and it will be difficult to make useful reference to natural immunity until it can be specified in pathological and genetic terms. The studies of WEDDELL and PALMER may well come to demonstrate the way in which some of the genes act, provided that some work is done on genetically specified material.

Most of the genetic variation between races and populations is quantitative rather than qualitative. The variation is in the frequency of particular genes rather than in the possession of genes unique to them. It is probable that the bulk of the inherited variation between races, with respect to leprosy, is due to variation in gene frequencies. Racial variation in leprosy is therefore a strong indication of individual variation. Distinction between 'racial immunity' and 'natural immunity' is therefore artificial when applied to the pathogenesis of leprosy since the same mechanisms are covered by both terms.

S. G. SPICKETT

**References**

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