

THE TUBERCULIN REACTION

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The Therapeutic Substances Act includes under the term tuberculin "preparations of fluid media on which the *Bacillus Tuberculosis* has been grown in artificial culture and which have been freed by filtration from the bacilli." There are other preparations consisting of bacilli, or products of their disintegration obtained by physical and chemical action, which have at times been called tuberculins, but these substances are now rarely used and by tuberculin we usually mean either Standardized Old Tuberculin (O.T.) or Purified Protein Derivative (P.P.D.) The choice between these two tuberculins lies with the physician. Most of the surveys and investigations on humans in this country have been done with Old Tuberculin and the majority of veterinary work is done with P.P.D. The relative superiority of the one tuberculin over the other is claimed by the respective enthusiasts. It is probable that P.P.D. has more advantages and fewer disadvantages than O.T. and it is possible that in the future it will be used more widely. Whichever tuberculin is used the reaction depends on the specific allergic response of the body tissues to the products of growth of the tubercle bacillus. The specificity of the reaction was in the past generally accepted but recent work has shown that non-specific reactions are not uncommon with lower dilutions of Old Tuberculin, furthermore the borderline between a positive and negative reaction is still too broad, irrespective of the technique employed. There is little difficulty in defining a definitely positive reaction. It can be said to be an induration of 5 mm. or more diameter with the Mantoux technique, induration with three or more vesicles with the Jelly patch flourpaper test, and six definitely indurated papules with the Heaf multiple puncture method. Any reaction less than these is doubtful or negative. With the Mantoux Technique we have to decide the lowest dilution that must be used to exclude a negative reaction. The World Health Organisation has agreed to use as the final test 1/2000 dilution of standardized O.T. (5 International Tuberculin Units) in all tropical countries. The Medical Research Council require 1/100 dilution O.T. (100 I.T.U.) for the final test, and in other countries 30 I.T.U. is the strength of the last test. It is important that in recording the results of the test the type and dilution of the tuberculin are stated and the technique used. The recent work of Edwards and Palmer (1953) shows

that low grade tuberculin sensitivity is associated with geographical factors. They are inclined to believe that there is an unknown non-specific factor that causes low grade sensitivity. It is more likely that the frequency or infrequency of a super-infection resulting from the degree of exposure to infection is one of the factors and that the variation in the character of the skin may be another agent influencing the results they obtained in various countries. The variation of the degree of tuberculin sensitivity with altitude can be explained by this frequent or infrequent re-infection factor as it is directly proportional to the density of population.

The tuberculin sensitivity of body tissue that has been infected with tubercle bacilli can be depressed by drugs, hormones or the products of other bacteria. D'Arcy Hart, Long and Rees (1952) noted that polyoxethylene ethers diminished sensitivity to the same degree but not in the same manner as cortizone. The action of the latter substance is dependent on dietary factors, as it is ineffective in guinea pigs fed on a cabbage diet. A similar depressant action is noted when animals on a diet deficient in ascorbic acid are given free ascorbic acid, but this depressant action is prevented by giving cabbage (Long, Miles and Perry 1951). Variation in tuberculin sensitivity may be noted in pregnancy and puerperium. Thyroxin will also reduce the sensitivity of tissues, whilst indian ink and certain dyes exert a local effect on the capillaries which reduce the inflammatory reaction following the introduction of tuberculo-protein into tuberculous tissue.

The tuberculin reaction is not a simple phenomenon that gives a clear definition on the presence or absence of tuberculous infection. The true positive reaction may be taken to indicate the presence of live tubercle bacilli in the body tissues; a negative reaction does not necessarily mean the absence of such infection. Assuming that the technique is correct a negative tuberculin reaction may occur under the following conditions:—

- (a) In the absence of tuberculous infection.
- (b) Where tuberculosis infection has taken place but
 - (1) complete sterilization of the lesion has occurred.
 - (2) insufficient time has elapsed since infection for allergy to have developed. The development of sensitivity usually takes from three to six weeks.
 - (3) The disease is so active and advanced that the tissues are saturated with tuberculo-protein.

- (4) The sensitivity has been depressed by
 - (a) concurrent infections, e.g. measles.
 - (b) drugs or hormones.
- (5) The tissue refuse to develop sensitivity for some unknown reason. That this occasionally occurs can sometimes be demonstrated after B.C.G. vaccination.
- (6) The tissues may have been artificially desensitised by:—
 - (a) repeated small doses of tuberculin.
 - (b) a single large dose of tuberculin.

This last method of desensitising is being used experimentally as an adjunct to treatment with antibiotics; the theory being that in the absence of sensitivity the fixation of the infecting tubercle bacilli in the tissues with the accompanying inflammatory and caseous reactions will be eliminated, so allowing easier contact of the antibiotic with the bacilli. Much more work will have to be done before this form of treatment can be accepted, as it is at present not without risk of producing progressive lesions which the antibiotic may not be able to control.

Certain factors have to be borne in mind when using the tuberculin test for determining the presence of tuberculous infection. First the possibility of a non-specific reaction arising from the injection of other proteins than tuberculo-protein. The frequency of this can be reduced by using Purified Protein Derivative tuberculin. Secondly the assumption that the skin gives an accurate measure of the sensitivity of the body tissues generally, and thirdly that the skins of all infected people will react similarly to infections of tubercle-protein. The great difference in the sensitivity of the skin of the guinea pig compared with that of the cow makes it reasonable to assume that the skins of different human races and even of individuals of the same race will show varying degrees of response to tuberculin infections.

In routine work the tuberculin reaction is sufficiently specific to be of practical value, but where scientific investigations are contemplated consideration must be given to all the known factors that influence the response of the tissues to tuberculo-protein.

1. EDWARDS, L. B., PALMER, C. E. (1953) *Lancet* i 53.
2. HART, P. D., LONG, D. A., REES, R. J. W. (1952) *B.M.J.* i 680.
LONG, D. A., MILES, PERRY (1951) *Lancet* i 1085.