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Vesiculation - Its Occurrence in the Differential Tuberculin Test

by

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SUMMARY During surveys of the differential tuberculin test in population groups in Ceylon, it was found that the occurrence of large reactions, painful swellings around reactions and vesicles and bullae at injection sites were causes of much distress to the subject. The occurrence of such reactions, in addition, interfered with investigations, as untested subjects refused to volunteer for testing when such reactions occurred among individuals (who had permitted testing) in their neighbourhood.

It was found that vesiculation occurred usually with PPD-S, from *Myco. tuberculosis* (with the exception of one case where it occurred with both PPDs S and Y and in another with PPD-G in a leprosy patient). Vesiculation occurred most commonly in tuberculous patients followed by leprosy patients and least commonly in the general population. The occurrence of vesiculation appeared to be much less common in Ceylon than in Denmark.

INTRODUCTION

A large tuberculin reaction, or even a moderate one with a degree of surrounding swelling and inflammation, could be a source of pain and distress to the subject. Even greater is the anxiety when the reaction is accompanied by the appearance of vesicles or necrosis at the test site. In the past much attention was focussed on the qualitative aspects of the tuberculin reaction (such as consistency, surrounding erythema, etc.). In more recent years this aspect appears to have been neglected while the emphasis has shifted to the quantitative aspect (the dimension of the reaction). The latter trend was perhaps a necessary corollary to the launching of world-wide, large scale tuberculin surveys which were carried out to define the parameters of the test and to assess its efficacy. The subjective characteristics of the qualitative assessment and the difficulties of comparing such assessment made by different workers in such surveys in various parts of the world, were factors probably responsible for the diminishing importance attached to the qualitative aspects of the test. In recent large scale studies of the differential tuberculin test in different population groups, carried out in Ceylon, the occurrence of vesiculation was an unwelcome complication which led to adverse publicity and resistance to the test on the part of the population.

This study is an evaluation of the incidence and possible significance of vesiculation as seen in the differential tuberculin test in various population groups.

MATERIALS AND METHODS

The subjects studied were drawn from four different population groups (Table 1) examined by the differential tuberculin test in recent studies in Ceylon and reported elsewhere (Pinto, Arseculeratne, Uragoda & Hemawardena 1972, 1973 ; Pinto, Arseculeratne & Uragoda 1973 ; Pinto, Arseculeratne & Weliange, 1973). Each subject was administered four Purified Protein Derivative (PPD) antigens by the standard Mantoux technique (WHO, 1963); some subjects refused one or more injections. Each individual was usually given PPDs S and G and two others. The PPDs used (kindly gifted by Dr. Lydia B. Edwards of the United States Public Health Service) were as follows :

PPD S — from *Myco. tuberculosis*

Y — from *Myco. kansasii* (Runyon's Group I)

G — from ' Gause ' strain Scotochromogens (Runyon's Group II)

B — from ' Battey ' bacilli (Runyon's Group III)

A — from *Myco. avium* (Runyon's Group IV) (this antigen was not used in the case of leprosy patients)

F — from *Myco. fortuitum* (Runyon's Group IV)

TABLE 1

Reaction Patterns of Individuals Showing Vesiculation

Subject group	Age	Sex	Reactions to different antigens Reaction diameter/Vesicle diameter S	Y	G	A	B	F
Non-vaccinated general population. Total tested 1275								
High altitude 6500 ft.	27	F	24/10		17	21		8
	35	M	23/13		17		15	5
	39	M	19/7	14	10		8	
	36	F	16/5		11		7	0
	40	M	22/10		6		0	0
	41	M	28/20	18/12	10	12		
Mid altitude 1500 ft.	24	M	18/9		9		10	7
	24	F	15/3	14	15	12		
	25	F	21/16		18			7
	53	M	45/14	12	18			6
	60	M	50/25		26	23	19	
Sea level	21	M	23/12		9	11		0
	28	M	15/5mm (S.V.)		10	9		7
	34	M	17/12	12	14			0

(Continued)

TABLE 1 (Continued)

Subject group	Age	Sex	Reactions to different antigens Reaction diameter/Vesicle diameter S	Y	G	A	B	F
BCG vaccinated general population. Total tested 147			No individuals showed vesiculation					
Tuberculosis patients. Total tested 248	35	F	25/20		other antigens not given			
	15	F	20/8mm (S.V.)	16			12	10
	17	F	20/10		16		14	1
	22	M	17/3	12	8	10		
	20	M	17/11	11	16			12
	23	F	19/10		14		15	8
	34	F	18/7	14	15			6
	36	M	18/3mm (S.V.)	7	5		10	
	42	M	27/7mm (S.V.)		13	13		5
	42	F	20/7mm (S.V.)	2	6		4	
	50	F	16/5	20	18		8	
	45	M	16/10	14	10	10		
	55	F	22/8		7	8	6	
	65	F	27/10	16	20	20		
Leprosy patients Total tested 153	45	M	8/8	4	8		11	
	45	F	15/6mm (S.V.)	10	15		10	
	45	F	0	2	18/*			4
	48	M	20/5mm (S.V.)	11	11		9	

S.V. = small vesicle

*S.V. = actual dimensions not recorded.

The reactions were read as the maximum palpable transverse induration 48-72 hours after injection. At the same time the presence of vesiculation was noted. Vesiculation is defined as the presence of single or multiple fluid containing blebs (or bullae) of any size situated at the test site. Vesiculation was recorded by measuring the maximum transverse diameter of the bleb when single, or the vesiculated area when multiple bullae were present. Where the bleb had ruptured and a dried crust or denuded area had formed, the maximum diameter of the latter was recorded as the diameter of vesiculation.

RESULTS

Vesiculation occurred with PPD–S only, except in two instances where-in one case it occurred with both PPDs S and Y (in a member of the general population) and in the other with PPD-G in a leprosy patient. The occurrence of vesiculation in the unvaccinated and vaccinated general pupulation at different altitude levels, in tuberculosis patients and leprosy

patients and the pattern of reaction sizes in the different individual subjects are presented in Table 1. The relationship of vesiculation to age and sex is shown in Tables 2 and 3, respectively. The correlation between diameter of vesiculation and that of induration in case of reactions to PPD-S is shown in Fig. 1. Here it is apparent that though vesiculation occurred usually with reactions showing large induration, the occurrence of large reactions was not necessarily associated with vesiculation. The smallest diameter of induration to PPD-S, which was associated with vesiculation was 15 mm, except in a leprosy patient where vesiculation occurred in association with an induration of 8 mm. Bullae size appears to increase with induration diameter when vesiculation does occur.

TABLE 2

Age Distribution of Vesiculators to PPD-S

Subject group	Age group — age in years				
	12—24	25—34	35—44	45—54	55
General population	3	4	5	1	1
Tuberculosis patients	5	1	4	2	2
Leprosy patients	—	—	—	4	—

TABLE 3

Sex Distribution of Vesiculators to PPD-S

Subject group	Male	Female
General population	10	4
Tuberculosis patients	5	9
Leprosy patients	2	2

Though no data was noted in this survey to evaluate this point, it was felt that vesiculation seemed to occur with greater frequency in reactions associated with a greater degree of local manifestations such as swelling, pain, redness, etc. However, vesiculation also did occur in the absence of these local features.

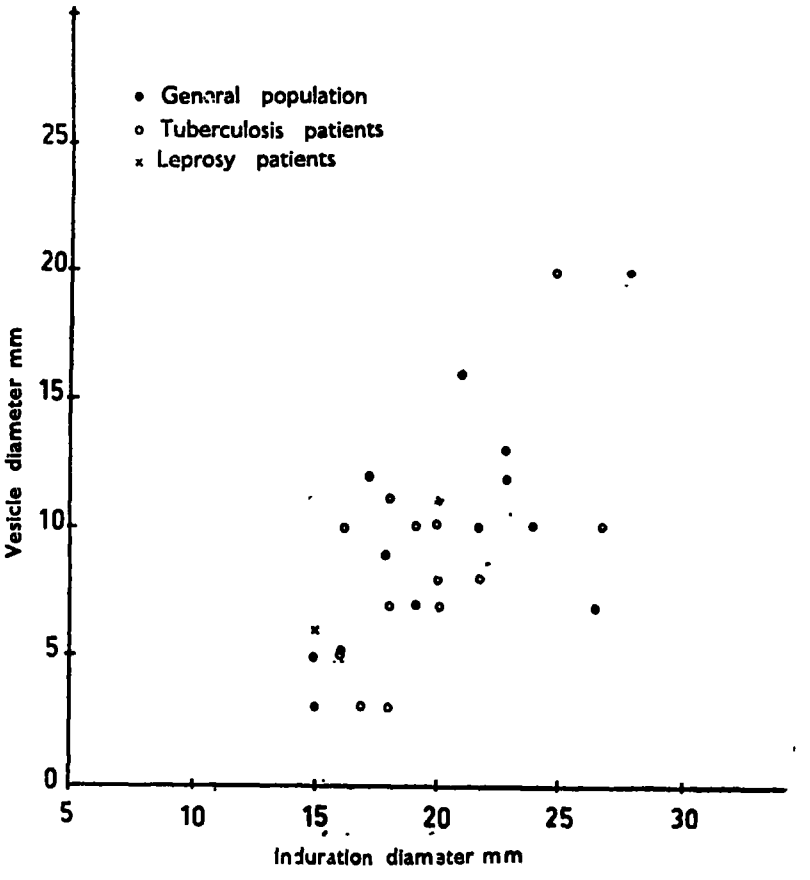

Fig. 1. Correlation between Vesicle size and Induration diameter.

The results of two persons with readings (reaction diameter/vesicle diameter) of 45/14 mm and 50/25 mm are not included in the diagram.

In those subjects showing vesiculation, comparison of the indurations to PPD-S with those to other antigens (Table 4) shows that in the unvaccinated general population the reaction size to PPD-S in the great majority of subjects (i.e. 13 out of 14) exceeded that of any other antigen. A similar pattern was seen in tuberculosis patients, but in one case of vesiculation the reaction to PPD-S was exceeded by reactions to both PPDs Y and G though the latter two reactions did not show vesiculation. The incidence of vesiculation was higher in tuberculosis patients than in any other group. There was no case of vesiculation in the BCG vaccinated group, though a similar number of leprosy patients had four subjects with these changes.

TABLE 5

Relationship of 'S' Reactions Showing Vesiculation to that of other Antigens used in the Differential Test in the same Subject

Subject group	Where 'S' is largest reaction		Where 'S' reaction is one of the largest reactions but is equalled (± 2mm) by reaction to some other antigen	Where 'S' reaction is smaller than that to another antigen
	Exceeding next largest by 6 mm or more	Exceeding next largest by 3-5mm		
General population	8	5	1	—
Tuberculosis patients	5	5	2	1
Leprosy patients	2	—	1	—
Total — all subjects	15	10	4	1

DISCUSSION

Comparison of the results of this study with data on the occurrence of bullae reported by workers in other countries (viz. Denmark) suggests that vesiculation is much less common in Ceylon. The data from these studies (WHO TB Research Office, 1955 a, b) are compared with those from Ceylon in Table 5. The occurrence of vesiculation in members of different population groups in Denmark appears to be even greater than that in tuberculosis patients in Ceylon. However, many differences in the features of mycobacterial infections are apparent between the two areas; for instance, Ceylon has a much higher incidence of non-tuberculous mycobacterial infection than Denmark.

The numbers showing vesiculation were too small for any definite conclusions to be reached regarding the occurrence of vesiculation in relation to age, sex, altitude, etc. But it is clear that vesiculation is much more common in tuberculosis patients than in any other group studied in Ceylon. Perhaps this is to be expected as this group is probably exposed to more intense antigenic stimulation by *Myco. tuberculosis.*

Earlier studies have shown that Ceylon is a country where non-tuberculous mycobacterial infection is apparently more common than tuberculous infection in the general population and therefore one would expect vesiculation to have occurred with non-tuberculous antigens in such a population. The non occurrence of vesiculation with the non-tuberculous PPDs is therefore a point in apparent contrast to the above findings. It is

possible that bullae formation and necrosis occurs with a more intense degree of hypersensitivity and as suggested in an earlier study it may be that the non-tuberculous mycobacteria have much lesser allergenising capacity than *Myco. tuberculosis* (Pinto *et al.*, 1972). Bullae are commoner when the induration of the tuberculin reaction is large. A large induration probably implies more intense antigenic stimulation. The occurrence of vesiculation with both PPD-S and Y in one case may be an indication of the closer antigenic relationship that exists between *Myco. tuberculosis* and *Myco. kansasii* (Castelnuovo & Morellini, 1965), the organisms from which these two antigens are respectively prepared. On the other hand the occurrence of vesiculation to PPD-G from a Runyon's Group II Scotochromogen in a leprosy patient is a finding that is not as easily explained.

TABLE 5

Comparison of Incidence of Vesiculation in Ceylon and Denmark

Population group	Approximate incidence of vesiculation percentage of those tested
Ceylon	
1. Rural general population	Less than 1
2. Tuberculosis patients	6
3. Leprosy patients	3
Denmark	
1. Rural general population (WHO Tuberculosis Research Office, 1955a)	In two areas 6 and 23
2. Mental defectives (WHO Tuberculosis Research Office, 1955b)	15

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REFERENCES

CASTELNUOVO, G. & MORELLINI, M. (1965) The antigens of mycobacteria and their identification by immunoelectrophoretic analysis. *American Review of Respiratory Diseases, Suppl. on International Conference on Mycobacterial and Fungal Antigens*, **92**, 29.

PINTO, M. R. M., ARSECULERATNE, S. N., URAGODA, C. G. & HEMAWARDENA, D. M. (1972). Differential tuberculin testing in rural populations in Ceylon. *Tubercle*, **53**, 182.

PINTO, M. R. M., ARSECULERATNE, S. N., URAGODA, C. G. & HEMAWARDENA, D. M. (1973). The differential tuberculin test in tuberculosis patients. *Tubercle*, **54**, March (in press).

PINTO, M. R. M., ARSECULERATNE, S. N. & URAGODA, C. G. (1973). The differential tuberculin test in a BCG vaccinated group. *Tubercle* **54**, June (in press).

PINTO, M. R. M., ARSECULERATNE, S. N. & WELIANGE, L. V. (1973). The differential tuberculin test in leprosy patients. *Leprosy Review*, **44**, (in press)

World Health Organization (1963). The WHO standard tuberculin test. *WHO/TB/Tech Guide/3*.

WHO Tuberculosis Research Office (1955a). The 5 T.U. versus the 10 T.U. intradermal tuberculin test. *Bulletin World Health Organization*, **12**, 169.

WHO Tuberculosis Research Office (1955b). Repeated tuberculin tests in the same site. *Bulletin World Health Organization*, **12**, 197.