Bull. Org. mond. Santé / *Bull. Wld Hlth Org.* 1955, **12**, 169-177

THE 5 TU VERSUS THE 10 TU INTRADERMAL TUBERCULIN TEST

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SYNOPSIS

With the growing demand in practical tuberculin-testing work for an effective single-dose intradermal test to replace the serial-dose procedures, the 5 TU and 10 TU doses have both been used for single-dose tests in recent years. The present study was undertaken for the purpose of determining the difference in the effects of these two doses.

The material was collected by testing large general population groups participating in the Danish mass campaign in two areas in Jutland ; 5 TU and 10 TU were given to alternate persons. Results are presented for 3,764 adults, none of whom gave a history of previous BCG vaccination.

With either dose, the population groups were clearly separated into two groups, reactors and non-reactors. The average diameter of reactions for 10 TU was larger by about 2-3 mm than for 5 TU, and the frequency of bullous reactions was only slightly greater with the stronger dose.

The two known sources of tuberculin sensitivity in Denmark, apart from BCG, are infection with human and with bovine tubercle bacilli. As both appear to result in a degree of sensitivity demonstrated about equally well with either 5 TU or 10 TU, either dose would seem to be suitable as a single-dose test for tuberculin-testing surveys in similar general populations.

Procedures for intradermal tuberculin-testing have been changed considerably during the past decade : the trend, in general, has been away from serial-dose testing toward a single-dose procedure.[4] The use of a three-dose series of tests with increasing strengths of tuberculin is giving way to a two-dose series and, by many workers, has been abandoned in favour of the one-dose test. In the search for a suitable dose for a one-dose test, the choice now seems to be narrowing to either 5 TU or 10 TU.

The present paper shows the differences found between the effects of the two doses when used as single-dose tests for tuberculin survey work in a general population.

* This study was carried out in connexion with the Danish mass campaign. Tuberculin-testing for the study was done by TRO nurses under the supervision of Johannes Guld. The material was analysed and the report prepared by Johannes Guld.

Study Populations

The work was carried out in connexion with the Danish mass campaign of 1950-52. This campaign was directed specifically toward the general population 1-7 and 15-34 years of age, though the participation of persons of any age was welcomed. All persons were given an intradermal tuberculin test with a dose of 10 TU (5 TU were used in a few counties) and an X-ray was taken of all adults on the first examination day. In addition, each person was carefully questioned about previous BCG vaccination and, though the answer was sometimes wrong,[1] there are good reasons for believing that the great majority of adults classified as unvaccinated really were unvaccinated. On the second examination four days later, the tuberculin reactions were read, BCG vaccination was offered to those with reactions of less than 6 mm, and the results of the X-rays were made known.

For purposes of the present study, arrangements were made for a team of TRO nurses to give and read the tuberculin tests in the mass campaign in two selected areas : one in Vejle County (central Jutland), with a largely rural population ; the other in the industrial town of Nørresundby in northern Jutland. Results are given only for persons between 15 and 60 years of age who stated that they had never been BCG-vaccinated, as this group was sufficiently large and uniform to justify detailed analysis. Other groups—children, old people, possibly or definitely BCG-vaccinated persons—were too heterogeneous or insufficiently represented to warrant inclusion in this report.

Procedure

In Vejle County an intradermal tuberculin test with 5 TU was given to every alternate person, a test with 10 TU to the others, in the order they happened to present themselves for the test. In Nørresundby the design was the same in principle, though a third dilution of tuberculin—for which the results will not be given here—was given to every third person.

Dilutions of PPD (RT XIX-XX-XXI, from the Statens Seruminstitut, Copenhagen) were used in two strengths : one containing 5 TU (0.0001 mg per 0.1 ml), the other containing 10 TU (0.0002 mg per 0.1 ml). The dilutions were labelled in code so that the strengths of the two doses would be unknown to the personnel giving and reading the tests. Non-leaking syringes were used, the 0.1 ml volume being gauged from the markings on the syringe and not from the size of the wheal (papule) raised by the injection.

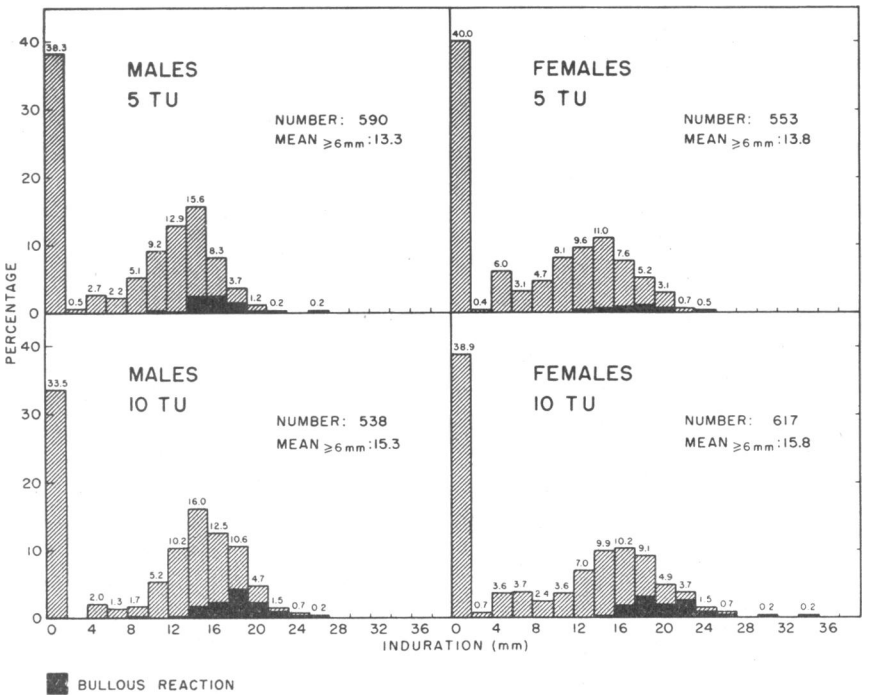
The reactions to all the tests were read by palpating the induration and measuring the transverse diameter. The results were dictated to a secretary : the reader was not allowed to see the record cards and thus could not know

whether any two persons had been tested with the same or with different dilutions. For purposes of the mass campaign, all results were treated as though the usual dose of 10 TU had been given.

Results

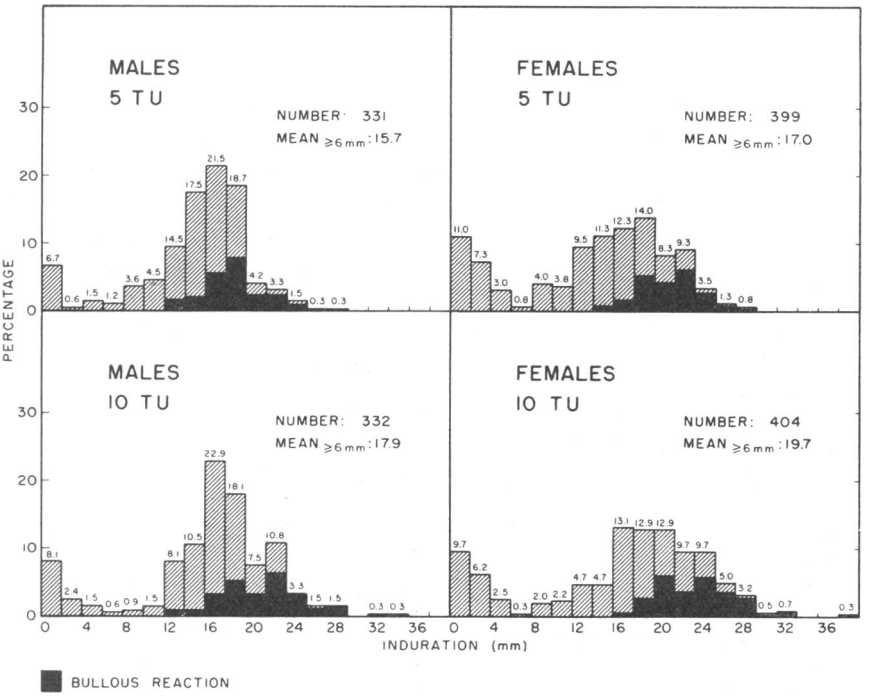
Results are combined for all persons between 15 and 60 years of age, as tabulations of the reaction distributions by 10-year age-groups within this range clearly showed that the average size and dispersion of " positive " reactions were surprisingly unaffected by age,[a] though the frequency of " positive " reactions increased with age, as one would expect. Sex, on the other hand, made a consistent difference throughout: " positive " reactions among women were definitely more varied in size, and were slightly larger on the average, than those in males. Results from the two areas also differed: fewer persons in Vejle County reacted to tuberculin, and those who did had smaller reactions than those in Nørresundby.[b] The results are therefore

FIG. 1. DISTRIBUTIONS BY SIZE OF TRANSVERSE DIAMETER OF TUBERCULIN REACTIONS IN AN ADULT POPULATION FROM RURAL DISTRICTS AND VILLAGES IN VEJLE COUNTY, JUTLAND



a For details on variations by age in a similar, though much larger, material, see page 261.
b For further discussion of the different reaction sizes in Vejle County and Nørresundby (Aalborg County), see page 277.

FIG. 2. DISTRIBUTIONS BY SIZE OF TRANSVERSE DIAMETER OF TUBERCULIN REACTIONS IN AN ADULT POPULATION FROM THE TOWN OF NØRRESUNDBY, JUTLAND



given separately as distributions by size of tuberculin reactions to 5 TU and 10 TU for males and for females in Vejle County in fig. 1 and in Nørresundby in fig. 2.

Discriminating " positive " reactions

Persons in each of the eight populations fall rather clearly into one of two groups: the one with definite reactions that may appropriately be called " positive ", the other with negligible or quite absent reactions that may be called " negative ". A few persons in between, with reactions of 4 mm to 8 mm, are not so easy to place; with no information on tuberculous infection other than the reactions themselves, any limit used for discriminating " positive " reactions must be rather arbitrary. For the present computations, a limit between 5 mm and 6 mm was chosen as being reasonably near the distribution minimum for all the population groups shown. Statistics for the distributions of " positive " reactions, thus defined, are given in table I.

One might fear that a fixed limit between " positive " and " negative " reactions (in the present case between 5 mm and 6 mm), irrespective of the dose of tuberculin, would introduce a bias in the comparisons of distribu-

TABLE I. STATISTICS OF DISTRIBUTIONS OF TUBERCULIN REACTIONS OF 6 mm OR MORE IN TRANSVERSE DIAMETER OF INDURATION

	Vejle County				Nørresundby			
	males		females		males		females	
	5 TU	10 TU	5 TU	10 TU	5 TU	10 TU	5 TU	10 TU
Total number of persons	590	538	553	617	331	332	399	404
Number with reactions ≧ 6 mm	345	347	297	351	302	292	314	330
Reactions ≧ 6 mm as percentage of total	58	64	54	57	91	88	79	82
Mean size (mm) of reactions ≧ 6 mm	13.3	15.3	13.8	15.8	15.7	17.9	17.0	19.7
Standard deviation (mm) of reactions ≧ 6 mm	3.2	3.5	3.9	4.6	3.6	4.1	4.5	5.0
Number of bullous reactions	42	67	22	68	78	88	89	108
Bullous reactions as percentage of reactions ≧ 6 mm	12	19	7	19	26	30	28	33

tions: some persons may tend to have reactions below 6 mm when tested with 5 TU and above 6 mm when tested with 10 TU; they would be counted as negative reactors to 5 TU and as weak positive reactors to 10 TU. Thus the average increase in reaction size for increasing the dose of tuberculin would be underestimated, as would the dispersion of the reactions to the weaker dose. If persons infected with tuberculosis have reactions that form a normal distribution (and non-infected persons are supposed not to have reactions above a certain size), the theory of " truncated " distributions can be used to estimate the degree of truncation.[3]

The present distributions of " positive " reactions have been thus treated, each for several points of truncation, but the resulting adjustments in the estimates of the percentages positive, of mean reaction size, and of dispersion were so small compared with sampling and other errors in estimating these parameters that the adjustments seemed to have little practical meaning. The estimates in table I are therefore given without any adjustments.

The distribution function of " positive " reactions

In reports from the Tuberculosis Research Office, distributions of " positive " reactions are described and compared in terms of means and standard deviations (or variances). Such descriptions are exhaustive only if the distributions are of normal shape, or at least nearly so.

How the present material fits this description is shown in fig. 3 and 4, where the cumulated distributions of " positive " reactions are plotted as probit diagrams.[c] The curves are good approximations to straight lines, indicating that the distributions may confidently be treated as normal.

Curves for the two doses are very nearly parallel for each sex, but the curves are steeper for males than for females, corresponding to the smaller variance of the distribution of the tuberculin reactions for males.

Bullous reactions

The frequency of bullae, in absolute numbers and as a percentage of " positive " reactions, is given in the last two lines of table I. Bullous reactions are also indicated by black shading in fig. 1 and 2. The frequency is higher with the stronger dose, but the difference is far from impressive in the results from Vejle County, where the frequency of positive reactions was low, and so small as to be scarcely significant in Nørresundby, where the frequency of positives was considerably higher.

[c] The probit diagrams are not based on the estimates in table I, but on the reactions 8 mm or larger in size, the distributions of these reactions considered as truncated normal distributions ; a small but unknown number of infected persons presumably has reactions smaller than 8 mm. The choice of 7½ mm as the point of truncation was made on the somewhat arbitrary assumption that reactions in non-infected persons would not exceed this size. The degree of truncation for each distribution, that is, the hypothetical fraction of infected persons with reactions smaller than 7½ mm, was estimated[3] from the shape of the distribution above 7½ mm; and this degree of truncation, expressed as a percentage, is the starting point for the probit curve at 7½ mm.

FIG. 3. PROBIT DIAGRAMS FOR DISTRIBUTIONS BY SIZE OF TRANSVERSE DIAMETER OF POSITIVE TUBERCULIN REACTIONS IN AN ADULT POPULATION FROM VEJLE COUNTY, JUTLAND

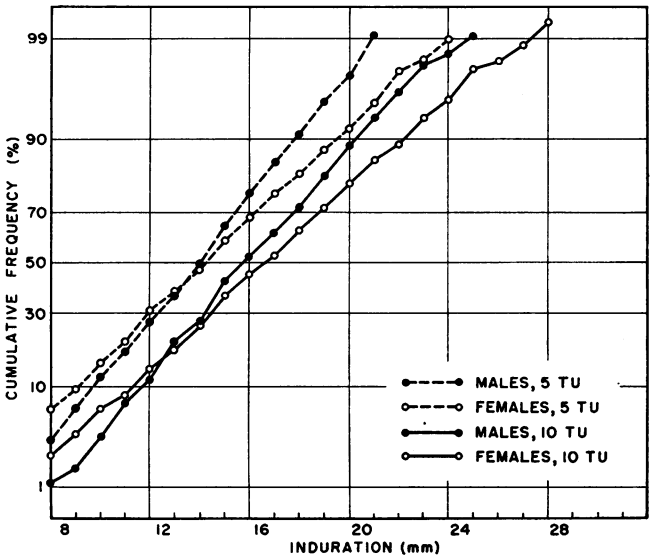
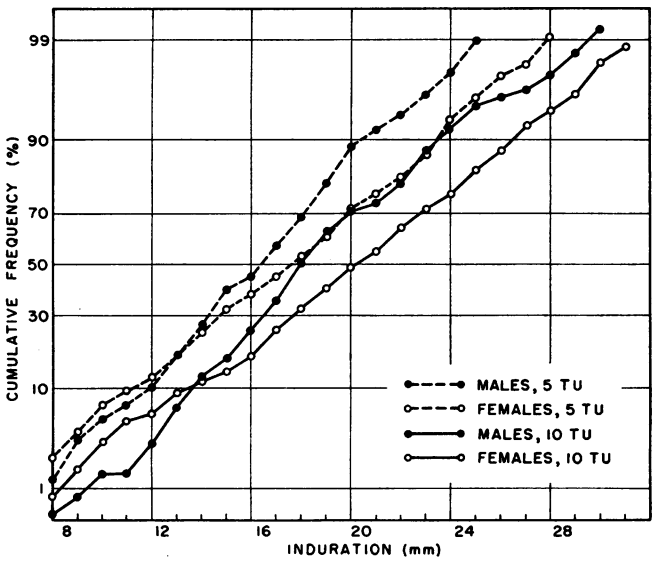


FIG. 4. PROBIT DIAGRAMS FOR DISTRIBUTIONS BY SIZE OF TRANSVERSE DIAMETER OF POSITIVE TUBERCULIN REACTIONS IN AN ADULT POPULATION FROM NØRRESUNDBY, JUTLAND



Discussion

The present study was undertaken to find the explicit differences between reactions to intradermal tests with 10 TU and 5 TU. Efforts were made to obtain unbiased alternation of the two doses, and unbiased readings of the reactions. Thus the populations tested with 5 TU and those tested with 10 TU are strictly comparable. The result of the study is surprisingly simple: the difference between reactions to the two doses is quantitative only and small, of a magnitude of 2 mm or 3 mm.

One might have expected some qualitative feature to be characteristic of the difference between the two doses: that the stronger dose would reveal more tuberculin-sensitive persons, that the stronger dose would produce intolerably strong reactions, or, perhaps, that the weaker dose would not effectively differentiate between sensitive and non-sensitive persons. That no such feature is characteristic of the present findings, that the findings are better described in terms of a simple, quantitative difference, is a reflection of the distribution of tuberculin sensitivity in the population used for this study. The problem of tuberculin sensitivity is treated in detail elsewhere (see page 63), and it must suffice to say here that the two known sources of tuberculin sensitivity in Denmark (apart from BCG) are infection with human and with bovine tubercle bacilli. Both apparently result in a degree of sensitivity that is demonstrated about equally well with either of the two doses of tuberculin. The small number of persons with unrecognized BCG-vaccination undoubtedly present in the population does not seem to disturb the picture (though they may be responsible for a considerable part of the dubious reactions in the 4-8 mm range). The prevalence of non-specific sensitivity is believed to be low in Denmark.

That the level of sensitivity found in this population reflects tuberculous infection of mammalian type is borne out by a comparison with the sensitivity found in tuberculous patients in a Danish hospital. As reported elsewhere (see page 63), the average size of reactions to 5 TU in the patients was 14.6 mm, which corresponds very closely to the present results.

It is a curious feature that reactions in women are larger and vary more in size than reactions in men. As the volume of tuberculin injected was carefully measured for each test, the sex difference cannot be explained as a mere artefact owing to different dosage by sex (as would have been possible had the tests been given according to wheal size).[2]

Whether 5 TU or 10 TU is the more suitable dose for a single-dose test would seem to be a matter of choice. The difference between the two doses is so small that even if one of them might be regarded as more suitable than the other for a particular population group—if, for example, 10 TU were deemed the ideal dose for males and 5 TU for females—even then the important (and practical) conclusion is that any dose of this magnitude would be suitable as a single-dose test in populations like those shown

here, and small variations in dosage would not be expected to create any serious difficulties.

In practice, inaccuracy in injecting the prescribed volume of dilution [2] and inaccuracy in the standardization of tuberculin preparations are probably as critical as whether 10 TU or 5 TU is selected as the dose of choice.

RÉSUMÉ

Pour l'exécution pratique de la tuberculino-réaction, on cherche de plus en plus à substituer aux procédés qui reposent sur l'administration de doses croissantes une épreuve efficace comportant l'administration d'une dose unique par voie intradermique : pour cette épreuve on a utilisé, ces dernières années, aussi bien la dose de 5 UT que celle de 10 UT. La présente étude a été entreprise en vue de déterminer les différences que présentent les résultats obtenus avec l'une et l'autre dose.

A cette fin, l'épreuve a été pratiquée sur de grands groupes de l'ensemble de la population : on a administré alternativement la dose de 5 UT et celle de 10 UT à toutes les personnes englobées dans la campagne antituberculeuse danoise, dans deux districts du Jutland. Les observations ont été faites sur 3.764 adultes dont aucun — selon les déclarations des intéressés — n'avait préalablement été vacciné par le BCG.

Que l'on ait administré l'une ou l'autre dose, il a été possible de répartir la population en deux catégories distinctes, selon que les sujets ont réagi positivement ou non. Le diamètre moyen des réactions obtenues avec la dose de 10 UT a été supérieur de 2 à 3 mm à celui des réactions qu'a provoquées la dose de 5 UT ; d'autre part, la fréquence des réactions bulleuses n'a été que légèrement plus élevée avec la dose forte. La distribution de fréquence des réactions positives d'après leur dimension (diamètre de l'induration) a donné une courbe d'allure à peu près normale. Chez les femmes, le diamètre moyen des réactions a été un peu plus grand que chez les hommes, avec une variance plus grande aussi.

Au Danemark, les deux causes connues de sensibilité à la tuberculine — abstraction faite de la vaccination par le BCG — sont l'infection soit par la tuberculose humaine, soit par la tuberculose bovine. Qu'il s'agisse de l'une ou l'autre éventualité, il apparaît que la sensibilité provoquée peut être mise en évidence aussi bien avec la faible qu'avec la forte dose ; il semble donc suffire d'administrer une seule fois l'une ou l'autre de ces doses pour pratiquer une épreuve tuberculinique lors de campagnes intéressant des ensembles de population présentant des caractères analogues.

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