CERTAIN STATISTICAL CONSIDERATIONS IN PATCH TESTING[1,2]

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Although patch testing procedures were not originally developed for bio-assay, they have been adapted for the detection and evaluation of the skin-irritating and sensitizing properties of chemical agents and materials. Information thus derived is used to prevent the exposure of the general population to such substances. In using the patch test to obtain such information a certain group of individuals is tested under control conditions, and the number of positive reactions noted. If a high incidence of reactions occurs in a test group, it indicates that a given substance is prohibitively skin-sensitizing or irritating, but if no positive reactions occur in a sample, for example of 100, this does not necessarily guarantee the absence of dermatitis-producing factors.

In order to interpret the results found on a test group of subjects in terms of the general population, certain statistical principles may be applied. The following discussion is confined solely to statistical considerations of sampling techniques as applied to patch tests, no attempt being made to discuss the quantitative relationship and variations between the reactions of persons subjected to a specific substance under test conditions and the reactions under normal exposures. From a statistical point of view two questions are of importance: (1) if no positive reactions or if a certain number of positive reactions to a patch test are observed in a given test group, what would be the maximum incidence likely to occur, under identical conditions, in a large number of individuals similar to the test group, and (2) how large a group must be tested to predict, with a given degree of certainty, that the rate of positive reactions in the general population lies within certain given limits.

To consider a concrete example, suppose that in a certain test no reactions were observed in a group of 100 subjects and we wish to know what range of positive reaction rates in a large population could give rise to such a finding. Theoretically any value from 0 up to but not including 100% could do so. It is obvious, however, that the larger the positive reaction rate in the population, the less is the likelihood that a sample of 100 will be drawn which shows no positive reactions. It can therefore be inferred with a certain degree of confidence that the given sample of 100 came from a population with a small positive reaction rate.

It can be shown that if no positive reactions occur in 100 subjects, the rate of positive reactions in the population is not likely to exceed approximately 2.9%, the likelihood being at the 95% level;[3] and that if one reaction is observed in 100

[1] From The Army Industrial Hygiene Laboratory Johns Hopkins School of Hygiene and Public Health, Baltimore, Md.

[2] Received for publication December 5, 1944.

[3] The likelihood level of 95% is a measure of the confidence with which it can be asserted that the population rate does not exceed the stated value. The likelihood level may be chosen at any point, depending on how conservative one wishes to be in his estimates. If a higher level, say 99%, is used, then the maximum estimate of the population rate would be increased, and it could then be asserted with greater assurance that the population rate did not exceed that higher value. The most frequently used likelihood or confidence levels are 95% and 99%.

TABLE I

Upper Limit of Positive Reaction Rate Estimated for the Population, with a 95% Likelihood, from Results of 0, 1, or 2 Positives in a Sample of Size n

NO. OF SUBJECTS IN SAMPLE	LIKELY MAXIMUM* RATE OF POSITIVE REACTIONS IN A LARGE NUMBER		
	If no reaction in sample	If one reaction in sample	If two reactions in sample
(n)	%	%	%
30,000	.01		
20,000			.03
10,000	.03	.05	.06
5,000	.06	.09	
4,000			.15
2,000	.15	.23	.30
1,000	.30	.45	
800	.37	.56	.75
600	.50	.75	1.0
500			1.2
400	.75	1.1	1.5
300	.99	1.5	2.0
250	1.2	1.8	2.4
200	1.5	2.2	2.9
160			3.7
150	2.0	3.0	
125	2.4	3.6	
120			4.9
100	3.0	4.4	5.8
80	3.7	5.5	7.3
60	4.9	7.3	9.6
50	5.8	8.8	
40	7.2	10.8	14.0
30	9.5	14.2	
20	13.9	20.8	27.0
10	26.9	38.2	

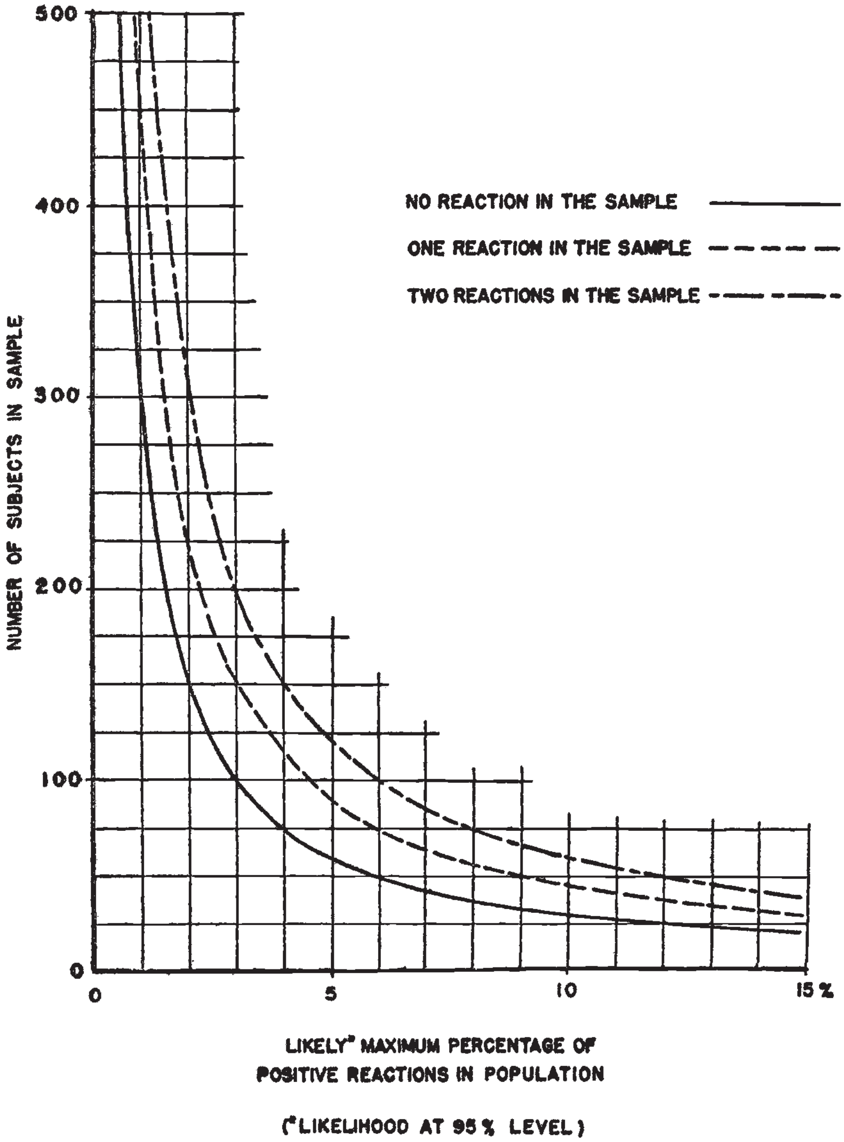
* 95% likelihood.

TABLE II

Number of Subjects Required, If There Are No Positives in the Sample to Predict with a 95% or 99% Likelihood That the Population Rate Does Not Exceed Certain Designated Values

MAXIMUM PERMISSIBLE PERCENTAGE OF REACTIONS IN THE POPULATION	NO. OF SUBJECTS FOR LIKELIHOOD OF	
	95%	99%
0.01	29,978	46,083
0.1	2,994	4,603
0.5	597	918
1	298	459
2	148	228
3	98	151

subjects, the likelihood is 95% that the rate does not exceed approximately 4.5%. Conversely, it can be shown that in order to insure, with a likelihood of 95%, that the rate of positive reactions in the population does not exceed 2%, 147



subjects must be tested and no reactions appear or 225 subjects must be tested and only one reaction appear.

The equations used for deriving these results are part of the statistical theory for the distribution of repeated results. If a certain number of positives are found in n individuals, and we want to estimate the reaction rate, p, so that the likelihood is 95% that the population value does not exceed p, the following equations[4] may be used for the estimation:

For 0 positive reactions in the sample of size n

$$(1 - p)^n = .05$$

For 1 positive reaction in the sample

$$n(1 - p)^{n-1}p = .05$$

For 2 positive reactions in the sample

$$\frac{n(n - 1)}{2}(1 - p)^{n-2}p^2 = .05$$

Calculations resulting from substitution in these equations are shown in Table I and Graph I, which give for various sizes of samples the "maximum" reaction rate estimated if 0, 1 or 2 positive reactions appear in the sample. By "maximum" here, we mean that the likelihood is 95% that it would not be exceeded. Table II gives for the case of no positives in the sample, the size sample necessary to determine with an assurance of 95% or with an assurance of 99% that the population rate does not exceed certain specified values.

The data may be used for two purposes.

(1) If 0, 1 or 2 positive reactions are observed in a sample of a given size, an estimate can be made as to the likely (95% likelihood) maximum rate of positive reactions in the population from which the sample was drawn.

(2) If it is desired to make reasonably certain (95% likelihood) that the rate of positive reactions in the population does not exceed a given figure, the size of sample necessary to accomplish this end may be determined (3 values will of course be obtained depending upon whether 0, 1, or 2 reactions in the sample is to serve as the criterion).

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[4] The equation for extimating with a likelihood of P, that the population rate does not exceed p, if *a* positives are found in n individuals is:

$$\int_0^p \frac{n!}{a!\,(n - a)!}(1 - p)^{n-a}p^a\,dp = P$$

In the range of p's involved in the present problem, an approximate solution is given by the following formula, which was used in our estimates:

$$\frac{n!}{a!\,(n-a)!}(1-p)^{n-a}p^a = 1-P$$