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PROFESSOR CALMETTE'S STATISTICAL STUDY OF B.C.G. VACCINATION.

BY

M. GREENWOOD, F.R.C.P.,

PROFESSOR OF EPIDEMIOLOGY AND VITAL STATISTICS IN THE UNIVERSITY OF LONDON.

IN the January issue of the *Annales de l'Institut Pasteur* Dr. Calmette publishes an article¹ on the statistics and results of his method of prophylactic inoculation from July, 1924, to December, 1927. Dr. Calmette's earlier report² was subjected to some little criticism both in the editorial columns of the *British Medical Journal*^{3, 4} and from individual writers^{5, 6}; recently Dr. Monod⁷ has expressed the hope that the latest report might allay the doubts that had been expressed as to the sufficiency of the statistical evidence.

Briefly, the objections which were urged against the earlier report were these: (1) that the enormous rate of mortality from tuberculosis said by Dr. Calmette to apply to the children of the tuberculous, or to children exposed to massive infection, in the first year of life was deduced from inadequate data or depended upon misinterpretations of published literature, and did not agree with such evidence as that of Kjer-Petersen and Ostenfeld⁸; (2) that the positive evidence of a statistical kind supplied by Dr. Calmette was ambiguous.

Thus, with respect to the first objection, I pointed out that Weinberg's very careful statistical study had been misrepresented; that, far from supporting the suggestion that anything like 25 per cent. of the children of the tuberculous died of tuberculosis in the first year of life, Weinberg's figures were in reasonable agreement with those of Kjer-Petersen and Ostenfeld, Bergman,⁹ and Dörner,¹⁰ making the rate of mortality of the order of 5 to 10 per cent. rather than of 25 per cent. With respect to the second objection, I showed that the data handled by Dr. Biraud, who used an adequate method of analysis, became so scanty within a few months of birth that it was difficult to have great confidence in the inferences—*prima facie* favourable—which appeared to be deducible from them.

An attentive study of Dr. Calmette's latest paper leads me to think that its distinguished author has either not read or not understood the criticisms of his former report, because, to put the matter quite plainly, this new paper repeats and even exaggerates former inaccuracies while introducing statistical errors peculiar to itself. I take first the contention that Dr. Calmette has again misrepresented the published work of other writers. Of Weinberg he writes under the heading *Mortalité par Tuberculose des nourrissons de zéro à un an nés et élevés en milieu bacillifère*:

"D'autre part, une statistique (déjà ancienne, mais portant sur un grand nombre d'enfants) publiée par Weinberg, avait établi qu'à Stuttgart, de 1873 à 1889, la mortalité des enfants de zéro

à un an par tuberculose était due: pour 30, 53 p. 100 à la mère tuberculeuse; pour 29, 88 p. 100 au père tuberculeux; pour 31, 92 p. 100 à la fois à la mère et au père tuberculeux."

This passage repeats the misrepresentation to which attention had already been drawn. The figures quoted are not for the mortality from tuberculosis, but from all causes, and, at the same epoch, the death rate in the first year of life of children of mothers who were not tuberculous was as high as 23.82 per cent. The present misrepresentation is rather worse than that of the first report (p. 210), because there the attribution of the mortality to tuberculosis was not quite so explicit.

Of Kjer-Petersen and Ostenfeld's recent work (again in the section dealing with mortality from tuberculosis in the first year of life), Dr. Calmette writes that they

"n'ont enregistré, pour 245 nourrissons suivis par eux, qu'une mortalité de 7,7 p. 100 de zéro à un an. Mais il faut remarquer d'abord que les 245 nourrissons dont il s'agit ne comprennent pas seulement des enfants nés de mères tuberculeuses, mais aussi et surtout des enfants qui ont simplement été en contact, pendant une période plus ou moins longue, avec un tuberculeux."

The mortality rate of 7.7 per cent. in Kjer-Petersen and Ostenfeld's series is the rate of mortality from all causes—namely, 19 deaths among 245 children, and of these 19 deaths only 12 were assigned to tuberculosis. The complete specification in the paper is as follows. Tuberculosis: 3 from tuberculous meningitis, 5 from pulmonary tuberculosis, 1 from abdominal tuberculosis, 1 after operation for tuberculous disease of the ear, 2 from generalized tuberculosis. The other deaths were thus classified: 1 cholera, 1 influenza and inflammation of the lung, 2 measles and inflammation of the lung, 3 inflammation of the lung. If we assume that the last three were really instances of tuberculous infection we shall reach 6.1 as the percentage death rate from tuberculous disease.

The authors set out their categories quite clearly, and one finds that 101 of the children had the mother or both parents tuberculous, and of these 101 children 4 died of tuberculosis, while the remaining 8 deaths from tuberculosis occurred among the 116 children whose fathers only were tuberculous. In other words, these data show a higher incidence of fatal tuberculosis upon the children of tuberculous fathers than upon the children of tuberculous mothers.

The fundamental importance of Kjer-Petersen and Ostenfeld's paper depends on the fact that it is based upon data compiled on statistically sound lines. Their means of access was the tuberculosis station of Copenhagen. They obtained a record of all births from July 1st, 1919, to June 31st, 1925, to families with at least one case of open tuberculosis, and they have excluded from the series instances where the child was born at least a month after a tuberculous father's death, or was isolated from the mother during the first year of life; that is, their data should give a maximal incidence for the class of population concerned. I shall return to the point later; at present I am merely describing Dr. Calmette's treatment of his sources. It is, I think, evident that no reader of his report who had not had access to Kjer-Petersen and Ostenfeld's paper (the locus of publication of which is not given by Dr. Calmette) could have formed a just impression of what these authors actually did.

The next example of Dr. Calmette's literary researches is even more interesting. On page 7 of the report under notice we are told that:

"Margarete Roepke, dans un tableau qui résume l'histoire de 78 enfants, trouve une mortalité de 30.8 p. 100 pour les nourrissons en contact avec des malades arrivant à la période ultime de leur tuberculose; de 25 p. 100 lorsqu'il s'agissait de lésions avancées, tandis que la mortalité était nulle lors des contacts avec des formes légères de la maladie."

Dr. Calmette does not actually give a reference to the locus of publication of M. Roepke's paper, but there is no doubt that the paper in question is that printed on pages 252-263 of vol. 54 (1923) of the *Beiträge zur Klinik der Tuberkulose*. The source of the above-quoted statement of Dr. Calmette is in fact the following table, which I have taken from Frl. Roepke's paper (p. 260), the only change I have made being to translate the letterpress into English.

TABLE IV.—Mortality from Tuberculosis of Infants Exposed to an Infection, in Relation to the Severity of the Disease in the Carrier of Infection.

| Infants in Families with Infectious Tuberculosis. | Carriers of Infection. | | | |
|---------------------------------------------------|------------------------|-----------|---------|---------------|
| | In the Last Stage. | Advanced. | Slight. | Not Reported. |
| Infected 23 | 10 | 7 | 5 | 1 |
| Not infected 13 | 3 | 1 | 8 | 1 |
| Total number of infants 36 | 13 | 8 | 13 | 2 |
| Deaths from tuberculosis 6 | 4 | 2 | — | — |
| Percentage deaths of exposed to risk ... 16.7 | 30.8 | 25.0 | 0 | — |

The reader will recognize in this table Dr. Calmette's percentages of 30.8 and 25, but what, he will ask, is the source of the 78 infants upon which, according to Dr. Calmette, the table is based? The answer is that if one adds up all the figures in the second column except the percentage, the sum is $23+13+36+6=78$; that is, we reach 78 by counting all the children who survived twice and all those who died three times! It is not easy to understand how this mistake could have been made, because even a person completely ignorant of German and without a dictionary would surely wonder why there were four categories of absolute figures, and would have noted that 6 is 16.7 per cent. of 36, not of 78. However this may be, the simple fact is that the percentage mortalities of 30.8 and 25 are based respectively upon 13 and 8 observations.

No further remarks upon Dr. Calmette's treatment of literature seem needed. I pass now to the contention that, in the present report, in addition to repeating errors in the citation of the literature, Dr. Calmette has introduced statistical errors of a novel kind. On page 11 of the report there is a section headed "Enfants vaccinés depuis moins d'un an au 1^{er} décembre 1927." The first paragraph of this section reads as follows (*italics are as in the original*):

"Sur les 5.749 enfants qui figurent dans notre fichier, 3.808 ne sont vaccinés que depuis moins d'une année au 1^{er} décembre 1927. A cette date, on avait compté parmi eux 118 décès dont 34 par maladies présumées tuberculeuses. Leur mortalité générale (par toutes causes de maladies) était donc de 3.1 pour 100, alors qu'en France la mortalité générale des non-vaccinés, avec ou sans contact tuberculeux, est de 8.5 pour 100 nés vivants. La mortalité générale de zéro à un an est donc de plus de moitié moindre chez les vaccinés en contact tuberculeux que chez les non vaccinés avec ou sans contact."

Now the ratio of 8.5 per cent. is the ordinary measure of mortality in the first year of life; that is, it purports to tell us—and, unless the fluctuations of natality or mortality from month to month and year to year are very large, it does effectively tell us—what is the proportion of live-born children who, being exposed to risk of death for a whole year from birth, will actually die within that year. But the 3,808 children in Dr. Calmette's report are definitely stated to have been vaccinated less than a year from the date of closing the observations. Therefore, if the record of mortality extended from birth to the first anniversary of birth it covered some part of the first year before they had been vaccinated at all; if it only covered the period during which the infants belonged to the vaccinated class it is not a record of the mortality of the whole of the first year of life, but only of a part of that year. On either hypothesis the ratio of the number of deaths to the number of children cannot be compared with the rate of mortality in the first year of life. From a consideration of the details printed amongst Dr. Calmette's documents it would appear that the second method was that adopted in compiling the data. Omitting three cases of death after the age of 1 year it is found that no less than 38.26 per cent. of the total deaths were at ages 6–12 months, and only 12.17 per cent. in the first month of life. It is well known that the greatest proportion of deaths in the first year occur in the first month of

life. Thus in England and Wales (1926) 45.38 per cent. of the total deaths under 1 year occurred in the first month of life, and only 23.28 per cent. at ages over 6 months. The explanation of Dr. Calmette's figures is presumably that he is dealing with the mortality, not from birth, but from (on the average) an older age, hence the large proportion of deaths at older ages. An elementary mistake in the handling of statistics has been made, and a mistake which would necessarily show a result favourable to any treatment.

I do not think that it is necessary to examine Dr. Calmette's statistical methods further; it seems to me to be proved that the latest report, where it differs from its predecessor, differs from it for the worse, and that it cannot be regarded as a serious contribution to scientific literature at all.

If the question were merely one of academic discussion it might well be left there—indeed, it might well never have been raised. To paraphrase Mr. Shaw, Dr. Calmette's excursion into statistics might properly have been received with that silence which falls upon ordinarily good-natured people when a man of distinction offers, as his contribution to the discussion of a matter he has never studied, an absurd blunder. But it has been suggested that those who are unable to accept these strange bibliographical and statistical methods are indifferent to the possible importance of the subject in its practical applications. As a statistician I naturally attach value to the statistical method as an instrument of research. If a scientific man claims that he has proved by some other method than the statistical that such-or-such a means of treatment is good, I am naturally not very ready to believe him; but I neither have nor claim the right to impose my belief upon others. If Dr. Calmette had stated that, on experimental grounds, he was satisfied that his method of vaccination was a valuable prophylactic, and had confined himself to the kind of reasoning contained, for instance, in the first pages and the fifth and sixth sections of his report, I should not have been convinced because, *inter alia*, I do not understand how a living vaccine—that is, something quantitatively indeterminate—can be a satisfactory means of therapeutics; but I should have felt that my knowledge of the literature and technique of modern immunology was so amateurish that it would have been an impertinence to bandy words with an investigator who has devoted his life to such studies. But Dr. Calmette has not adopted this course; he has deliberately appealed to the statistical method, and, in my submission, his use of that method has been so gravely defective that no confidence can be placed either in his statistical inferences or in the reliability of the data which he has assembled. The collection of data is at least as delicate a business as their analysis, and a writer who shows so little respect for logic in analysis is not likely to have been more circumspect in assembling data for analysis. I see no hope of obtaining statistical data from France. If an appeal is to be made to statistical methods in other countries, we should be quite clear what conditions have to be fulfilled to give the statistical court jurisdiction.

If we confine ourselves to the case of the incidence of fatal tuberculosis in the first years of life, and desire to learn whether a particular treatment applied at the beginning of life reduces the risk of death, our first difficulty is the smallness of the material. The total number of registered deaths from all forms of tuberculosis at ages under 1 year in England and Wales in 1926 was only 862, or 1.8 per cent. of the whole number, 48,757, of deaths under 1, and 1.24 per 1,000 of the total number of live births, 694,563. Suppose, then, we were to take by lot every tenth registered live birth and to divide the sample of, say, 70,000 live births into two sets of 35,000 each, to treat one moiety and leave the other as a control series. We should expect, on the average, some 43 deaths from tuberculosis in the control series, the expectation being subject to an error of sampling of approximately 6.6. If, then, in the treated series there were 23 or fewer deaths from tuberculosis, we should reasonably conclude that it was easier to believe that the treatment had really been beneficial than that a very improbably large divergence had arisen by the luck of sampling. Such a comparison, if the conditions of random sampling had been strictly fulfilled,

would be perfectly satisfactory. But in actual practice the larger the "sample" the less probable is it that the conditions will be fulfilled, and the possibility of controlling a sample of the order of 10 per cent. of the whole annual births is virtually an impossibility. Take a less ambitious scheme, and suppose that in some town of moderate size, a town of some sixty or seventy thousand inhabitants, with an annual quota of, say, 1,000 births, the children could be treated randomly—for example, every second child whose birth was registered from January 1st in some year to be treated. We should expect on the average less than one registered death from tuberculosis in the control 500, and no strong presumption of advantage would be raised by a *nil* return from the treated series, taking only a year's experience.

Evidently it was a sound instinct to seek for a decision amongst the class of material where a higher rate of mortality was to be expected. That is the significance of Kjer-Petersen and Ostenfeld's work. What can we conclude from their investigation as to the probable range of mortality in the first year of life of in-contacts? We can, of course, at once dismiss the preposterous suggestions of rates of mortality of the order of 25 per cent., even from all causes. Had such a rate really prevailed in the population sampled by Kjer-Petersen and Ostenfeld, their "expectation" would have been 61 deaths with a standard deviation of 6.77. Actually they observed 19, and the odds against such a deviation as 42 are of the order of a thousand millions to one. If, however, one might postulate a rate of mortality from tuberculosis in the first year of life even of the order of 5 to 10 per cent., the comparison of samples of order 500 would not be waste of time. We should expect

in our control 500 from 25 to 50 deaths, and if the treated sample returned, say, only some 15 to 30 or fewer deaths, a case would have been made out which would be rather strong. Whether it would be practically possible to use this method, here or in America, it is hard to say. The number of instances of births in families with one or more cases of open tuberculosis which come to the notice of the public health authorities within any one area and within a limited period of time is small, and the difficulty of strict random sampling is great. We are concerned, not with guinea-pigs, but with human beings, and it is not easy to induce those who have the medical charge of human beings to administer to any of them a treatment which they regard as worthless, or to abstain from administering to any of them a treatment which they regard as valuable. None of us can dramatize this conflict with the art of Mr. Sinclair Lewis in *Martin Arrowsmith*, but all of us have, to a greater or less degree, participated in it. I do not expect that the value of B.C.G. will be determined on these lines. Like most methods of treatment, its use or neglect will be determined by psychological considerations. But to the still small, but increasing, number of medical men who attach importance to statistical accuracy it is of some moment that methodological errors having the sanction of the name of a distinguished investigator should at once be pointed out. That is my reason for writing this article.

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VITAL CAPACITY IN HEART DISEASE.*

BY

H. WALLACE JONES, M.Sc., M.D., M.R.C.P.,

SENIOR HONORARY ASSISTANT PHYSICIAN, LIVERPOOL ROYAL INFIRMARY.

(From the Heart Department of the Royal Infirmary.)

It has been the aim of investigators for many years to devise some simple test to estimate the functional capacity of the heart, apart from the subjective sensations of the patient. Many tests have been introduced from time to time for this purpose, based as a rule on the response of the heart to some form of exercise—the simplest consisting of taking the pulse rate before a fixed amount of exercise, immediately after the exercise has ended, and after an interval of a few minutes. An exercise tolerance test of this type has largely been made use of by the Ministry of Pensions for purposes of assessment of cardiac disabilities.

A test like this one, based on changes in the pulse rate, however, is open to the objection that it is more a measure of the excitability of the sino-auricular node than an indication of the capacity of the heart, and depends on many other factors quite independent of the cardiac reserve power. After vital capacity had been introduced as a measure of the extent and progress of certain lung conditions this test was applied to patients suffering from cardiac disabilities by several observers (see references 1 to 4), who found that the vital capacity was very much below normal standard when any serious cardiac condition was present; while Peabody and Wentworth⁵ also drew attention to the fact that there was a definite relationship between diminution in the vital capacity and a tendency to dyspnoea on exertion.

Before considering the changes which occur in cardiac patients it is advisable to consider what is meant by vital capacity. Hutchinson⁶ many years ago divided the volume of air in the lungs into the following divisions:

1. *Residual air*—air which cannot be expelled and is left in the lungs.
2. *Reserve air*—air which can be expelled by effort at the end of normal expiration.
3. *Tidal air*—air which is inspired or expired during normal respiration.
4. *Complementary air*—air which can be inspired after normal inspiration.

* Based on a paper read before the Liverpool Medical Institution.

5. *Vital capacity*—the sum of the reserve air, tidal air, and complementary air—that is, the greatest amount of air which can be expelled after the deepest possible inspiration.

In this investigation a simple water spirometer (Fig. 1) has been used, graduated in cubic centimetres and balanced so that no effort is required to raise the cylinder. A large number of glass mouthpieces were provided, so that they could be readily disinfected between each patient without loss of time.

It is always advisable to explain fully the working of the machine before actually taking the measurement, as it is necessary to get the patient's whole-hearted co-operation to obtain an accurate result. Each patient was given three attempts, the highest being taken as the vital capacity. In taking the reading, if there is any tendency to expire through the nose this should be closed by pinching during expiration. When patients were not confined to bed the record was always taken standing, and generally in their ordinary clothes. With regard

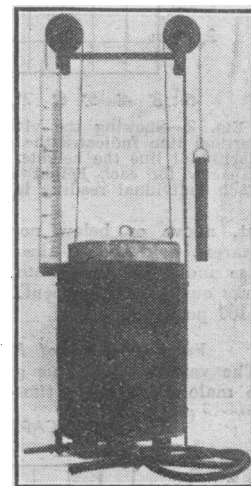


FIG. 1.—Water spirometer.

to the patients who were confined to bed they were all able to sit up in bed when taking the reading, so that it was not necessary to correct the reading for the 5 per cent. diminution in the vital capacity which has been shown by Christie and Beams⁶ and Rabnowitch⁷ to occur when the reading is taken in the recumbent position. Owing to the variability of the vital capacity according to the height, sex, age, and race of the individual concerned, the simple reading of the number of cubic centimetres expired gives little indication of the deviation from the normal, unless the reading is expressed in percentages of the standard vital capacity for that individual.

In this investigation the vital capacity is expressed as percentages of the standard vital capacity for that particular patient. It would be out of the scope of this paper to enter into all the different methods for calculating the