performed normally or only by the aid of a permanent increase of glomerular pressure.

The test is as follows. On the first day the patient, after passing urine, drinks 1,500 c.cm. of water within half an hour. Urine is passed at half-hourly intervals for the next four hours, each specimen being saved separately and tested for volume and specific gravity. Normally the whole 1,500 c.cm., often more, is excreted within the four hours, and the specific gravity falls to 1002 or less. The second day ordinary meals are given, but the amount of fluid is limited to 500 c.cm. for the whole twenty-four hours, taken in four roughly equal portions. Fruit should not be given, or should be reckoned as fluid. Urine is passed as and when the patient wishes, and each specimen is again collected separately and tested for volume and specific gravity. The total urine for the day should not exceed 750 c.cm., and the specific gravity should rise to at least 1027.

In cases of renal insufficiency the volume of urine on the first day is too little, while that on the second day

is too much, as excretion tends to continue at the same rate irrespective of variations in the requirements of the body. The limits of variation in specific gravity become more and more narrowed as the disease progresses, until at length a fixed point of about 1009 is reached. Often the dilution test will show a minimum of about 1005 and the concentration test a maximum of about 1015 long before the patient complains of any symptoms or the blood shows any evidence of uraemia.

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VALUE OF THE NEGATIVE SUBCUTANEOUS TUBERCULIN TEST

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In the Epitome of Current Medical Literature published with the *British Medical Journal* of March 17th, 1934, (p. 44, para. 227), there occurs the heading "Limited Diagnostic Value of Subcutaneous Injections of Tuberculin." This refers to two articles by N. Lindborg in the Swedish journal *Hygiea*,¹ in which the author reports that on following up sixty-six subcutaneous negatives* obtained in doubtful cases of active pulmonary or hilar tuberculosis in a Swedish sanatorium eleven instances were found in which tuberculosis subsequently developed. Five of these cases developed the disease within a year, one of them within three months, with pleurisy, and one, a boy of 8, died after an illness of two weeks' duration of tuberculous meningitis three months after the negative test. These five cases Lindborg considers to be "indisputable" evidence that a negative test does not always agree with the clinical event or exclude the possibility of the development of tuberculous disease within a short time.

Lindborg finds support for his conclusion in the figures of Kettelkamp² (the Robert Koch Hospital, St. Louis, Missouri) and Steidl and Heise³ (the Trudeau Sanatorium, New York), 13 per cent. and 6.6 per cent. respectively of clinical tuberculosis found to have occurred in a follow-up of their similarly tested negative cases. The results of Berg⁴ (Wiipuri, Finland)—namely, no subsequent tuberculosis in his small group of ten negative cases†—are thought by Lindborg to be "perhaps due to differences in the material, conditions, infection possibilities, or treatment."

Veterinary Reports

Lindborg's conclusion also finds support in certain veterinary reports. "During the year 1922," writes Parker⁵ (Newcastle-upon-Tyne), "while examining a number of carcasses and internal organs of dairy cows which, immediately prior to slaughter, had been subjected to the subcutaneous tuberculin test, the writer was

surprised to find lesions of tuberculosis in a considerable proportion of those which had given no reaction whatever." In a special research on the subject Parker found that among fifty subcutaneously tested animals eleven of the nineteen negatives showed post-mortem evidence of tuberculosis. In only one of these were the post-mortem findings confirmed by the microscope or by guinea-pig inoculation. Three of the failures were classed as "ceased reactors." One failure to all tests was an attractive-looking animal that had never been known to suffer from illness of any description. She was tested on four occasions by the subcutaneous method, at intervals of not less than one year, also by the ophthalmic and intradermal methods. The result of the test on every occasion was completely negative. Yet on post-mortem examination, within seventy-two hours of the final test, lesions of tuberculosis were found in the bronchial, mediastinal, portal, and mesenteric lymphatic glands. Jowett⁶ (Capetown) made a comparative study of subcutaneous and intradermal tests, checked by post-mortem examination, in 225 cattle. In his table of results he gives nine cases that were subcutaneously negative, post-mortem tuberculous, and intradermally positive. One of his negative cases (positive three and a half years previously) showed at post-mortem three fibro-caseo-calcareous tuberculous lesions in the left bronchial lymphatic gland, each the size of a pea, which were proved by guinea-pig inoculation to contain living virulent tubercle bacilli. Rutherford (Ottawa), in an article on "Open-air Experiments with Tuberculous Cattle,"⁷ gives the interesting post-mortem records of six cases that became "ceased reactors" and of sixteen cases that became "ceased reactors" but subsequently reverted to the positive state. One of his negative cases, a healthy and thrifty 2-year-old heifer, showed that an animal "while still retaining externally the appearance of health may within a comparatively short period become infected to such an extent as to nullify the action of tuberculin." She passed the subcutaneous test successfully on four occasions, yet the post-mortem record is: "Right lung contained six purulent cavities each as large as an egg; tuberculous process involving visceral, diaphragmatic, and costal pleural surfaces, right side of thorax; anterior and posterior mediastinal glands also tuberculous." His experiences led him to conclude that open-air treatment was "not likely to exercise any marked curative influence on animals already tuberculous, especially when reinfection is possible through cohabitation with clinical cases."

* Number of cases tested, 260; of followed-up cases alone (139), 66 negative—that is, over 25 per cent.

† Number of cases tested, 120, of which 10 were negative—that is, 8.3 per cent.

The impression derived from these and other similar reports is forcibly expressed by Lignières.⁸ "The importance of the failures of tuberculin (that is, the subcutaneous tuberculin test) is such that it is impossible to base alone on its use the prophylaxis of tuberculosis." That is exactly the question raised by Lindborg's articles. In the campaign against this disease, even in individual doubtful or suspicious cases, can the subcutaneous tuberculin test be relied upon to discriminate correctly between tuberculosis, however minute, and the non-tuberculous condition, either initial or cured?

Koch's Claim

In contrast to its use for treatment in man, tuberculin very soon after its discovery in 1890 came to be generally accepted as an invaluable means of diagnosis in cattle. In 1901 Koch reported:

"In proof of the diagnostic value of tuberculin, I point to its extensive use as a means of ascertaining tuberculosis in cattle. According to the calculations which Voges has collected from numerous reports, and according to the careful investigations of Eber, it gives, if properly applied, correct diagnosis in 97 to 98 cases in a hundred."

This statement requires some qualification. The often quoted figures of Voges—7,327 cases with 2.78 per cent. of failures—were compiled from sixty-nine sources, two of which, comprising no fewer than 5,526 cases, were collections of positive reactors only, that proved on being slaughtered to be tuberculous.¹⁰ These cases no doubt demonstrate the correctness of the positive test, so far as they individually are concerned, but they are clearly inadmissible as evidence of the average number of failures, positive or negative, in a hundred head of cattle. When they are deducted the figures from reports collected by Voges fall more or less into line with those collected by Eber and Bang. The reports collected by Eber¹¹ make the average of error 13.14 per cent., those collected by Bang 9 per cent.

Eber set himself to a careful study of the discrepancy in the reports of the various authors. He made careful observations of the upper and lower limits of temperature in clinically normal animals, noted the daily variations, recognized records that were suspiciously pathological and others that were definitely so, and on the basis of these observations formulated rules for guidance in the interpretation of the reaction. With a limited degree of preliminary fever certain precautions were necessary in reading the result in order to avoid error, and with a still higher preliminary temperature the test was more or less unreliable. In this way he was led to recognize a doubtful class, in which a decision was only to be arrived at after, or in conjunction with, the most exact clinical examination. The practical value of these observations was demonstrated by Eber in ninety tested animals that were subsequently slaughtered and divided by careful examination into tuberculous and non-tuberculous. The error of the test carried out in this careful way was only 1 to 2 per cent. It is the great merit of Eber to have demonstrated thus by actual figures and post-mortem examination that the subcutaneous tuberculin test in cattle gives, *if properly applied*, correct diagnosis in 97 to 98 cases in a hundred. A similar result was arrived at by Bang¹²; "in leaving out doubtful cases and those that were observed under unfavourable conditions, this figure denoting error fell from 9 per cent. to 3 per cent. (9 out of 272 necropsies)."

Recognized Exceptions

In one of his earliest communications on tuberculin Koch described minutely its action on lupus.¹³ Its

peculiar selective action, he said, was limited to the living tuberculous tissue, even the smallest most inconspicuous nodules participating in the reaction. Purely cicatricial tissue, caseous masses, necrosed bone, etc.—secondary products of the tuberculous process—were not affected. The symptom-complex of the tuberculin reaction was attributed by Koch to this focal activity, from which it might be inferred that the intensity of reaction would be relative, partly at least, not to the amount of secondary products, but to the amount, vascularity, and activity of the living bacillus-impregnated tuberculous elements. Theoretically the latter would require to have arrived at some perceptible degree of magnitude before reaction in typical form could be expected. This applies to the course of events following the entry of the bacillus into the body, before its actual establishment in the tissues, the so-called incubation stage. Fibrosed calcified caseous lesions, so shut off from the organic chemistry of the body as to leave no biological basis for reaction, belong to the same group of non-reactors, though they may contain living virulent tubercle bacilli, as happened in Jowett's case of fibro-caseo-calcareous nodules mentioned above. In such cases there may be recurrence of disease, accompanied by renewed positive tuberculin reaction, as no doubt occurred in some of the sixteen cases reported by Rutherford. A negative case described by Hamman and Wolman,¹⁴ in which at operation a small well-walled-off focus of tuberculous caries was found in a rib, is interesting in this connexion.

Failure of the test to provoke reaction in certain advanced cases has been recognized in veterinary practice since the early days of tuberculin. In some of these cases the failure may be attributable to exhaustion *per se*, a certain amount of vital energy being necessary for reactivity of any sort. In acute tuberculous fever, where the disease is exerting its full toxicity, injections of tuberculin may fail to produce additional focal disturbance with sufficient further elevation of temperature to constitute a reaction. Eber discusses this question in cattle. On the basis of his results in twenty febrile cases he concludes that while a moderate degree of fever does not necessarily invalidate the test provided certain precautions be observed, temperatures over 39.9° C. (103.8° F.) before testing may do so. (Temperature of the clinically normal cow 100.4° F. to 103°.) In man all such febrile cases are rightly excluded from the test on the ground of danger, so that in medical practice the question is narrowed down, for practical purposes, to cases that are either afebrile or can be rendered so by rest. If we further exclude those that can be definitely diagnosed by clinical means it is evident that this class of case is a small one.

Rare instances of failure to react in cases of widespread tuberculosis without clinical evidence, as in the cases reported by Parker and Rutherford, suggest that sometimes a certain balance between the activity of the disease and the immunity reactions resulting from the injections may prevent the characteristic reactive spurts of temperature. The temperature record during the administration of tuberculin in therapeutic doses in cases of persistent slight fever in children occasionally raises the same suggestion, neither a reactive rise nor a smoothing-out of the temperature giving a definite indication, notwithstanding ultimate proof of tuberculosis being the responsible factor.

The most effective dose of tuberculin has been fixed empirically at 0.4 or 0.5 c.cm. pure tuberculin for fully grown cattle. In man, Koch adopted, also empirically, a series of five injections—0.001, 0.002, 0.005, and 0.01 c.cm. repeated—in order to reach the dividing line without severe or dangerous reaction. Although many cases react

typically to the smallest of these doses, particularly where the blood supply is active in the affected area and focus, as in pulmonary and kidney conditions, and although cases of tuberculosis of every type or degree are almost certain to react to one or other of the full series, it has been shown that there are exceptional cases that will react first only to still larger doses. It need hardly be added that the tuberculin used should be definitely ascertained to be of standard strength. It is not enough merely to state that the same batch has proved its activity by its results in other cases.

Lindborg's most Striking Case

Lindborg's most striking case is that of the 8-year-old boy who died of meningitis three months after a negative test. As this boy was a sanatorium in-patient suspected of pulmonary or hilar tuberculosis in an active stage we can only assume, in the absence of post-mortem evidence, that meningitis occurred as the result of the liberation of tubercle bacilli from a tuberculous focus in lung or gland into pulmonary vein or thoracic duct, at all events from some pre-existing focus. Why, then, did he not react, in virtue of this originating focus? The question calls for production of the temperature and pulse charts with the test doses recorded thereon and full clinical notes of the case. Presumably, in view of the age and condition of the patient, the first dose was a reduced one. Lindborg seems to agree with the view that reaction first to a dose of 0.01 c.cm. is of little value as an indication of active disease, though a positive result to smaller doses is more significant. How far up were the doses carried in this case—to 0.005 c.cm.? Probably not further, if so far. No precise information is given. Were there any clinical features in this case that might have led an investigator like Eber or Bang to place it in the doubtful class for further consideration? We may speculate as to the original source, whether it was such as to conduce to non-reaction by reason of being well walled off like the cases of Jowett or Hamman and Wolman, or whether there may have been an advanced condition, non-reactive by reason of some obscure balance of immunological attack and defence. We have not been given the material on which to form an independent opinion. As presented the case does not do more than suggest that caution is required in the interpretation of results, and that there is need for detailed investigation of apparent anomalies.

Favourable Opinions

Lindborg's articles are in effect a plea for caution in accepting a negative subcutaneous test as of absolute value. Relative and practical value is admitted. Kettelkamp expresses a similar guarded opinion. "Even the most sceptical critic will allow a 75 per cent. reliability. If this be so, then, if our other means of diagnosis have failed and the patient is negative to subcutaneous tuberculin, we can inform him that the chances are at least three to one that he has no tuberculosis, an assurance which is certainly worth while, and very gratifying to an anxious tuberculosis suspect. . . . It has been the custom at the Robert Koch Hospital, on discharging the negative cases, to advise them to observe precautions as anyone should against tuberculosis, and to report to the clinics for observation periodically, but that so far as science could determine they had not active tuberculosis at that time." Lawrason Brown and F. Heise,¹⁵ from an experience of 324 tested cases (13 per cent. negative), express much the same view. "Patients who fail to react to this dose [a second dose of 0.01 c.cm.] may be safely returned home and to work . . . recent pulmonary tuberculosis is in all probability not present . . . a negative reaction in selected cases is so infrequently followed by relapse as

to be fairly negligible." Finally, these words of McFadyean,¹⁶ whose long and intimate knowledge of tuberculin and its literature in veterinary medicine give them great weight, are of interest in this connexion.

"None of the methods of tuberculin is perfect . . . but there are two methods that have stood the test of trial on a huge scale, and no country that can find the means to finance a scheme of eradication need now hesitate from fear that it would fail because of inability to diagnose the disease. When the object is to stamp out tuberculosis from a herd complete reliance should not be placed on one method of testing. When intelligently employed two different methods reduce the chance of error nearly to the vanishing point."

Conclusion

A critical examination of Lindborg's interesting papers, and of the writings of the authors quoted in support of his thesis, in the light of a wide survey of the subject, leads to the conclusion that in these communications sufficient detail has not been presented to warrant acceptance of the cases and statistics at face value. For the purpose of ascertaining absence of tuberculous infection or biological cure, not to mention the estimation of the relative importance of latent disease, the subcutaneous test stands firm. Satisfactory proof has not been advanced that it fails to do what Koch claimed for it—in the case of the negative, "that the case is not one of fresh or progressive tuberculosis demanding specific treatment." Nor is there anything in what has been brought forward to disturb confidence in the reliability of the test, when properly performed, as a sound basis for the elimination of tuberculosis either in cattle or in man.

The value of newer and simpler methods is a separate question.

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