# THE LÜBECK CATASTROPHE

## A GENERAL REVIEW

In the early part of last year there occurred at Lübeck in Germany one of those happily infrequent disasters which have from time to time accompanied the use of prophylactic vaccination. The vaccine used on this occasion was prepared from the B.C.G. strain of tubercle bacillus, which, as is well known, has, as the result of subculture for several years on a glycerin-bile-potato medium, become almost entirely avirulent to man and animals. During a period of two months, stretching from February 24th to April 25th, 1930, this vaccine was administered to 249 newly born infants. Of these many developed acute tuberculosis during the next few weeks and died; others developed subacute lesions, while a considerable proportion remained perfectly well. The total death roll up to January 29th of this year was seventy-five. Inquiry into this catastrophe was rapidly set on foot, and papers have been published, particularly by Professor Ludwig Lange[1 2] of the Reich Health Office, and Professor Bruno Lange[3 4] of the Robert Koch Institute in Berlin, dealing with the results of the investigation. Pending the issue of an official report containing all the findings, it is perhaps worth while summarizing the knowledge which has so far been gained of this most regrettable incident.

### PREPARATION AND DISTRIBUTION OF THE VACCINE

On July 27th, 1929, a strain of B.C.G. was sent from the Pasteur Institute in Paris to Dr. Altstaedt of Lübeck, who handed it to Professor Deycke of the General Hospital. Some time after its arrival the culture was inoculated into animals, and apparently proved to be avirulent. According to Calmette[5] the same strain was also sent to Mexico and to Riga, and the following subculture was used for the preparation at the Pasteur Institute of a vaccine which was administered to 3,016 infants without any detrimental result. There is therefore very little doubt that the culture originally sent from Paris was avirulent.

It has been the practice of Calmette and Guérin to keep their B.C.G. strain in the laboratory on a glycerin-bile-potato medium, and for the preparation of vaccine to grow it in Sauton's liquid medium. Deycke, however, after using the potato medium for a short time, subcultured his strain on egg medium, with or without the addition of haematin, and used these solid cultures for the subsequent preparation of his vaccine.

Before the receipt of the B.C.G. strain, Deycke was in possession of a number of cultures of tubercle bacilli, but owing to an accidental rise in the temperature of the incubator in which they were kept these were all killed.

For a time, therefore, the B.C.G. strain was the only culture of tubercle bacilli in the laboratory. In September, 1929, however, a strain, reputed to be of human type, was obtained from Kiel. This strain was isolated in 1927 from a child with hip-joint disease at the Charité Hospital, Berlin, and was handed over in 1928 to the Robert Koch Institute, where it was given the label H29; in April, 1929, a subculture was forwarded to the Hygienic Institute at Kiel. In Deycke's laboratory the B.C.G. strain was kept in an incubator in a small room and was subcultured on a solid medium; the Kiel strain was kept in an incubator in a large room, and was subcultured only on a fluid medium. The actual preparation of the vaccine was entrusted to a woman assistant, who had been with Deycke for seventeen years.

On December 9th, 1929, a preliminary inoculation was made of one child, which had been removed at birth from a mother suffering from open tuberculosis. A second child was vaccinated on December 30th, 1929. The first child developed cervical lymphadenitis, which was attributed to congenital infection, and inoculation of an excised gland into a guinea-pig gave rise to general tuberculosis. The second child remained well, but developed a positive tuberculin reaction. One further preliminary inoculation was made on February 10th; this child subsequently developed mild symptoms of tuberculosis. The main series of vaccinations was commenced on February 24th, 1930, and between this date and April 25th 249 infants, about 50 per cent. of those born in Lübeck during this time, were inoculated, the usual three doses being given in the first ten days of life. Though suspicions were early aroused by the clinical condition of the vaccinated infants, nothing definite occurred till April 17th, when a child, vaccinated thirty-three days previously, died; unfortunately, permission for a necropsy was forbidden. On April 20th a second child died, and was found post mortem to have generalized tuberculosis; since the lesions were most marked in the lungs, it was concluded that the child had been infected by the respiratory tract from its mother, who was suffering from tuberculosis, though not of the open type. It was not till the third and fourth children died, on April 25th and 26th respectively, that the pathogenic nature of the vaccine was fully realized, and further distribution was stopped. At this juncture Professor Deycke, in order to avoid any possible error, destroyed all the remaining vaccine in the laboratory, together with the existing subcultures of the B.C.G. strain. This unfortunate step, which was clearly open to more than one interpretation, added greatly to the difficulties of the subsequent investigation.

### TIME DISTRIBUTION OF THE DEATHS

According to Professor Bruno Lange,[4] on October 18th, 1930, the figures were as follows. Of 252 inoculated children 67 had died from tuberculosis; 5 children had died from other causes, but in 2 of them tuberculosis was found; 21 children still living were severely ill, and 87 slightly ill; 72 children were apparently well. According to Professor Calmette,[6] in an article published on January 24th, 1931, the death roll had mounted to 75. One of the remarkable features of the deaths was their peculiar time distribution in relation to the issue of the vaccine. They may be divided into the following periods (see table).

*Morbidity and Mortality According to Position on October 18th, 1930*

| Period | No. of Vaccinated Infants | Died from Other Causes | Remained Well | Slightly Ill | Severely Ill | No. Dying | Percentage Dying |
|---|---|---|---|---|---|---|---|
| 9/12/29 to 10/2/30 | 3 | 0 | 1 | 2 | 0 | 0 | 0 |
| 24/2/30 to 27/3/30 | 129 | 1 | 10 | 40 | 17 | 61 | 47 |
| 28/3/30 to 7/4/30 | 32 | 2 | 20 | 9 | 1 | 0 | 0 |
| 8/4/30 to 10/4/30 | 21 | 0 | 6 | 10 | 1 | 4 | 19 |
| 11/4/30 to 25/4/30 | 67 | 2 | 35 | 26 | 2 | 2 | 3 |
| Total ... | 252 | 5 | 72 | 87 | 21 | 67 | 27 |

It will be noted that the highest mortality followed the vaccine distributed in the last week of February and the first four weeks of March; subsequently came a period of ten days in which the vaccine was comparatively innocuous; then there was a short period of three days during which it again proved pathogenic; and finally, a period lasting for a fortnight characterized by a marked fall in its virulence. In the cases that proved fatal the time elapsing between administration of the vaccine and

death varied considerably ; figures for the complete series of cases have not been published, but the average period seems to have been about twelve weeks, with a minimum of thirty-three days. As regards sex, the male infants suffered more severely than the female ; thus, of 139 boys vaccinated 38, or 27 per cent., died ; of 110 girls vaccinated only 17, or 15 per cent., died.

### CLINICAL AND POST-MORTEM FINDINGS

According to Dr. M. Klotz,[7] director of the Children's Hospital at Lübeck, the early symptoms observed were failure to thrive in spite of breast-feeding, mild febrile attacks, vesicular eruptions, and swelling of the cervical glands. Later, in the more severe cases, the cervical glands enlarged to the size of hen's eggs, and caused interference with respiration and swallowing ; and there developed an extreme degree of anaemia, high intermittent fever, prolonged vomiting, profuse diarrhoea, and very severe meteorism, generally localized to one or two parts of the abdomen, and found at necropsy to result from innumerable strictures of the gut with consequent strangulation through adhesions and enlarged glands. Tubercle bacilli were found without difficulty in the vomit, sputum, and stools.

Post mortem the picture was uniformly that of the type of tuberculosis commonly found after alimentary infection. Besides involvement of the intestine, with numerous ulcers and strictures, and enlargement of the mesenteric glands, the lungs were infiltrated, often one or more lobes being affected, and the infiltrated areas looking like Perlsucht nodules. The glandular enlargement was enormous. Purulent discharge sometimes flowed from the nose, and ulcerating skin rashes were occasionally found. Pleural and peritoneal exudates were not uncommon. But, strangely enough, no meningitis or cerebral tuberculosis was seen. The condition of the bronchial glands is not mentioned.

### EXAMINATION OF THE AVAILABLE CULTURES

Considerable difficulty was experienced in obtaining suitable cultures for examination, since the B.C.G. subcultures and the vaccine in Deycke's laboratory had been destroyed ; the following material was ultimately collected, and examined by Professor Bruno Lange.

1. Organs from four infants who had died after vaccination, together with a culture obtained by Deycke from a cervical gland of a sick infant. The organs, when inoculated into guinea-pigs, gave rise to tuberculosis of a type considerably less severe than that normally following the injection of a fully virulent mammalian strain. Three strains recovered from the organs gave rise to a mild, fairly generalized tuberculosis, with a tendency to retrogression in animals injected with small doses. Subcutaneous inoculation of rabbits with organ suspensions led to nothing more than a local lesion. Intravenous inoculation with a pure culture (dose not stated) led in one rabbit killed eight weeks later to moderately extensive lesions in the lungs, and to a few submiliary nodules in the spleen, and in another rabbit killed five months later to several caseous areas in the lungs, up to a bean in size, to numerous miliary caseous tubercles in the liver, and to one large tubercle in the cortex of the right kidney. Culturally the three strains from the organs gave a moist, smeary growth on serum egg medium, typical neither of the human nor of the bovine type, though more closely resembling the former. Lange is unable to come to any definite conclusion as to the type of tubercle bacillus in these cultures. The strain recovered by Deycke behaved similarly to the three organ strains.

2. A culture isolated by Deycke on April 17th, 1930, from a guinea-pig injected on March 6th with a culture of B.C.G. ; this is referred to as the B.C.G. guinea-pig passage strain. According to Deycke four guinea-pigs were inoculated with the B.C.G. strain, and four more with material from a cervical gland of a vaccinated infant. Both sets of animals were injected six weeks later with 0.5 c.cm. of tuberculin, with the result that all of them died. At post-mortem, however, while three of the guinea-pigs inoculated with the glandular material showed generalized tuberculosis, the four guinea-pigs inoculated with B.C.G. showed lesions confined to the great omentum. Examination of the guinea-pig passage strain by Lange proved that it was capable of producing fairly severe progressive tuberculosis in guinea-pigs, while proving avirulent to rabbits. Culturally it resembled the human type.

3. A culture found in the middle of May, 1930, in the laboratory of the Lübeck Hospital, and labelled " B.C.G. 14.3.30." The sister cultures had probably been used about the end of March or beginning of April for the preparation of vaccine. Two subcultures of this strain, which is referred to as B.C.G.143, were also found. On subcutaneous injection of guinea-pigs it gave rise to no more than a local lesion, with some involvement of the regional glands, and even large doses failed to set up progressive generalized tuberculosis. To rabbits injected subcutaneously with 10 mg. and intravenously with 0.01 mg., it was completely avirulent. Culturally, it behaved more or less like a bovine strain, though growing freely on glycerin agar and glycerin broth. Lange concludes that it was probably a B.C.G. strain, though rather more virulent than the B.C.G. strain in the Robert Koch Institute, which was tested for comparison. It is probable, he considers, that not all strains of B.C.G. given out by the Pasteur Institute have been of the same degree of avirulence.

4. The culture received by Deycke from Kiel in September, 1929. This strain, which had come from the Robert Koch Institute in Berlin and was reputed to be of human type, proved to be of attenuated virulence for guinea-pigs, and to be almost avirulent for rabbits. Culturally it was of human type, but Lange considers the pathogenicity experiments to be too ambiguous to enable a definite diagnosis of type to be made.

5. A culture of the same strain as No. 4, but kept in the Robert Koch Institute since 1928. This strain, which was labelled H29, had been isolated in 1927 from a child with hip-joint disease in the children's clinic of the Charité Hospital, Berlin, and had been handed over to the Robert Koch Institute in 1928. In April, 1929, it was sent to Kiel, and in September, 1929, a subculture was forwarded from Kiel to Lübeck. Professor Opitz, who originally isolated it, suspected it of being bovine in type. When tested in 1930, it proved to be of definitely attenuated virulence for guinea-pigs. Rabbit inoculations gave inconstant results ; some rabbits developed tubercles in the lungs, one showed no disease, and one died with numerous tubercles in the lungs, kidneys, and liver. Culturally it resembled the human type, but Lange does not decide whether it was of human or bovine type.

Other material was collected and examined by Professor Ludwig Lange at the Reich Health Office. A full report of his investigations has not yet been published, but according to information given to the press by the Ministry of the Interior in July, 1930,[8] the following material was examined.

1. A strain of B.C.G., which since its arrival at Lübeck from Paris had been kept on a fluid medium. This strain, which was not used for vaccine preparation, proved avirulent to guinea-pigs, behaving, therefore, like a typical B.C.G. strain.

2. Two cultures of B.C.G., one corresponding to a batch of vaccine that gave rise to little disease and no deaths ; and one put up during the second half of April, and never used for vaccine preparation. Both of these cultures proved avirulent to animals.

3. The remains of four batches of vaccine, apparently in the possession of midwives. Two of these batches

corresponded to a high morbidity and mortality. They are still under examination, but according to Neufeld[10] both virulent and avirulent bacilli were recovered.

4. A culture that had been isolated by Deycke from a guinea-pig inoculated on March 6th, 1930, with a presumably pure culture of B.C.G. on a solid medium. This culture, which had been put up in Lübeck on April 17th, was found in the Reich Health Office laboratories to be highly virulent for guinea-pigs and only slightly virulent for rabbits, behaving, therefore, like a human type.

5. A guinea-pig inoculated by Deycke on April 17th with another, presumably pure, culture of the B.C.G. strain, was taken to Berlin, and when killed 109 days after inoculation was found to have extensive tuberculosis.

## DISCUSSION

Numerous hypotheses have been put forward by different workers to explain the virulence of the Lübeck vaccine, and it has even been suggested that, in order to increase the immunizing effect of the B.C.G. strain, small doses of virulent tubercle bacilli were intentionally added to the vaccine (Ascoli[9]). The real point at issue is whether another strain of tubercle bacillus became mixed with, or substituted for, the B.C.G. strain in the preparation of the vaccine, or whether the B.C.G. strain actually underwent a spontaneous increase in virulence.

In considering the first possibility it is necessary to remember that in the laboratory at Lübeck, throughout the time at which the vaccine was prepared, there was only one other strain of tubercle bacillus ; that this strain, which was either of attenuated human or attenuated bovine type, was kept in an incubator in a different room ; and that while the strain of B.C.G. used for vaccine preparation was subcultured on a solid medium, this strain was subcultured on a fluid medium. Confusion of the two cultures in these circumstances does not, on *a priori* grounds, seem to be very probable. Professor Bruno Lange, who upholds this hypothesis strongly, appears to be influenced in his judgement chiefly by a strong prejudice against believing in the possibility of a spontaneous reversion to the virulent form of the B.C.G. strain, and partly by the recovery from fatal cases of cultures more or less resembling in virulence the strain of reputed human type received by Deycke from Kiel.

In this connexion it may be remarked that at the outset of the inquiry great hope was entertained of the results of typing the bacilli recovered from the vaccinated cases. The B.C.G. strain was of bovine origin ; the Kiel strain was supposed to be of human type. Clearly, if one or other type was found in the organs of infants who had died after vaccination, it would be reasonable to assume that it was the corresponding type which had been present in the vaccine. Unfortunately, however, this hope was doomed to failure. In the first place it was forgotten that the bacteriological method of typing tubercle bacilli was capable of giving clear-cut results only with strains more or less freshly isolated from the animal body, which had not been accustomed to growth for long periods of time on artificial media. It so happened, however, that both the B.C.G. strain and the Kiel strain were old laboratory cultures, and could not, therefore, be expected, after a single passage through the body, to behave like typical strains. In the second place, it is not by any means certain that the Kiel strain was of the human type. Professor Opitz suspected it of being of bovine type, and Professor Bruno Lange was unable to determine whether it was of human or bovine type. The argument has been put forward that, because this strain was avirulent to rabbits, it must necessarily have been of human type ; but since its virulence for guinea-pigs was attenuated, it is impossible to lay any stress on this point. Many cultures of bovine type, which are becoming attenuated, behave exactly in this manner, losing their virulence for the rabbit before that for the guinea-pig. It is therefore clear that no definite conclusion can be reached whether the strains isolated from the vaccinated infants were identical with the Kiel strain. Professor Bruno Lange regards this as probable, but he is admittedly unable to prove it conclusively. He is supported, however, in his general inference by Professor Neufeld,[10] who believes that the Kiel strain was incorporated in the vaccine.

The other hypothesis, involving the spontaneous reversion of the B.C.G. strain to the virulent state, has been put forward by numerous workers both in Germany and abroad, and is sponsored by no less an authority than Professor E. Friedberger.[11] It is unnecessary to recapitulate here the experimental evidence that has been obtained in various countries in favour of this possibility. Experiments by absolutely independent workers have shown that the virulence of the B.C.G. strain is not fixed, but that under certain cultural conditions, either *in vitro* or *in vivo*, it may be rendered more or less completely virulent to animals.

To assert, as Calmette does, that in all these experiments the culture has become contaminated with another strain of tubercle bacillus is to offer an excuse that becomes increasingly tenuous with each additional piece of evidence brought forward. The fact that when kept on a glycerin-bile-potato medium, and when given to newborn infants, it proves to be avirulent, does not in any way disprove the possibility of its becoming virulent when exposed to other conditions. There is rapidly growing up a mass of careful observations, made on bacteria of different species, which indicate that the cultural appearances, the antigenic structure, and the virulence of an organism may be altered by a number of different environmental factors, and no one who was not completely ignorant of recent work in the field of bacterial variation would dare to maintain that a given culture was of fixed and immutable virulence.

In favour of the second hypothesis it has been pointed out by Friedberger and others that the Lübeck strain of B.C.G. was subcultured, not on glycerin-bile-potato, but on an egg medium ; and these workers have suggested that growth on this medium may have led to an increase in its virulence. So far no experimental evidence has been adduced to support this suggestion, and the few experiments made by Saenz[12] to test it have proved negative. The results obtained by examination of the various cultures at Lübeck can equally well be explained by assuming that the B.C.G. strain had acquired a certain degree of virulence as that it had become mixed with the moderately virulent Kiel strain.

Frankly it is impossible, on the basis of these results, to decide which of the two hypotheses is correct. In the absence of definite evidence it is wise, though unsatisfying, to maintain an open mind as to the real cause of the Lübeck catastrophe. The moral, however, is plain. The preparation of vaccines for large-scale distribution should be undertaken only under the most rigidly controlled conditions in laboratories set aside for this and for no other purpose.

## REFERENCES


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