

### THE GERM THEORY OF DISEASE

like to mention is the question of what information on the nature of the bacillus is revealed by the staining characteristics. Since I have found that the outer layer is completely impermeable to the action of strong mineral acid, it would seem that this condition would have a practical interest regarding the light it may throw on the question of sterilization or disinfection. It may be that all disinfecting agents which are acidic will be without effect on this bacillus, and one will have to be limited to alkaline agents.

I will now report the results of my examinations using this method. All of the cases which I examined were frank cases of Phthisis pulmonum. I examined in all 26 cases and in all of them the bacillus could be demonstrated. In the examination and preparation of these sputums, I took no special cares and made no special selection. In almost all cases it was sufficient to examine a single preparation, and in most only a single microscopic field. Only

#### Comment

This paper presents the first staining procedure for the tubercle bacillus which makes use of its acid-fast characteristics. The Ziehl-Nielsen method currently used differs in detail but not in principle from Ehrlich's method. This paper also illustrates an early stage in Ehrlich's scientific development. He attempts to consider

what properties of the tubercle bacillus are revealed by this remarkable acid-fastness and considers briefly the practical implications for disinfection. We will see later (page 176) how he uses such considerations to develop the whole field of chemotherapy.

in one case was it necessary to examine both preparations.

Naturally I have convinced myself through control experiments with other lung diseases, that there were no bacilli present. As further proof I can indicate a certain case. I had asked a friend to send me phthisistic sputums. I obtained one sputum in which I could find no bacilli. After questioning, I discovered that this sputum had been sent to me mistakenly from a man who did not have phthisis, but a perforated empyema.

The further question of what prognostic significance can be derived from this discovery cannot be answered without further experiments. I have found in certain acute cases a large number of bacteria, while in other more chronic cases, I have found a smaller number. On the other hand I have found a large number of bacilli in cases which are only progressing slowly.

### PART III

### Immunology

An inquiry into the causes and effects of the variolae vaccinae, a disease discovered in some of the western counties of England, particularly Gloucestershire, and known by the name of The Cow Pox

1798 • Edward Jenner

Jenner, Edward, M.D., F.R.S. 1798. An inquiry into the causes and effects of the variolae vaccinae, a disease discovered in some of the western counties of England, particularly Gloucestershire, and known by the name of The Cow Pox. Abridged from a facsimile edition published in 1923 by R. Lier and Co., Milan.

THERE IS A DISEASE TO WHICH THE Horse, from his state of domestication, is frequently subject. The Farriers have termed it *the Grease*. It is an inflammation and swelling in the heel, from which issues matter possessing properties of a very peculiar kind, which seems capable of generating a disease in the Human Body (after it has undergone the modification which I shall presently speak of), which bears so strong a resemblance to the Small Pox, that I think it highly probable it may be the source of that disease.

In this Dairy Country a great number of Cows are kept, and the office of milking is performed indiscriminately by Men and Maid Servants. One of the former having been appointed to apply dressings to the heels of a Horse affected with *the Grease*, and not paying due attention to cleanliness, inadvertently bears his part in milking the Cows, with some particles of the infectious matter\* adhering to his fingers. When this is the case, it com-

\* [Considering the early date of this paper, Jenner analyzes the disease in extremely modern terms.]

monly happens that a disease is communicated to the Cows, and from the Cows to the Dairy-maids, which spreads through the farm until most of the cattle and domestics feel its unpleasant consequences. This disease has obtained the name of the Cow Pox. It appears on the nipples of the Cows in the form of irregular pustules. . . . These pustules, unless a timely remedy be applied, frequently degenerate into phagedenic ulcers, which prove extremely troublesome. The animals become indisposed, and the secretion of milk is much lessened. Inflamed spots now begin to appear on different parts of the hands of the domestics employed in milking, and sometimes on the wrists. . . .

Thus the disease makes its progress from the Horse to the Nipple of the Cow, and from the Cow to the Human subject.

Morbid matter of various kinds, when absorbed into the system, may produce effects in some degree similar; but what renders the Cow-pox virus so extremely singular, is, that the person who has been thus affected is for ever after secure from the infection of the Small Pox; neither exposure to the variolous effluvia, nor the insertion of the matter into the skin, producing this distemper.

In support of so extraordinary a fact, I shall lay before my Reader a great number of instances.

Case I. Joseph Merret, now an Under Gardener to the Earl of Berkeley, lived as a Servant with a Farmer near this place in the year 1770, and occasionally assisted in milking his master's cows. Several horses belonging to the farm began to have sore heels, which Merret frequently attended. The cows soon became affected with the Cow Pox, and soon after several sores appeared on his hands. Swelling and stiffness in each axilla followed,

and he was so much indisposed for several days as to be incapable of pursuing his ordinary employment. Previously to the appearance of the distemper among the cows there was no fresh cow brought into the farm, nor any servant employed who was affected with the Cow Pox.

In April, 1795, a general inoculation \* taking place here, Merret was inoculated with his family; so that a period of twenty-five years had elapsed from his having the Cow Pox to this time. However, though the variolous matter was repeatedly inserted into his arm, I found it impracticable to infect him with it; an efflorescence only, taking on an erysipelatous look about the centre, appearing on the skin near the punctured parts. During the whole time that his family had the Small Pox, one of whom had it very full, he remained in the house with them, but received no injury from exposure to the contagion.

It is necessary to observe, that the utmost care was taken to ascertain, with the most scrupulous precision, that no one whose case is here adduced had gone through the Small Pox previous to these attempts to produce that disease.

Had these experiments been conducted in a large city, or in a populous neighbourhood, some doubts might have been entertained; but here, where population is thin, and where

\* [Even in this early time, people were inoculated for smallpox by using scabs from another individual suffering with the disease. If just the right amount of material was used, the inoculant suffered a mild smallpox infection, recovered, and was forever immune. Frequently, however, the inoculations were a failure, and the person either did not get any infection and was thus not immune or got too severe an infection and was seriously incapacitated or died. Therefore, in Jenner's time, inoculation for smallpox was a rather controversial procedure.]

such an event as a person's having had the Small Pox is always faithfully recorded, no risk of inaccuracy in this particular can arise. . . . [Then follow 15 other cases which follow this same pattern.]

Case 17. The more accurately to observe the progress of the infection, I selected a healthy boy, about eight years old, for the purpose of inoculation for the Cow Pox. The matter was taken from a sore on the hand of a dairy maid, who was infected by her master's cows, and it was inserted, on the 14th of May, 1796, into the arm of the boy by means of two superficial incisions, barely penetrating the cutis, each about half an inch long.

On the seventh day he complained of uneasiness in the axilla, and on the ninth he became a little chilly, lost his appetite, and had a slight headache. During the whole of this day he was perceptibly indisposed, and spent the night with some degree of restlessness, but on the day following he was perfectly well.

The appearance of the incisions in their progress to a state of maturation were much the same as when produced in a similar manner by variolous matter. The only difference which I perceived was, in the state of the limpid fluid arising from the action of the virus, which assumed rather a darker hue . . . but the whole died away (leaving on the inoculated parts scabs and subsequent eschars) without giving me or my patient the least trouble.

In order to ascertain whether the boy, after feeling so slight an affection of the system from the Cow-pox Virus, was secure from the contagion of the Small-pox, he was inoculated on the 1st of July following with variolous matter, immediately taken from a pustule. Several slight punctures and incisions were made on both his arms,

and the matter was carefully inserted, but no disease followed. The same appearances were observable on the arms as we commonly see when a patient has had variolous matter applied, after having either the Cow-pox or the Small-pox. Several months afterwards, he was again inoculated with variolous matter, but no sensible effect was produced on the constitution. . . .

[The material from this boy was used to inoculate another person, with the same results. The material was passed from one person to another through five passages from the cow.]

These experiments afforded me much satisfaction, they proved that the matter in passing from one human subject to another, through five gradations, lost none of its original properties, J. Barge being the fifth who received the infection successively from William Summers, the boy to whom it was communicated from the cow.

I shall now conclude this Inquiry with some general observations on the subject and on some others which are interwoven with it. . . .

They who are not in the habit of conducting experiments may not be aware of the coincidence of circumstances necessary for their being managed so as to prove perfectly decisive; nor how often men engaged in professional pursuits are liable to interruptions which disappoint them almost at the instant of their being accomplished: however, I feel no room for hesitation respecting the common origin of the disease, being well convinced that it never appears among the cows (except it can be traced to a cow introduced among the general herd which had been previously infected, or to an infected servant), unless they have been milked by some one who, at the same time, has the

care of a horse affected with diseased heels. . . .

The active quality of the virus from the horses' heels is greatly increased after it has acted on the nipples of the cow, as it rarely happens that the horse affects his dresser with sores, and as rarely that a milk-maid escapes the infection when she milks infected cows. . . .

It is singular to observe that the Cow-pox virus, although it renders the constitution unsusceptible of the variolous, should, nevertheless, leave it unchanged with respect to its own action. I have already produced an instance to point out this, and shall now corroborate it with another.

Elizabeth Wynne, who had the Cow-pox in the year 1759, was inoculated with variolous matter, without effect, in the year 1797, and again caught the Cow-pox in the year 1798. . . .

It is curious also to observe, that the virus, which with respect to its effects is undetermined and uncertain previously to its passing from the horse through the medium of the cow, should then not only become more active, but should invariably and completely possess those specific properties which induce in the human constitution symptoms similar to those of the variolous fever, and effect in it that peculiar change which for ever renders it unsusceptible of the variolous contagion.

May it not, then be reasonably conjectured, that the source of the Small-pox is morbid matter of a peculiar kind, generated by a disease in the horse, and that accidental circumstances may have again and again arisen, still working new changes upon it, until it has acquired the contagious and malignant form under which we now commonly see it making its devastations amongst us? And, from a consideration of the change which

## IMMUNOLOGY

the infectious matter undergoes from producing a disease on the cow, may we not conceive that many contagious diseases, now prevalent among us, may owe their present appearance not to a simple, but to a compound origin? For example, is it difficult to imagine that the measles, the scarlet fever, and the ulcerous sore throat with a spotted skin, have all sprung from the same source,\* assuming some variety in their forms according to the nature of their new combinations? The same question will apply respecting the origin of many other contagious diseases, which bear a strong analogy to each other. . . .

At what period the Cow-pox was first noticed here is not upon record. Our oldest farmers were not unacquainted with it in their earliest days, when it appeared among their farms without any deviation from the phenomena which it now exhibits. Its connection with the Small-pox seems to have been unknown to them. Probably the general introduction of inoculation first occasioned the discovery.

Its rise in this country may not have been of very remote date, as the practice of milking cows might formerly have been in the hands of women only; which I believe is the case now in some other dairy countries, and, consequently that the cows might not in former times have been exposed to the contagious matter brought by the men servants from the heels of horses. . . .

Should it be asked whether this investigation is a matter of mere curiosity, or whether it tends to any beneficial purpose? I should answer, that notwithstanding the happy effects of Inoculation,† with all the improvements which the practice has received since its first introduction into this

\* [This idea is now known to be wrong.]

† [Meaning inoculation with smallpox itself.]

## Jenner • *The causes and effects of the variolae vaccinae, or cow pox*

country, it not very unfrequently produces deformity of the skin, and sometimes, under the best management, proves fatal.

These circumstances must naturally create in every instance some degree of painful solicitude for its consequences. But as I have never known fatal effects arise from the Cow-pox, even when impressed in the most unfavourable manner . . . and as it clearly appears that this disease leaves the constitution in a state of perfect security from the infection of the Small-pox, may we not infer that a mode of Inoculation may be introduced preferable to that at present

adopted, especially among those families, which, for previous circumstances we may judge to be predisposed to have the disease unfavourably? . . .

Thus far have I proceeded in an inquiry, founded, as it must appear, on the basis of experiment; in which, however, conjecture has been occasionally admitted in order to present to persons well situated for such discussions, objects for a more minute investigation. In the mean time I shall myself continue to prosecute this inquiry, encouraged by the hope of its becoming essentially beneficial to mankind.

### Comment

Smallpox is a disease that has been known since antiquity. Its symptoms are characteristic, and because of this, it was easy to observe its transfer and to determine that it was infectious. We know today that it is caused by a large filterable virus, although we use the word virus in a different sense than did Jenner.

The process of inoculation had been practiced for centuries in the Far East. It was introduced into England from Turkey by Lady Mary Montagu, the wife of the British ambassador to Turkey. Although the process first was greatly resisted, it eventually became established in England. But because complications often arose, inoculation was not without its dangers.

Today we would consider cowpox virus to be a mutant of smallpox virus which has lost some of its virulence for man. It still retains the ability to induce the production of virus-neutralizing an-

tibodies in man. It is this fact which makes the process of inoculation with cowpox possible. This process was called vaccination (*vacca* = cow), and this word has later been applied to all artificial immunization procedures.

Jenner's observations are quite acute. He was able to bring together a number of diverse facts, and in so doing, arrive at a theory which seemed reasonable. He was fortunate that he could readily test his theory and clearly show that he was right. It is interesting that Jenner attempted to publish in the *Transactions of the Royal Society* the results of his first case. When the work was rejected, he then collected twenty-three cases and published his book. Because of the simplicity of the vaccination procedure and its high degree of safety, it has eventually become accepted as a common medical procedure, although Jenner met much resistance when his book was first published.