MILESTONES IN THE HISTORY OF INOCULATION.[1]

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1720. Smallpox inoculation introduced into England by Lady Mary Montagu.
1798. Introduction of vaccination by Edward Jenner.
1880. Pasteur immunizes against chicken cholera by attenuated culture.
1881. Introduction of the anthrax vaccine by Pasteur.
1885. Pasteur introduces protective inoculation against hydrophobia.
1888. Isolation of the toxin of diphtheria by Roux and Yersin.
1890. Discovery of the antitoxin of diphtheria by von Behring.
1897. Almroth Wright introduces preventive inoculation against typhoid by killed cultures.
1913. Introduction of the susceptibility test for diphtheria by Schick.

There must be few medical men who have not read or seen Mr. Bernard Shaw's admirable play, "The Doctor's Dilemma."

Those of you who are familiar with this work will, no doubt, recall that the play opens in the consulting room of Colenso Ridgeon, who has just been knighted for his discovery of a vaccine for the cure of tuberculosis. Among the doctors who come to congratulate him on his knighthood is an old cynic, Sir Patrick Cullen, who addresses Ridgeon in these words: "But your discovery's not new. It's only inoculation. My father practised inoculation until it was made criminal in eighteen-forty . . . I've tried these modern inoculations a bit myself. I've killed people with them; and I've cured people with them; but I gave them up, because I never could tell which I was going to do." Whatever we may think of Mr. Shaw's views, his accuracy in historical matters is beyond question, and he is perfectly correct when he tells us that inoculation is not new, and that it was made illegal in 1840.

Students of medical history cannot have failed to notice the curious fact that many so-called modern discoveries are but re-introductions of ancient customs. For example, inoculation for the prevention of disease, commonly regarded as a comparatively recent discovery, is in fact a very old one, practised—in the East at any rate—from time immemorial. This much is certain: but the period of its discovery and how it originated are purely matters for conjecture. There can be little doubt, however, that even in remote times it must have been recognized by man that certain diseases occur once only in the life of an individual, or that after recovery he is generally immune against further visitations of the same disease. It was also noticed probably that even a mild form of some maladies often

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confers protection against a recurrence of a similar infection. Thus we can assume that a vague appreciation of the principles of immunity existed at a very early period. From this knowledge it was but a short step to the artificial production of certain diseases by taking material from the sick and deliberately inoculating the healthy. Since those early times inoculation has become a more comprehensive process and includes, as you are well aware, the introduction into man and animals of many different substances, in many different ways, and for many different purposes. From old documentary records it appears that many primitive peoples used to protect themselves and their animals against various diseases in a crude kind of way, but with methods which are now recognized as essentially sound. Thus, certain tribes in South Africa attempted to render themselves immune against the bites of poisonous snakes by rubbing into the skin a mixture of snake venom and gum. The Moors immunized their cattle against pleuro-pneumonia by placing some virus of the disease under the skin of the animal. But of the many diseases which afflicted mankind there was none against which protection was more urgently needed than the smallpox. According to tradition smallpox had its origin in the Far East; but the evidence concerning its first appearance is scanty and unconvincing. It is certain, however, that smallpox was a familiar scourge in India and China long before the Christian era. Moreover, there are numerous accounts by various observers which show that there existed in early times in Eastern countries, as a means of protection against smallpox, the practice of inoculation or variolation. The process consists of introducing into the skin of a healthy person matter taken from a pustule of an active case of smallpox; the result is an attack of the disease, usually, though by no means invariably, mild.

Inoculation against smallpox is said to have been practised in India from a very remote period. It was performed by Brahmins who went on circuit at regular seasons for the purpose. Their method was to rub the skin of the part intended for inoculation with a cloth until small drops of blood appeared, and then to take a piece of wool charged with variolous matter, apply it to the wound and secure it with a bandage. In China, inoculation for smallpox was practised many centuries before it was known to the medical profession of Europe; the process was called "sowing the smallpox," and was carried out, either by plugging the nostrils with cotton saturated with an emulsion of smallpox scabs and water, or by grinding into a powder the crust from a pustule and blowing it into the nose through a bamboo pipe. Smallpox inoculation was also a well-known custom in Persia, Georgia, Armenia and Arabia. From Asia and Africa the practice passed into Europe by way of Greece to Constantinople, where it was known towards the end of the seventeenth century. In Western Europe inoculation was performed in certain districts of France, and was a well-known practice in Paris during the eighteenth century. It is interesting to note how a burning question of the day may be reflected even in the

fashions of the times. Thus, the writer of the life of Mdlle. Rose Bertin, milliner to Marie Antoinette, relates how a method of dressing ladies' hair was introduced to coincide with the inoculation of the young King Louis XVI; this was known as the "Pouf à l'Inoculation," and every lady who wished to be in the fashion was obliged to adopt this coiffure.

It is difficult for the present generation to realize the prevalence of smallpox and its terrible consequences in the days of our forefathers. Some idea, however, of the ravages of this disease in Europe, prior to the introduction of vaccination, may be gathered from the estimates of the number of deaths from smallpox made by various writers.

Bernouilli, the celebrated mathematician, calculated that no fewer than 15,000,000 of human beings died of smallpox every twenty-five years. The French physician, De la Condamine, estimated that smallpox destroyed, maimed or disfigured a fourth part of mankind. In the words of Thebesius: "No nation, no rank, no constitution, neither age nor sex, escaped smallpox; all trembled in mentioning its name."

Macaulay portrays in striking language the horror with which smallpox was regarded in England at the end of the seventeenth century. In speaking of the death of Queen Mary II from smallpox, in 1694, he says: "That disease over which science has since achieved a succession of glorious and beneficial victories was then the most terrible of all the ministers of death. The havoc of the plague had been far more rapid; the plague had visited our shores only once or twice within living memory, and the smallpox was always present, filling the churchyards with corpses, tormenting with constant fears all whom it had not yet stricken, leaving on those whose lives it spared the hideous traces of its power, turning the babe into a changeling at which the mother shuddered, and making the eyes and the cheeks of the betrothed maiden objects of horror to the lover."

So prevalent was smallpox at this time that it was looked upon as practically unavoidable. Indeed, the difficulty of getting through life without it was expressed in a popular saying current in Germany during the eighteenth century: "*Von Pocken und Liebe bleiben nur wenige frei.*" (Few remain free from smallpox and love.) But although smallpox was regarded as an almost inevitable accident of human life, it was found by experience that nobody was attacked with the disease a second time. This immunity from a second attack seems to have been generally recognized and advantage taken therefrom, for people used to advertise for servants who had already suffered from smallpox, in much the same way as we advertise nowadays for dogs who have "got over" distemper. Here is an advertisement taken from a London newspaper of the period:—

"Wanted, a man between 20 and 30 years of age, to be a footman and under-butler in a great family; he must be of the Church of England and have had the smallpox in the natural way. Also, a woman, middle aged, to wait upon a young lady of great fashion and fortune; the woman must be

of the Church of England and have had the smallpox in the natural way, very sober, steady and well-behaved, and understand dress, getting up lace and fine linen, and doing all things necessary for a young lady that goes in to all public places and keeps the best company. Enquire of the printer of this paper. October 1, 1774."

Such then, in brief, was the position as regards smallpox and its prevention up to the early part of the eighteenth century.

I have taken as my first milestone in the history of inoculation the year 1720, because the interest of medical science in the subject began about that time owing to the introduction of smallpox inoculation into England by Lady Mary Wortley Montagu. It appears that Lady Montagu, the wife of the British Ambassador at the Turkish Court in Constantinople, was much impressed by the harmlessness of the Turkish method of smallpox inoculation, and in 1717 wrote on the subject to a friend in England. An extract from her letter is worth quoting:—

"*Apropos* of distempers, I am going to tell you a thing that I am sure will make you wish yourself here. The smallpox, so fatal and so general among us, is here entirely harmless by the invention of ingrafting, which is the term they give it. There is a set of old women who make it their business to perform the operation every autumn in the month of September, when the great heat is abated. People send to one another to know if any of their family has a mind to have the smallpox. They make parties for this purpose, and when they are met (commonly fifteen or sixteen together) the old woman comes with a nutshell full of the matter of the best sort of smallpox and asks what veins you please to have opened. She immediately rips open that you offer to her with a large needle (which gives you no more pain than a common scratch) and puts into the vein as much venom as can lie upon the head of her needle, and after binds up the little wound with a hollow bit of shell; and in this manner opens four or five veins. . . . Every year thousands undergo this operation; and the French Ambassador says pleasantly that they take the smallpox here by way of diversion, as they take the water in other countries. There is no example of anyone who has died in it, and you may believe I am very well satisfied of the safety of the experiment, since I intend to try it on my dear little son. I am patriot enough to take pains to bring this useful invention into fashion in England."

Lady Mary was true to her word and had her son inoculated by Maitland, the surgeon to the British Embassy. Four years later the experiment was repeated on her baby daughter in England in the presence of several of the Court physicians. The event excited the greatest interest throughout the country, both in fashionable as well as in medical circles, but the British public regarded the practice with suspicion, and so for a time it made little progress.

In August, 1722, a suggestion was made to inoculate some condemned criminals at Newgate as test cases. Six criminals were, accordingly,

inoculated under the direction of Sir Hans Sloane with satisfactory results. Indeed, the success of this experiment in some measure re-assured the minds of the people as to the safety of the practice. Towards the close of the year public attention was again drawn to the subject, by the announcement that the two daughters of the Princess of Wales had been inoculated. The practice thus encouraged by royal favour received a fresh impetus and began to spread throughout the country.

It was not long, however, before grave doubts as to the safety of inoculation arose by the announcement of several cases which had terminated fatally from smallpox after inoculation. Violent opposition to the practice sprang up both from members of the medical profession and the clergy, and a heated dispute rapidly developed. One doctor called inoculation "a barbarous and dangerous invention," another, "an artificial way of depopulating a country." A well known divine denounced inoculation in his pulpit as "a dangerous and sinful practice." Notwithstanding these outcries and many others of a similar kind, inoculation slowly gained ground in England, and in 1746 a hospital for the inoculation of the poor was established in London. However, as controversy still continued on the vexed question, the Royal College of Physicians decided in 1754 to issue a manifesto upholding the practice.

Inoculation reached America a few months after its introduction into England. George Washington and Benjamin Franklin were staunch advocates of the measure. Washington, in fact, had a general inoculation of all troops under his command, and gave orders that all recruits should undergo the same treatment.

In England, inoculation was not firmly established until more than a quarter of a century after its introduction. As time went on and inoculation continued to be practised, it gradually became evident that the benefits expected were far from being realized. For, not only did inoculation fail to exterminate smallpox, but actually spread it by keeping alive the natural disease and by causing its diffusion among those who were not protected by inoculation. In many instances smallpox was introduced by inoculation into towns which had previously been free from the disease. Moreover, as inoculated smallpox was just as contagious as true smallpox, and as few precautions against infection were taken, each case only served to disseminate the disease and smallpox continued to spread. There can be little doubt that inoculation protected those who submitted to it, by diminishing the chances of an attack of smallpox, and by lessening the virulence of the disease in those attacked; at the same time, it should be remembered that inoculated smallpox, although usually mild, was not always so, and many deaths occurred from the inoculated variety. Indeed, the Bills of Mortality clearly proved that in London more persons had died of smallpox since the introduction of inoculation into the country. In short: inoculation protected the individual, but endangered the community. Gradually the practice fell into disuse and

disappeared some years after the advent of vaccination, smallpox inoculation finally being made illegal by the Act of Parliament in 1840.

The close of the eighteenth century saw the dawn of a new era in preventive medicine by the discovery and establishment of vaccination by Edward Jenner. He proved by his carefully-planned experiments that cowpox protects against smallpox, and to Jenner belongs the credit of giving to the world the priceless boon of vaccination. The protective value of cowpox against smallpox had been recognized by the cowherds and dairymaids of England as a vague tradition for some time—the milkmaids of Gloucestershire and elsewhere had found out this fact for themselves; but it was Jenner who by his insight and tireless labours translated a piece of folk-lore into a scientific truth, and persuaded the medical profession all over the world to accept it as such.

Jenner, at the age of 13, was apprenticed to a surgeon of Sodbury near Bristol, with whom he remained for six years. It was during this period of his life that the following incident occurred. A young woman came to seek medical advice, and the subject of smallpox being mentioned in her presence, she exclaimed, "I cannot take that disease, for I have had cowpox." Her remark, doubtless, made a deep impression on Jenner and suggested to him a new line of research. In 1770, when Jenner was 21, he went up to London to study under the great John Hunter, and there assisted him to form his museum. During his pupilage, Jenner told Hunter that he thought cowpox would prevent smallpox; but Hunter, apparently, was not much impressed with Jenner's idea. He did, however, give his pupil an excellent piece of advice, "Do not think," said Hunter, "but try, be patient, be accurate." There is no doubt that the influence of the master exerted a lasting effect on the pupil, who became an expert anatomist, a careful experimenter and a shrewd observer. Jenner soon got tired of life in London and returned to his native place—Berkeley in Gloucestershire, and there he lived, except for a short absence, a country doctor the rest of his days.

While at Berkeley he pursued his studies on cowpox by careful observation and experiment. Many years were to pass, however, before the crowning discovery of the prophylactic value of vaccination. At length an excellent opportunity occurred for making an important experiment. Cowpox broke out at a farm near Berkeley, and a dairymaid, Sarah Nelmes, contracted the disease from one of her master's cows. Jenner seized this opportunity and resolved to put his theories to a practical test. On May 14, 1796, Jenner took some cowpox matter from a pustule on the girl's hand and with it inoculated—or in other words, "vaccinated"—James Phipps, a healthy boy of 8 years. Six weeks later Jenner reinoculated the boy with variolous matter taken directly from a patient with smallpox, and much to Jenner's delight no small-pox followed. The continued absence of cowpox from the dairies in the neighbourhood prevented Jenner for some months from carrying out further experiments. However, when cowpox

reappeared in the district two years later, Jenner repeated his first successful experiment on several occasions, and was thus able to demonstrate beyond doubt that cowpox, a mild and trivial disease, can be readily transferred from man to man, and, more important still, that it protects against smallpox. The chain of evidence was complete; but Jenner proved his theory to his own satisfaction before making known the facts to the public. Writing of his discovery he says: "I placed it upon a rock, where I knew it would be immovable, before I invited the public to take a look at it." Hence, it was not until 1798, after twenty years or more of careful observation and research, that he published his now famous *Inquiry* announcing his discovery to the world.

The practice of vaccination thus introduced by Jenner was soon taken up in London and rapidly accepted both in Europe and America as a valuable protective measure against smallpox. It was adopted with enthusiasm in Switzerland, Italy and France. The Spanish Government fitted out an expedition in 1803 for the purpose of diffusing the knowledge of vaccination throughout all the Spanish possessions. The Empress of Russia, who was a staunch champion of Jenner, urged her subjects to be vaccinated and decreed that the first child vaccinated should be named "Vaccinoff" and be educated at the expense of the State. Jenner was a great favourite with Napoleon. The story is told of how Jenner petitioned the Emperor to allow two Englishmen detained in captivity abroad to return home. Napoleon was about to refuse the petition when he was reminded that it came from Jenner. "Ah, from Jenner!" said the Emperor, "what that man asks is not be refused." And so the prisoners were released and sent back to England. Napoleon also demonstrated his confidence in Jenner's methods by ordering all soldiers, who had not suffered from smallpox, to be vaccinated.

It was hardly to be expected that so great an advance in preventive medicine could be made without opposition. The "Anti-vaccinationists" came into being shortly after vaccination was introduced. "Smallpox," they said, "is a visitation from God and originates in man; but cowpox is produced by presumptuous impious men; the former Heaven ordained, the latter is perhaps a daring and profane violation of our Holy Order." Tracts were published denouncing vaccination and sermons were preached to show the wickedness of the practice. Alarming stories of the evil effects of vaccination were noised abroad. One man declared that inoculation of the cowpox had been discontinued in the town in which he had been staying, because those who had been vaccinated "bellowed like bulls." It was also rumoured that women who had been vaccinated gave birth to children resembling calves. Another writer on the subject tells the story of a lady who complained that "since her daughter had been vaccinated she coughs like a cow, and has grown hairy over her body." Notwithstanding these fulminations, vaccination made steady progress throughout all classes of the population and every country vied in honouring its discoverer.

A little more than one hundred and thirty years have passed since Jenner's epoch-making experiment in 1796. He believed that smallpox might be banished from the earth by the universal adoption of vaccination. His hopes have not been fully realized. Sound as Jenner's principles were, he fell into one error; he thought quite naturally, but wrongly, that one vaccination in childhood was sufficient to protect for life, and the discovery later that this was not so shook the faith of many in his methods. Nevertheless, Jenner's discovery, despite its many traducers, is a milestone of outstanding importance, not only in the history of inoculation, but also in the history of medicine itself. Since its introduction to the world in 1798, vaccination has made steady progress throughout all classes of the community, with the result of gradually diminishing the frequency of smallpox epidemics, the severity of the disease, its incidence on the population, and its death-rate. The principles which Jenner advocated and put into practice still remain the only effective means of protection against one of the most dreaded scourges that afflict mankind, and Edward Jenner will ever be remembered as one of the greatest benefactors of humanity.

Many years elapsed before Jenner's principles of vaccination were applied to other diseases. It is very largely to the brilliant researches of Louis Pasteur, and his investigations into the causation and prevention of disease, that we owe the foundation of the scientific era of inoculation which has produced such remarkable developments in recent times.

Pasteur's early work on fermentation and putrefaction led him to believe that infectious diseases were due to micro-organisms. While studying the disease chicken cholera, Pasteur made by chance a remarkable discovery—the only accidental discovery of his memorable career, but one which was to have far-reaching effects in the future. Pasteur discovered that micro-organisms could be modified in virulence. One day it happened that Pasteur inoculated some hens with an old culture of chicken cholera made some weeks before in his laboratory. Much to his surprise, the hens did not die; they sickened for a few days and then recovered. Clearly the virulence of the bacilli had disappeared. Some time later Pasteur reinoculated these same hens with a virulent culture, only to find that they remained well, while inoculation with the same culture was fatal to other healthy hens. Evidently Pasteur had lighted upon a method of producing immunity. With characteristic energy he set himself the task of finding out what had lessened the virulence of the bacilli in his old culture. After weeks of patient labour he proved that, by keeping cultures of chicken cholera a certain length of time in contact with the air, their virulence could be so diminished or attenuated as to be no longer capable of producing the disease. Furthermore, Pasteur discovered that, if hens were inoculated with the attenuated culture, they would become immune to infection with the normally virulent bacilli. Pasteur's discovery in 1880 of a method of producing immunity against

chicken cholera by means of an attenuated culture is an important milestone in the history of inoculation—it might almost be called a foundation stone, for upon it was established the principle of bacterial vaccination—a principle which paved the way for the use of vaccines in many other diseases.

The experiments on the use of vaccines for chicken cholera formed the basis of Pasteur's investigations on anthrax or "charbon," the mysterious disease which was at that time causing such destruction among the cattle of France. The anthrax bacillus, discovered by Davaine in 1860, had already been isolated and identified in its various stages by Robert Koch. Pasteur's first attempts to produce a protective vaccine met with failure; but after numerous trials he was able to announce in February, 1881, that by cultivating the anthrax bacillus at an abnormal temperature (41° C.), he could obtain an attenuated form, which when introduced into cattle and sheep rendered them proof against anthrax. At first Pasteur's discovery was greeted with scepticism, and he was challenged by the Melun Agricultural Society to a public demonstration of his claim. Pasteur accepted the challenge and fifty healthy sheep were placed at his disposal; he was to vaccinate twenty-five of them, the remainder were to be used as controls, and later all fifty were to be inoculated with virulent anthrax bacilli. "You will see," wrote Pasteur with confidence, "the twenty-five unvaccinated sheep will perish, and the twenty-five vaccinated ones will survive." A further milestone was set up, which marks an occasion famous in the history of medicine, when in the spring of 1881, in a farmyard at Pouilly-le-Fort, before a large gathering of doctors, veterinary surgeons and farmers, the final test experiment was carried out, and, as Pasteur had predicted, the twenty-five vaccinated sheep remained well, while every one of the unvaccinated sheep died. It was, indeed, a great triumph for Pasteur. The success of this experiment led to the use of preventive inoculation against anthrax, now practised in all parts of the world where the disease is prevalent. It is interesting to note that Pasteur gave the name "vaccination" to his methods of protective inoculation as a compliment to Jenner.

Before, however, the completion of the discovery of the anthrax vaccine, Pasteur had embarked on a series of investigations of still greater importance, namely, those into the cause and prevention of rabies in dogs and hydrophobia in man.

In studying rabies, Pasteur concluded that the seat of the rabid virus was not in the saliva only, as it was previously thought to be, but was also in the cerebral tissues. His next step was to attenuate the virus for use as a preventive against the infection in dogs. This he succeeded in doing by drying in air the spinal cords of rabbits artificially infected with rabies. Furthermore, he found that dogs, inoculated in ascending doses with preparations of these dried cords, were immune to rabies when subsequently bitten by rabid animals. Pasteur, however, wished to go

further. His next experiments were carried out to see whether inoculation with the attenuated virus would have a curative effect on animals already bitten; for he considered that, if this could be proved, it might then be possible to apply his treatment to human beings.

His hopes were expressed in a letter written to a friend in March, 1885, which runs as follows :—

"I also have some new experiments on rabies in hand, which will take some months. I am demonstrating this year that dogs can be vaccinated or made refractory to rabies after they have been bitten by mad dogs. I have not yet dared to treat human beings after bites from rabid dogs, but the time is not far off, and I am much inclined to begin by myself, inoculating myself with rabies, and then arresting the consequences; for I am beginning to feel very sure of my results."

As it happened the time was near at hand for trying his treatment on a human being, for, some months after this letter was written, a little Alsatian boy, who had been severely bitten two days previously by a mad dog, was brought to Pasteur's laboratory by his mother. Pasteur was persuaded to try his vaccine on the boy, and so give him the only apparent chance of recovery. A series of inoculations was therefore carried out over a period of thirteen days with no ill-effects. During the next few weeks, Pasteur became a prey to anxiety and dreaded to hear any moment that the boy had developed hydrophobia. The daily reports, however, were all favourable and the boy remained well. It was in October, 1885, that Pasteur made his statement on this case before the *Académie des Sciences*. By this time, three months and three days had passed and the boy had remained free from the disease. Directly Pasteur's great discovery was made known, people, who had been bitten by mad dogs, hastened to Paris from all parts of Europe, and a regular anti-rabic service was rapidly organized. Pasteur became immensely popular, and a subscription list was opened to the people of France for the establishment in Paris of an institute to bear his name. Thus was founded the *Institut Pasteur*. The example set in Paris was soon followed by other countries, and by 1889 there had been established at least twenty anti-rabic institutes in other parts of the world. Pasteur's discovery was confirmed by a Commission appointed by the British Government in 1886 to verify the facts. After fourteen months spent in investigating his treatment, they reported as follows: "It may be considered as certain that Monsieur Pasteur has discovered a prophylactic method against hydrophobia which may be compared with that of vaccination against smallpox. It would be difficult to over-estimate the utility of his discovery, both from the point of view of its practical side and of its application to general pathology."

Enthusiasm for Pasteur was spreading everywhere, and he was inundated with letters suggesting that he should find cures for such and such a disease. One day he received these lines: "You have done all the good a man could do on earth. If you will, you can surely find a remedy

for the horrible disease called diphtheria. Our children, to whom we teach your name as that of a great benefactor, will owe their lives to you.—A Mother."

Pasteur, in spite of his failing strength, had hopes that he would yet live to see a method of dealing with this disease devised. About this time Roux and Yersin, two pupils of Pasteur, were busily working at the Pasteur Institute to find a remedy for diphtheria. The bacillus, already discovered by Klebs in 1883, had been isolated in the following year by Löffler. Roux believed that the bacillus formed a toxin, and proclaimed his belief in a lecture delivered to the London Royal Society. "Microbes," declared Roux, "are chiefly dangerous on account of the toxic matters which they produce." Accordingly, Roux and Yersin set themselves to work out this problem, eventually in 1888 making the brilliant discovery that by filtering a broth-culture of diphtheria bacilli through unglazed porcelain they could obtain in the filtrate the toxin of the bacillus.

Before passing on to the next milestone, it is necessary to mention the theory of phagocytosis advanced by Metchnikoff a year before the discovery of the diphtheria toxin; for out of this famous theory arose the notion of making use of the serum of the blood as a therapeutic agent. It had been shown by bacteriologists that the serum of the blood plays an important part in resisting disease, and the idea of combating the toxins produced by pathogenic bacteria with resistant serum presented itself to several workers. This line of inquiry was followed up, and in 1890 came the classical discovery of the antitoxin of diphtheria by von Behring and the antitoxin of tetanus by Kitasato. These two workers proved that immunity against the toxins of diphtheria and tetanus could be obtained by the transference of the serum of animals previously immunized by a course of inoculation with such toxins—in short, that the serum of immunized animals is curative. Roux was mainly instrumental in bringing the subject from the experimental to the practical stage; for he discovered an easy method of making horses immune, and was thus able to obtain large quantities of antitoxin. Diphtheria antitoxin was placed in the hands of the medical profession in 1895—the year that Pasteur died. Since that date its value has been abundantly proved, not only as a curative agent for the protection of those suffering from diphtheria, but also as a prophylactic measure for those in contact with the infection.

The discovery of diphtheria antitoxin was a triumph of laboratory research and constitutes yet another milestone in the history of inoculation; for its introduction, together with that of the antitoxin of tetanus, into practical human therapeutics, laid the foundation of serum therapy.

It is impossible in the time available to consider the enormous developments of prophylaxis and treatment by specific inoculation since the new era of bacteriology was inaugurated by Pasteur, Koch and their immediate followers. It will be sufficient to say that our knowledge of this branch of preventive medicine has advanced along two distinct lines. On

the one hand is the method directed to the active immunization of persons by means of the various forms of protective inoculation with suitable vaccines; on the other is the method directed to the passive protection of persons by the transference of the serum of animals actively immunized by inoculation against certain specific diseases.

I have taken the year 1897 as another important milestone, because the use of killed organisms as a prophylactic measure against disease dates from that time. To Almroth Wright must be given the credit of initiating and exploiting a method of protecting against typhoid fever by means of killed cultures of *B. typhosus*. Further, it is largely owing to the advocacy of Wright that killed cultures have come to occupy an important position in the prophylaxis and treatment of many infections which can be definitely associated with a known type of organism. Wright's anti-typhoid vaccine was first tried on a large scale at Barming's Heath Asylum in 1897. Two years later it was used in India, when 4,000 British soldiers were inoculated. Then came the South African War, during the course of which Wright and Leishman prepared a vaccine and supervised the inoculation of 100,000 soldiers. The results, however, were disappointing. Leishman explained the lack of success by saying that the vaccine may have been rendered less effective by the use of too great a heat in killing the bacilli; further, no account was taken of the paratyphoid fevers, against which inoculation with the single typhoid culture offered no protection. Nevertheless, it was clear that a new weapon of great prophylactic value had been placed in the hands of Army medical officers. The results obtained with the anti-typhoid vaccine, especially under war conditions, and notably during the Great War, have been extremely satisfactory, and prophylactic vaccination against the enteric group of fevers has now established its position in preventive medicine.

This brings me to my last milestone—the discovery of the susceptibility test for diphtheria by Schick of Vienna. It can be asserted confidently that this discovery ranks in importance almost with that of the discovery of the antitoxin; for what the use of the antitoxin has done to improve the treatment of the disease, this method of detecting susceptibility together with the immunisation of susceptibles is now doing for its prevention. The discovery of this simple test in 1913 was soon followed by an easy method of immunizing susceptible persons against diphtheria. Several types of preparations have been used for the purpose; but all have as their basis diphtheria toxin which has been modified, either by association with antitoxin, or by treatment with some chemical agent. The method of immunization thus rendered available has been employed for some years in New York and other towns of America, and the diminution of diphtheria has been truly remarkable in the American communities in which this method has been adopted. Since 1920, Schick testing and immunization have been practised in a number of residential institutions and schools

throughout Great Britain with extremely favourable results. Although it is too early to dogmatize on this subject, the evidence which is steadily accumulating points to the conclusion that the Schick test together with the artificial immunization against diphtheria constitute one of the most notable of the recent advances in preventive medicine.

I have told you nothing original nor new. Indeed, it seems almost an impertinence to discourse before an audience of medical men, upon such well-known names as Jenner and Pasteur, and upon such familiar subjects as vaccination and inoculation.

This brief and imperfect outline of the history of inoculation makes no pretension to completeness; but from the "milestones" cited some measure, perhaps, of the debt we owe to these pioneers in preventive medicine may be gathered. Almroth Wright's prophecy that the physician of the future will be an immunizator has to a great extent been fulfilled. Numerous diseases have come under the immunizator's control; and yet we cannot forget that there are many, which yearly take a heavy toll of human life, against whose ravages he is at present powerless. I do not wish to conclude on too pessimistic a note, nor in any way minimize the great achievements of medical science; but one cannot help thinking that there is a good deal of truth in the words of a writer in a recent number of the ROYAL ARMY MEDICAL CORPS NEWS AND GAZETTE.

> "At last, through centuries of pain and cruelties that shocked her,
> Our Mother Earth achieved for us the Scientific Doctor.
> He knows the cause of all disease; our doubts he can dispel;
> Yet even now, as in the past—some die and some get well.
> There surely must be, you'll agree, some all pervading factor;
> For Doctor, Christian Scientist, Coué and Chiropractor,
> All seem to do their best or worst to cure this mortal shell;
> And always with the same result—some die and some get well."

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