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Nobel Prize in Medicines 1954



John Franklin Enders Thomas Huckle Weller Frederick Chapman Robbins

The Nobel Prize in Physiology or Medicine 1954 was awarded jointly to John Franklin Enders, Thomas Huckle Weller and Frederick Chapman Robbins "for their discovery of the ability of poliomyelitis viruses to grow in cultures of various types of tissue".

The principles of cultivation of bacteria were laid down in the late 1870's by Robert Koch. Since that time the bacteriologists could study systematically the diseases caused by bacteria, isolate the causative agents in pure culture and make themselves familiar with their nature. With the aid of the culture technique they were able to trace the routes, along which infection is transmitted, to detect carriers and other sources of infection thereby making a rational combat of epidemics feasible. They could produce therapeutic sera and prophylactic vaccines. Finally, the culture technique was instrumental in the discoveries of the modern wonder drugs, sulfa, penicillin, streptomycin, etc.

The 75 year old fight against the bacterial diseases has been successful. Although not completely eradicated, plague, cholera, typhoid, diphteria, and sepsis have ceased to be a threat to mankind. Tuberculosis seems to be under control. The trends are clearly

reflected in the vital statistics. Since the turn of the century the rate of mortality from bacterial infections in this country has been reduced by more than 90%.

Turning to the virus diseases we meet an entirely different picture. It is true that smallpox is brought under control thanks to the efficient vaccine that Nature itself has provided. Yellow fever was checked by means of mosquito control and with the aid of Theiler's vaccine, an achievement awarded the 1951 Nobel Prize. The spread of epidemic typhus can be prevented by the use of DDT - a feat likewise awarded a Nobel Prize - and the disease itself successfully treated with antibiotics. In all the others, however, our art fails us. Worst of all, many virus diseases are on the increase, a tendency particularly evident in poliomyelitis. After having been practically unknown at the turn of the century, poliomyelitis in this country is now responsible for almost one fifth of all deaths from acute infections. Similarly epidemic jaundice seems to increase; it presented serious problems particularly during the last World War. Many more examples could be mentioned.

It is not difficult to find the reason why the virologists have failed where the bacteriologists were so successful. They have been severely handicapped by the difficulties connected with the cultivation of viruses. Unlike bacteria and other microorganisms, virus is incapable of multiplying in artificial life less culture media. In the test tube it appears as an inert chemical substance; only in the interior of a living cell its hidden forces are liberated. Here, it turns the more active and incites a process which may, sometimes within a few minutes, lead to cell destruction and the production of hundreds of new virus particles.

At first the virologist had to resort entirely to animal experiments, hoping that inoculation of the test material would produce a typical disease. Instead of studying the virus itself he must be content to observe the animal's reaction to infection and try to deduce therefrom some information on the properties and the nature of viruses. This indirect method is more labor and time consuming, more expensive and above all less easily interpreted than the bacteriological culture technique. It is hardly possible to use it on such a scale a needed for the control of epidemics. Furthermore, the laboratory animals

often fail us, as many viruses have so completely specialized on the human race that they do not attack any other living beings. Experiments on human volunteers, sometimes resorted to in such cases are hardly advisable.

Then, in 1949 there appeared from a Boston research team a paper, modest in size and wording but with a sensational content. John Enders, director of the Children's Hospital's Research Laboratory and his associates Thomas Weller and Frederick Robbins reported the successful cultivation of the poliomyelitis virus in test-tube cultures of human tissues. A new epoch in the history of virus research had started.

The art of growing animal tissues isolated from the organism was learned already in the first decade of this century. The metazoan cell may be regarded as a micro-organism, more highly specialized than free-living bacteria, that is true, for its existence dependent upon the symbiosis with its fellow cells in the organism, and yet capable of leading its own life if only it is offered a suitable medium. Therefore, the principles of tissue culture are largely the same as those applied in cultivation of bacteria. The greatest difficulty encountered by Carrel, a French-American to whom the development of the technic should be credited, was prevention of contamination of the cultures by micro-organisms, which multiply rapidly thereby destroying the tissue. To meet this end Carrel introduced a complicated ritual. Tissue culture developed almost into tissue cult, a mystery the secret rites of which were revealed only to a narrow circle of inaugurates with Carrel as their high priest.

Already at an early stage the virologists sensed that tissue culture might prove a valuable tool, but the technical difficulties discouraged them. Not until 1925 Parker and Nye were able to present conclusive evidence that a virus could multiply in tissue cultures. The year 1928 is also worth remembering in the present connection. Then, the Maitlands, in Manchester, introduced a considerably simplified technique by which cells could be made to retain their viability for a short period of time and to exert a certain activity, although growth was inconsiderable. However, a virus capable of rapid multiplication might find sufficiently favorable conditions to permit by this technique its maintenance and

to a certain extent its study without resort to laboratory animals. The Maitland technique has found application for certain practical purposes. It was, for instance, instrumental in the development of Theiler's yellow fever vaccine. It is not equivalent to the bacteriological culture methods, however. Thus, it cannot be used for isolation of a virus from a test material.

Enders' interest in tissue-culture methods dates back to around 1940. He was convinced that the Maitland cultures were but an unsatisfactory ersatz, not answering the requirements of the exacting viruses, and for this reason found a return to the more intricate Carrel technique inevitable. In the 1940's together with Weller and a few other associates he studied the viruses of vaccinia, influenza and mumps, thereby gathering valuable experience.

At last, time was ripe for experiments on the poliomyelitis virus. The prospect of a favorable result could not be considered particularly bright. Other scientists had previously attacked the problem with very moderate success. It was generally held that the final word had already been said by Sabin and Olitsky who in 1936 tried to grow the virus in Maitland cultures of various tissues from chick embryos, mice, monkeys, and human embryos. Their results remained completely negative except in cultures of human embryonic brain tissue in which the virus at least seemed to maintain its activity. These findings were taken as a definitive confirmation of the accepted concept of the virus as a strictly neurotropic agent, i.e. capable of multiplying in nerve cells exclusively. Accordingly, the hopes of a practicable method for the cultivation of the poliomyelitis virus were temporarily shelved. Of all tissues, nerve tissue is the most specialized, the most exacting and consequently the most difficult to cultivate. As, at that, there seemed to be no alternative to the use of human brain tissue, the general resignation is easily understood.

In the 1940's the belief in the neurotropism of the virus began to falter, however, and Enders, Weller and Robbins decided to repeat Sabin and Olitsky's experiment with an improved technique. In their first experiments they used human embryonic tissue. To the great surprise of everybody except perhaps the experimenters themselves they registered

a hit in their first attempt. The virus grew not only in brain tissue but equally well in cells derived from skin, muscle, and intestines. Furthermore, in connection with the multiplication of the virus, typical changes appeared in the cellular structure, finally leading to complete destruction, easily recognizable under the microscope. This observation furnished a convenient method of reading the results. Furthermore, immune serum was found to inhibit specifically the virus multiplication, the technique therefore being applicable also in immunity tests. Subsequently, Enders, Weller and Robbins found that tissues secured from operations on children as well as adults could be used to advantage; all tissues except bone and cartilage seemed to be equally suitable. Finally they tried to isolate the virus from various specimens directly in tissue cultures. This was likewise achieved. In the latter observation probably the greatest practical importance of their discoveries is to be found. The virologists finally had a tool in the same classes the culture technique of the bacteriologists.

These discoveries incited a restless activity in the virus laboratories the world over. The tissue-culture technique was rapidly made one of the standard methods of medical virus research, among which it now holds an undisputed first place. So far it has been applied primarily in the study of poliomyelitis. It has been tested and excellently held its own in all possible connections, as a diagnostic tool of clinicians and epidemiologists, in vaccine production and for purely theoretical purposes. Its field of application is not limited to poliomyelitis research, however. The use of cultures of human tissues has permitted attacks on many virus problems previously out of reach because of the lack of susceptible laboratory animals. Already at an early stage Enders, Weller and Robbins discovered agents representing a previously unknown group of viruses. Other scientists have systematically pursued this line and the answer to the question of the causes of a number of common-coldlike diseases now seems to be at hand. Weller has succeeded in cultivating the agents causing varicella and herpes zoster, Enders that of measles, viruses previously almost inaccessible for study. The method has also been successfully applied to several problems in the field of veterinary medicine.

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We now possess essentially improved technical facilities for the combat of viral diseases. We should be aware, however, of not claiming any victories in advance. It took 75 years to achieve those results in the field of bacteriology to which we now point with pride. Much effort and a considerable time will be required for equivalent achievements in the fight against the virus diseases. However, thanks to Enders, Weller and Robbins' discovery we may look with confidence to the future.

Dr. John Enders, Dr. Frederick Robbins, Dr. Thomas Weller. Karolinska Institutet has decided to award you jointly the Nobel Prize for your discovery of the capacity of the poliomyelitis virus to grow in test-tube cultures of various tissues. Your observations have found immediate practical application on vitally important medical problems, and it has made accessible new fields in the realm of theoretical virus research.

By giving the virologists a practicable method for the isolation and study of viruses you relieved them of a handicap, burdening them from the birth of their science and placed them for the first time on an even footing with other microbe hunters. We may now look with confidence to the future and may justifiably expect equally spectacular achievements in the fight against virus diseases as were already accomplished on the bacteriological battlefield.

The electronics, radioactive isotopes, and complicated biochemistry of our age has threatened to turn medical science into something dangerously resembling technology. Now and again we need to be reminded of its fundamental biological elements. Against this background we express our admiration of the biological common sense, characterizing your approach to important medical problems, and of the wonderful simplicity of the solutions you have presented. It is my privilege and pleasant duty on behalf of Karolinska Institutet to extend to you our sincere felicitations.

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