

# 75 Years of Infectious Disease Research

In 1887 the Public Health Service set up the Laboratory of Hygiene in an attic room of the Staten Island Marine Hospital. This one-room laboratory was the ancestor of the National Institutes of Health, the Communicable Disease Center, and other Service institutions. On November 29, 1962, the 75th anniversary of the laboratory's founding was observed in Bethesda, Md., by leading scientists.

Bacteriology was in its infancy in 1887 when Dr. Joseph Kinyoun returned from talks with Koch, Ehrlich, and Pasteur in Europe to establish the laboratory. Since that time, Public Health Service laboratory research has been distinguished by Goldberger's classic epidemiologic studies of pellagra; Stiles' work on hookworm; Rosenau's work on anaphylaxis; Francis' on tularemia; Armstrong's experiments with poliomyelitis virus in rodents; Mahoney's studies of syphilis therapy; the work of Dyer and Topping on typhus and other rickettsial diseases; and Spencer's studies of Rocky Mountain spotted fever.

The 75th anniversary program included speakers whose names are synonymous with the development of the Public Health Service. Two of the talks that were available in manuscript form, one by Dr. John F. Enders on prospective problems in virology and the other by Dr. Joseph E. Smadel on the future of rickettsiology, are summarized below.

Dr. Enders, Harvard University professor and winner of the 1954 Nobel Prize in Medicine and Physiology, noted that work on viral reproduction holds the central position in current virological research. He stated that, as the details of viral reproduction are revealed, the life and maintenance of the cell itself will also be more clearly understood.

Enders suggested that the current hypothesis that a virus merely takes over a cell's normal metabolic machinery may be modified in the future. There are indications, for example, that some viruses may direct the synthesis of an enzyme or enzyme system that is new to the cell's normal metabolic equipment.

Developments in synthesizing nucleic acids and reassembling virus particles in the absence

of cells encourage renewed efforts to propagate viruses in cell-free media, Enders said.

He next cited problems that remain concerning viral pathogenicity. The precise definition of the factors responsible for virulence is yet to be established. Certain factors underlying pathogenicity as expressed in the infected animal are also unknown. We are still at a loss, for instance, to account for symptoms of severe toxicity which may accompany a simple attack of influenza.

The effect of viruses on the fetus and newborn will also continue to be a subject of investigation, Enders said. He cited Swann's classic study on the rubella virus for stimulating many investigations in this field. No correlation as dramatic as that of fetal defects with rubella has been revealed by these studies, but it has been shown that intrauterine infections with certain enteroviruses may occur toward the end of pregnancy or at birth and cause serious and even fatal myocardial, hepatic, and cerebral injury. In extensive longitudinal studies supported by the Public Health Service, the relative importance of viral infection as a cause of congenital defects is being evaluated.

"Of the various ways in which viruses may affect the normal economy of cells, their capacity to accelerate cell multiplication and induce neoplastic changes is perhaps the most intriguing and in the near future, at least, will occupy the attention of an increasing number of investigators concerned with various aspects of cancer," Enders said. Great interest in this field has been generated by the demonstration that forms of leukemia as well as solid malignant tumors are caused in mice by viruses.

In the search for effective therapies for virus diseases, events such as the discovery of anti-viral factors in the abalone and oyster by Li and in bacteria by Carver and Naficy, as well as Kaufman's demonstration of the therapeutic effect in herpes simplex infections of the topical application of certain halogenated nucleotides, encourage the hope that nontoxic substances that inhibit viral multiplication in host tissues will be found, Enders said. While it seems clear that the empirical approach to

therapy will continue and may well achieve success, it is equally possible, he said, that success may have to await the more precise knowledge of viral replication.

In regard to the future of vaccination against viral infections, Enders offered the opinion that we should not presume that the present armamentarium of vaccines will be greatly expanded: "Immunization has proved highly effective against diseases such as smallpox, yellow fever, and poliomyelitis in which the etiological agent is represented by only one or a very few antigenic types and in which natural immunity is of long duration. The agents of measles, mumps, and varicella also belong in this category, and the development of satisfactory vaccines against them has either been accomplished or soon will be. The virus of infectious hepatitis may also be included if reliable techniques for its cultivation become available. When, however, we visualize the procedures involved in manufacture and administration, to say nothing of the immunological feasibility, of any attempt to vaccinate whole populations against the ever-swelling numbers of antigenically distinct viruses responsible for diseases of the respiratory, gastrointestinal, and nervous systems, the difficulties seem insuperable.

"It has been suggested that these difficulties will be diminished when practical methods become available for the preparation of polyvalent antigens consisting of purified viral proteins. While this may prove true, in order to induce and maintain an effective level of immunity against this legion of viruses, an enormous and continuous effort would still be necessary, except perhaps in special groups such as military forces. Since the illnesses caused by these viruses are in general mild, it may well be concluded when the time comes that here the game of vaccination is not worth the candle.

"Possibly, then, investigations in this area will be directed principally to improving the potency, purity, and safety of the vaccines now available or soon to become available.

"As a long-range forecast, I should say that the purely biological and biochemical aspects of animal virological research will be increasingly stressed as control of viral diseases becomes

highly effective. Since such control will ultimately be achieved, our discipline seems destined to undergo eventually the same metamorphosis as that which medical bacteriology has lately experienced."

Dr. Smadel, chief of the Laboratory of Virology and Rickettsiology, National Institutes of Health, and winner of the 1962 Albert Lasker Clinical Research Award, discussed the medical importance of and unsolved problems in rickettsial diseases in the United States.

Reported cases of murine typhus in the United States dropped from 5,401 in 1944 to 46 in 1961, probably as a result of the general use of insecticides rather than public health control measures such as applications of DDT to rat runs, Smadel said. He said that if commensal rats are the sole reservoir of *Rickettsia mooseri*, murine typhus may disappear in this country, but if wild rodents are also involved, as serologic data have occasionally suggested, eradication of the disease cannot be expected.

While the use of insecticides may have contributed to the drop in incidence of Rocky Mountain spotted fever from 500 to 200 cases annually, eradication is unlikely because of the many natural foci of infection, Smadel said. Among the unanswered questions regarding this disease are those concerning the variations that may be possible in the cycle of infection. Studies have suggested a wider range of hosts and vectors than that presently recognized.

Rickettsialpox continues to be endemic in New York City, with about 100 cases occurring each year, Smadel reported. A few cases have been found in other cities. As with murine typhus, rickettsialpox could probably be eradicated in the United States by adequate use of insecticides. Whether the cycle of infection in the United States involves wild rodents as well as commensal rodents is yet to be established.

Q fever is a growing health problem in this country. The disease has slowly spread eastward, and cases are now beginning to appear among veterinarians and abattoir workers in Atlantic Coast States where serologic surveys found no evidence of infection a decade ago. While domestic animals are the primary source of infection in the United States, the cycle of infection in nature should be evaluated, Smadel stated.