58TH ANNUAL REPORT 1970–1971

CONNAUGHT MEDICAL
RESEARCH LABORATORIES
UNIVERSITY OF TORONTO

by the use of untreated blood. The poultry producers were in no mood to suffer while bureaucratic procedures delayed the development of an approved turkey herpes vaccine.

The Canadian Department of Agriculture appealed to Connaught to mount an accelerated production program of turkey herpes virus, under a temporary licence, promising concurrent field testing under government auspices. The Department of Agriculture required us to use Dr. Burmester's strain of herpes virus although Dr. Gregg of our Veterinary Division had already isolated a strain from Canadian turkey flocks which seemed at least as good.

The problem then was to develop methods of producing about one million doses a month as soon as possible. The only vaccines which Connaught has ever before produced at this rate were the polio vaccines. It was, therefore, gratifying that we were able to call upon the assistance of Dr. Hilda Macmorine and her experienced associates to produce the large volumes of chick cells in tissue culture required to grow the virus to make vaccine.

Another problem was presented by the instability of the virus. It would have been desirable to distribute the virus in freeze-dried form. This was not possible. Losses in potency were too great. It was necessary to send it out in canisters of liquid nitrogen. Even dry ice is not cold enough to preserve the virus.

The decision to make Marek's disease virus was taken on September 1, 1970. On the 15th of November 1970, the first lots were available for delivery. Production has continued at close to one million doses per month. The results in the hatcheries have been very satisfactory. Field trials under government auspices are continuing. We hope and expect to receive our regular licence by the end of 1971.

Tuberculins Tuberculosis is to a large extent a forgotten problem in Canada. New drugs introduced during the late 1940's and the 1950's have increased the efficacy of treatment so dramatically that the mortality rate has been reduced in recent years to less than 5% of what it was in 1945. The reduction in mortality rates has been particularly striking among children and young adults. Programs of early detection of infection, and immediate treatment before symptoms appear have been most effective in causing the decline in mortality, which is still continuing. Such programs also decrease the incidence of disease by reducing the spread of infection.

Perhaps the most effective tool in early diagnosis of infection, before any symptoms of disease are evident, is the use of various preparations of tuberculin.

For many years the preparation most commonly used was called Old Tuberculin, which is a crude filtrate of cultures of *Mycobacterium tuberculosis*. The Connaught Laboratories have been making and distributing Old Tuberculin for nearly forty years, and in recent years a refined preparation called Purified Protein Derivative (PPD).

In general, tuberculins are applied to the skin by one of several methods, e.g. injection, scratch, puncture, or prolonged contact. If the recipient is harboring a tuberculous infection, even without symptoms, a red reaction to the tuberculin will appear in 24 to 48 hours, indicating sensitivity to the tubercle bacillus. In certain groups, particularly children and workers in hospitals, a positive reaction to tuberculin may indicate a recent infection with tubercle bacilli which could develop into serious disease. Such persons may be treated with suitable drugs to prevent the disease.

The interpretation of reactions to tuberculin has been the subject of extensive study for many decades, and so has the composition of tuberculin for the purpose of identifying

the substance which is the indicator of specific sensitivity. Neither of these problems has been completely resolved, because as knowledge increases new complexities become apparent. For example, it has been recognized that many infections besides the usual organisms causing tuberculosis in humans and in cattle can induce sensitivity to tuberculin. Among such are the atypical mycobacteria. Some of these produce serious disease in humans and require different treatment from ordinary tuberculosis. Others are harmless and require no treatment.

It is clear, therefore, that more specific tuberculins are required to increase the accuracy of diagnosis of tuberculous infection and thus the effectiveness of preventive measures. Research to these ends has been in progress in the Connaught Medical Research Laboratories for many years under the direction of Dr. S. Landi. As a start, work was directed to stabilizing and standardizing the refined preparation referred to above, which is called Tuberculin Purified Protein Derivative (PPD). After years of investigation, Dr. Landi's methods were recognized and adopted by the Division of Biologics Standards in the U.S.A. In order to provide a standard preparation of PPD which could be used both for production and as a reference for comparison, Dr. Landi produced a sufficient amount to do 4.5 billion skin tests. This is certainly the largest single lot of PPD available in the world today.

Although PPD, as its name signifies, is a highly refined product, it is not a pure substance. It is not the specific indicator of sensitivity conferred by any particular species or variety of mycobacteria. It would be desirable to have a series of very specific tuberculins to indicate infections by atypical mycobacteria. Since 1967 Dr. Landi has received generous grants from the National Sanitarium Association to study the antigenic components of atypical mycobacteria and to identify the specific active components of tuberculins.

One result of this work has been the development of a PPD for one of the important atypical mycobacteria known as the Battey strain. This was licensed for distribution in Canada in 1970. It will presumably be licensed in the U.S.A. in due course. Good progress is also being made toward isolating specific active fractions of PPD.

Dr. Landi's substantial contributions to research in this field were appropriately recognized when he was appointed in 1970 to the Scientific Committee of the International Union against Tuberculosis.

Cholera About the middle of August 1970, the news media began to report occurrences of cholera in several countries around the Mediterranean. Piquancy from the journalistic viewpoint was added by the suggestion that not all countries were reporting cases.

Soon our Export Department was overwhelmed by enquiries from many countries and voluntary agencies for large quantities of cholera vaccine. At the same time, demands from Canadians planning to travel abroad increased greatly. It soon became apparent that the numerous agencies trying to buy cholera vaccine were magnifying the real demand for a very limited world supply of vaccine. Fortunately, within a few weeks the World Health Organization undertook to co-ordinate the demands from different countries; to order vaccine from many manufacturers; and to distribute it according to rational priorities. Fortunately too, cholera vaccine does not take nearly as long to make as do the polio vaccines. Our Cholera Vaccine Department went to work with great vigour and much overtime. Some 250,000 doses were produced for the W.H.O. in about 3 months. We understand that the Government of Canada provided the funds to W.H.O. to make this purchase.