the serum bilirubin on the second day, to foretell which infant would develop kernicterus on the sixth. Unfortunately this did not prove to be the case, for he found later that though babies developing kernicterus had higher levels than normals on the second day (8.1 compared with 4.8 mg. % bilirubin) the majority of the babies whose levels were above 8 mg. % on the second day did not develop kernicterus. Prevention of kernicterus in these babies can therefore be carried out only by following up serum bilirubin levels from day to day, and giving exchange transfusions to those whose levels appear to be rising above 18 mg. %. An exchange of 60-80 ml. per lb. body weight is usually adequate. The umbilical vein can nearly always be used; blood of the same ABO and Rh group as the recipient should be used.

In this context it should be remembered that both menadiol sodium diphosphate (Synkavit)[23] and sulfisoxazole[24] have been shown to increase the depth of jaundice in prematures; the dose of the former should therefore be kept to a minimum, 1 to 2 mg., and the latter should be avoided.

I am grateful to my colleagues at the University Hospital for access to their cases.

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RÉSUMÉ

Bien que l'ictère nucléaire ait été décrit en 1875, son étiologie ne fut comprise qu'avec la découverte du facteur Rh. En 1950 Diamond démontra d'une façon concluante qu'une exsanguinotransfusion précoce peut épargner l'atteinte aux noyaux gris centraux chez la plupart des nouveaux-nés souffrant de la maladie hémolytique. Il appartint à Hsia de démontrer que l'ictère nucléaire dépendait directement de l'intensité de la jaunisse et du taux de bilirubine du sérum. Il faut quand même se rendre à l'évidence que cet ictère peut aussi se produire dans toutes les formes de jaunisse qu'elle soit causée par la prématurité, la maladie hémolytique familiale, l'hépatite, etc. On a récemment démontré que le pigment biliaire incriminé dans cette affection est la bilirubine à réaction indirecte, de sorte que tout nouveau-né souffrant d'hémolyse ou de lésions hépatiques ne permettant pas la conversion de bilirubine "indirecte" en bilirubine "directe" est exposé à être atteint d'ictère nucléaire. On a observé que plus l'enfant est petit à sa naissance plus élevé sera le taux de bilirubine dans les premiers jours de vie et plus bas sera le seuil passé lequel apparaîtra l'ictère nucléaire. En pratique cependant, ce n'est que par des déterminations répétées du taux de bilirubine que l'on peut prévoir quel enfant en sera atteint et quel autre en sera exempt.

ORIGINAL ARTICLES

PRESENT STATUS OF POLIOMYELITIS VACCINATION*

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IT IS LITTLE MORE THAN four years since Dr. Jonas Salk[1] reported the first use of a preventive vaccine against paralytic poliomyelitis which he had prepared. The vaccine contained polioviruses of the three identified types, inactivated by formalin, and the observations were made on 161 children in Pittsburgh, U.S.A. It has been estimated that by May of this year (1957) more than 60 million persons in the United States and four million persons in Canada had received at least one dose of vaccine. The vaccine is in general use in Europe, South Africa, Australia, New Zealand and other countries. This is a development that is unique in medical history. Credit is due first to the National Foundation for Infantile Paralysis, New York, which since its organization in 1938 has generously supported research while providing treatment for every needy case of poliomyelitis in the United States. Among the

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recipients of assistance in research in 1951 was Dr. Salk of the University of Pittsburgh. Without the planning and support of the National Foundation, the evaluation of the vaccine which he prepared would have required many years. A field trial of a vaccine against poliomyelitis had to be planned on a very large scale and it was necessary that trial areas include representative sections of the whole country, since there is no way of foretelling in what part of the country the disease may be epidemic in any one year. The field trials conducted by the National Foundation in 1954 included 217 test areas in 44 states, two provinces of Canada, and Finland. In the United States approximately 1,830,000 children in the first three grades of school were kept under observation for the last six months of 1954. Of these about 440,000 had received, beginning in April, one or more injections of vaccine; about 210,000 received injections of a placebo; the remaining children, 1,180,000 were observed as controls. Blood samples were taken from about 40,000 children and the content of poliomyelitis antibody was determined before and after the injections of vaccine. This serological work was conducted in 27 laboratories. All data accumulated in the field trial were studied in an independent Polio Vaccine Evaluation Center established at the University of Michigan under the direction of Dr. Thomas Francis, Jr. This was the largest field trial ever undertaken, one of the most carefully planned and conducted, and one in which the results were evaluated in a minimum time. The findings were announced by Dr. Francis[2] at a scientific meeting at the University of Michigan on April 12, 1955. On the basis of the survey he reported that the vaccine was 80-90% effective against paralytic poliomyelitis, 60-70% effective against type 1 virus, and 90% or more effective against types 2 and 3.

CANADA'S CONTRIBUTION TO THE UNITED STATES FIELD TRIAL

This field trial depended on having sufficient vaccine, fully tested and available. Canada, through the Connaught Medical Research Laboratories, had an important part in this aspect of the trial. In speaking of this, Dr. Hart E. Van Riper,[3] then Director of the National Foundation, made reference to four contributions. The first was the contribution of Morgan, Morton and Parker[4] in 1950 in preparing a purely synthetic medium for maintaining animal cells in tissue culture. This medium, known as mixture No. 199, or a minor modification of it has been used by all manufacturers of the vaccine. A second contribution was the development in 1953 of methods for quantity production of polioviruses in cultures of monkey kidney tissue by Rhodes, Farrell, Wood, Franklin, Shimada and Macmorine.[5] A third contribution was the introduction of safeguarding tests, recognizing the possible presence of contaminating viruses derived from monkey kidney tissue, notably Virus B;[6] and a fourth, the actual production of more than 5000 litres of poliomyelitis virus culture fluids[7] for use in making vaccine. Of this amount, 3280 litres were made available to U.S. manufacturers who had undertaken to supply the vaccine. From this supply the bulk of the vaccine used in the field trial was prepared. Research work which led to the production of polioviruses in quantity, and the cost of the actual production of the large quantities of virus fluids, were made possible by the generous support of the National Foundation for Infantile Paralysis.

THE CANADIAN FIELD TRIAL

With the announcement of the plans for a field trial in the United States, the Dominion Council of Health, Canada, an advisory body composed of deputy ministers of health of the provinces and five other members, recommended to the Department of National Health and Welfare that plans be made to prepare the vaccine in Canada to permit a field trial in the following spring (1955). It was proposed that sufficient vaccine be prepared in the Connaught Laboratories to permit the administration of three doses to 500,000 children in the ten provinces. The plan was approved, the vaccine was prepared, and its administration was commenced on April 1, 1955, some days prior to the announcement of the results of the 1954 field trial in the United States. The cost of the vaccine used in this program and in subsequent programs conducted by the provincial and local departments of health has been shared equally by the Department of National Health and Welfare and the provinces.

Following the Francis report, immediate and nation-wide use of the vaccine was commenced

in the United States. Within three weeks, however, grave fears were expressed regarding the safety of the vaccine following a tragic occurrence of poliomyelitis among some of those who had received the first dose of vaccine; these children had received vaccine from one manufacturer. Additional cases were reported and the Surgeon General of the United States Public Health Service conducted a thorough investigation immediately. Temporary discontinuance of distribution of vaccine by all manufacturers was ordered until additional regulations relating to the preparation and testing of the vaccine were formulated and issued. A poliomyelitis vaccine surveillance program, established by the Public Health Service, required the reporting of all cases occurring among vaccinated persons. In all, 204 cases of paralytic poliomyelitis and 11 deaths were reported, 79 of which were among those receiving vaccine. One hundred and five were family contacts of these patients and 20 were community contacts. The work of this surveillance unit has been continued, and reports issued have indicated that the vaccine as prepared under the revised regulations has been entirely safe.

During the following six months, wide differences of opinion were expressed in the United States regarding the use of the vaccine. In Canada, however, the program was continued without interruption and with success. The original field trial in Canada planned for the administration of three doses to 500,000 children during the months of April, May and June, 1955. This number was increased as a result of the recommendation made by Dr. Salk, at the time that Dr. Francis presented his report, that the second dose be given one month after the first and that the third dose be administered not sooner than seven months after the second. The adoption of this recommendation in the Canadian program made possible the administration of the vaccine to 800,000 children in place of providing three doses for 500,000 children as originally planned. In two provinces, the original plan of three doses given at one-month intervals was followed.

PRODUCTION OF VACCINE IN CANADA

During the summer and fall of 1955 the Connaught Medical Research Laboratories, in common with other laboratories preparing the vaccine, encountered major technical difficulties which resulted in delay of the programs of vaccination as planned by the various provinces during the fall months. In November, further amendments were made to the regulations controlling vaccine production, and this created problems relating to the antigenicity or effectiveness of the vaccine. It was not until the late spring that vaccine production was again established in the Connaught Laboratories as routinely successful and quantities of vaccine were made available to the provincial departments of health for their program. In spite of these difficulties, sufficient vaccine was supplied during the spring months of 1956 to provide 2,200,000 doses. During the fall of 1956 and the first six months of this year regular supplies, more than 6,000,000 doses, have been furnished to the provincial departments of health. With the overcoming of problems associated with the presence of preservatives, the vaccine is now being distributed in multiple-dose, rubber-capped vials. These are more convenient for use in private practice. Preparation of the vaccine has also been undertaken in the Institute of Microbiology in the University of Montreal.

CANADA'S SATISFACTORY EXPERIENCE

The 1955 Canadian field trial was eminently successful. Through the Department of National Health and Welfare and the provincial departments of health, all data relating to poliomyelitis vaccination, including the investigation of every case of poliomyelitis occurring in a vaccinated person, have been collected and studied. Reports issued during the year 1956 have recorded that not one death from paralytic poliomyelitis occurred among the vaccinees.

The Department of Health and Welfare of British Columbia[8] was most helpful in analyzing the early results. During the period July 1 to November 30, 1955, 45,067 children aged 5, 6 and 7 years received two or three injections of vaccine. A total of 12,488 children in the same age groups did not accept the vaccine and these constituted a suitable control group for observation. Among the vaccinated children no cases of paralytic poliomyelitis were reported, whereas among the non-vaccinated children there were 10 cases of paralytic poliomyelitis.

The experience in Ontario in 1955 and 1956 is presented in a recent report[9] by the Department of Health, Ontario. During the spring months of 1955, 309,585 elementary school

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children in grades 1, 2 and 3 received two doses—approximately 90% of the children in these grades. The study group consisted of all children between the ages of 5 and 12 years, and the unvaccinated children in this group served as controls. Laboratory examination of stool specimens was conducted. In the 1955 study three cases of paralytic poliomyelitis occurred among the vaccinated and four among the non-vaccinated. During the spring of 1956 an additional number of children were vaccinated, bringing the total by July 1 to 840,000 elementary school children. During 1956 there were only five cases of paralytic poliomyelitis among the 840,000 vaccinated children in contrast to 71 cases among the 960,000 non-vaccinated children. The laboratory studies were of great interest. In 1955, of 62 illnesses reported as possible poliomyelitis 43 were finally classified as meningoencephalitis and of these 43 cases, 23 yielded on tissue culture examination a Coxsackie or an ECHO virus. In the 1956 study 180 cases were classified as meningoencephalitis and 103 yielded a cytopathogenic virus other than a poliomyelitis virus on tissue culture. It is necessary, therefore, that laboratory confirmation be obtained in all cases of non-paralytic poliomyelitis.

PREPARATION OF VACCINE

Poliomyelitis vaccine as currently prepared, following the method of Salk, is a suspension of three types of poliomyelitis virus, type 1 (Mahoney), type 2 (M.E.F.1) and type 3 (Saukett), grown in monkey kidney tissue in synthetic medium No. 199 and inactivated with formalin. The strains Brunhilde (type 1), Lansing (type 2) and Leon (type 3) were the archetypes used in establishing the types in 1951 but these strains were not used by Dr. Salk in preparing vaccine.

VIRUS CULTURE FLUIDS AND TESTS

The three strains (Mahoney, M.E.F.1 and Saukett) are grown in monkey kidney cells. With the exception of certain adapted strains, polioviruses will grow only in the tissue cells of primates; therefore, monkeys are used, and kidney tissue is employed as kidney cells permit a good growth of polioviruses. Healthy rhesus monkeys, tuberculin-negative, are anæsthetized and the kidneys removed aseptically. The animals are autopsied with special reference to the liver, spleen and lymph glands, and if any evidence of disease is found the kidneys are discarded. After removal of the capsules, the kidneys are minced, using scissors. After washing to remove blood serum, the minced tissue is added to large bottles[5] containing culture medium. The original medium No. 199 devised by Morgan, Morton and Parker contains amino acids, dextrose, vitamins and minerals—a total of some 60 ingredients—that have been shown necessary for optimal growth of cultured tissues. A minor modification of this medium is now used in vaccine production in the Connaught Laboratories. Penicillin, 200 units per c.c., and streptomycin 200 μg. per c.c., are added to the culture bottles to control possible bacterial contamination.

The culture bottles containing the minced kidney tissue are incubated for six days at 36° C. to allow the maximum growth of cells. The medium is replaced with fresh medium and the bottles are inoculated with one of the three strains of poliovirus. Penicillin is now being omitted from the medium used in this step, so that the vaccine distributed in the latter part of this year will contain only a minute quantity of penicillin. Incubation of the bottles containing cells and virus is continued for four to five days to allow the maximum of virus growth. Assays are made to determine the titre of the virus. Bacteriological tests, tests for the presence of contaminating viruses such as virus B, and assays of virus titres are made. Toxicity tests and tests for *M. tuberculosis* are made in animals. Virus fluids which do not meet all of these tests are discarded.

INACTIVATION OF VIRUS

The virus fluids are then filtered, using Seitz filters, to remove tissue-cell debris and to ensure bacteriological sterility. Filtration is a highly important step, as serious loss of virus will reduce the potency of the finished vaccine. The filtered virus fluids of the three strains are inactivated, separately, by adding formalin (1:4000) and holding the containers at 37° C. for a period of 12 days. During the first three days, virus assays are made to determine the rate of inactivation. At the end of seven days the vaccines are again filtered and incubation is continued for five days. This filtration has been added as a further safeguard in case some par-

ticulate matter might pass the first filtration or form subsequently, and might surround particles of virus, preventing their inactivation by formalin. Three days before the end of the inactivation, a minimum of 500 c.c. are tested in tissue culture for the presence of live virus. After the 12-day period of incubation a second test of equal volume is done. This test will reveal the presence of virus B or other simian viruses as well as polioviruses if present in these volumes. A preliminary test using monkeys is made to determine the antigenic value of the vaccine.

POOLING AND TESTING

When all tests are satisfactory, the vaccines of the three strains are pooled to form the trivalent vaccine. The formaldehyde is neutralized with sodium bisulphite, and a suitable preservative is added. The official antigenicity tests are made on the trivalent vaccine to confirm that the vaccine meets the antigenic standards. If the bacteriological tests are satisfactory, the vaccine is filled into sterile glass vials for clinical use. Bacteriological tests are made of the filled vials and tests are conducted to establish that there are no pyrogenic substances present. Confirmation of the safety of the triple vaccine is provided by testing 1500 c.c. of the filled vaccine in tissue cultures. In addition, a minimum of 20 monkeys are inoculated intracerebrally, intraspinally and intramuscularly with the vaccine. These monkeys are injected with cortisone to render them more susceptible to polioviruses and thus reveal the presence of any traces of living viruses. They are observed for 17-19 days and are then sacrificed. The central nervous system is examined for any lesions suggestive of poliomyelitis. Lastly, samples of the trivalent vaccine are sent to the Laboratory of Hygiene, Department of National Health and Welfare, Ottawa, where the bacteriological, safety and antigenic tests are repeated. The vaccine is approved for use only if found satisfactory in both laboratories.

ADMINISTRATION

The experience on this continent has established that poliomyelitis vaccine (Salk) which meets the present government standards is entirely safe and that it is an effective agent in the prevention of paralytic poliomyelitis. The vaccine is clear and cherry-red in colour. Until recently, it was distributed by the Connaught Laboratories in sealed glass ampoules, since the usual preservatives were found to be injurious to the vaccine. This problem has been overcome and the vaccine is now being distributed in rubber-stoppered vials. If only part of the contents of a vial is removed, the air introduced into the vial may, on standing, cause the cherry-red colour to become a deep red shade owing to slight change in the alkalinity of the vaccine. Such vaccine is satisfactory for use, but any turbidity or sediment in the vial may indicate that the contents have become contaminated and the vial should be discarded. As previously mentioned, penicillin and streptomycin are added during the preparation of the vaccine, but only a very small amount of penicillin is present in the vaccine as distributed.

In regard to age, federal and provincial authorities urge that the vaccine be given to all persons under the age of 40 years. In the United States, last year there was a shifting of the highest incidence of paralysis from the age group five to nine years to the age group under five years, with the peak in the one to two year age group. From the age standpoint it is important to note that one-quarter of the cases with paralysis occur in adults. Pregnant women should receive the vaccine.

The vaccine may be administered subcutaneously or intramuscularly. It is recommended that three doses of 1 c.c. each be given, with an interval of four weeks between the first and second doses, and an interval of not less than seven months between the second and third doses.

If the series of injections be interrupted, it is not necessary to repeat the doses but simply to complete the series; an extension of the time interval between doses is not detrimental. It is of interest that even one dose of 1 c.c. appears to confer some measure of protection. It should be noted that the present evidence indicates that recall doses will be necessary to maintain protection and that these should be given after intervals of two or more years.

Is the administration of polio vaccine contraindicated during an epidemic of the disease? The possibility that the incidence of paralytic poliomyelitis might be higher and that paralysis might occur more frequently in the arm or leg in which hypodermic injections of various types were made has been carefully studied. On this

continent, the consensus of opinion favours the carrying out of immunization during the summer months and in the presence of an epidemic of the disease. Polio vaccine was first used during an epidemic at the naval base in Hawaii in the fall of 1955. There was no evidence of an increased incidence of paralysis among the vaccinated. Poliomyelitis occurred as an epidemic in Chicago in August 1956; more than 1100 cases were reported, 75% of which were paralytic cases. It was decided to administer poliomyelitis vaccine to as many persons under 40 years of age as possible. More than 1,000,000 doses were given after the epidemic had commenced. It is of interest that not one case of paralytic poliomyelitis occurred in a person who had received three properly spaced doses of vaccine. Preliminary studies indicate that the occurrence of paralysis was not more frequent among the vaccinated than the unvaccinated. The vaccine was used also during an epidemic in Upstate New York in September, October and November of 1956, without incident. It is not considered that the use of the vaccine under such circumstances would materially affect the incidence of the disease; its value lies in providing protection against paralytic poliomyelitis on subsequent exposures.

REACTIONS

It is definitely established that the administration of poliomyelitis vaccine is remarkably free from reactions, local or general. Administration of many millions of doses of vaccine has established that reactions are very infrequent and generally of a mild nature. In administering vaccine to persons definitely known to be sensitive to penicillin or to the vaccine every precaution should be taken, including the use of a 1/10 c.c. initial dose given subcutaneously followed by gradually increasing doses. The possible occurrence of a severe reaction must always be remembered in administering hypodermically any product. It is desirable, therefore, to have epinephrine hydrochloride solution (1-1000) available as a safeguard.

CURRENT DEVELOPMENTS

Of great interest are the efforts to prepare vaccines containing attenuated living polioviruses in place of the inactivated virus vaccine now employed. Vaccination against smallpox with vaccinia virus, a living virus, brings to mind the advantages of a living virus vaccine, namely one inoculation and an extended period of protection. Yellow fever vaccine is another example of a living virus vaccine in which an attenuated strain of the virus is employed. It is recognized that recall or booster doses are necessary after a period of two or more years when vaccines prepared of killed bacteria or their products are used. The present polio vaccine (Salk), containing inactivated virus, requires the administration of three doses at intervals extending over a period of nine or more months and a recall dose will likely be needed after a period of two or three years. Insufficient time, however, has elapsed to permit a more definite statement.

Two groups of workers have developed attenuated living vaccines and preliminary clinical trials have been made. Koprowski[12] and his co-workers have developed a type 1 strain designated SM and type 2 strains TN and M.E.F.1. The strains TM and SM have been adapted to mice and are attenuated in that monkeys are not paralyzed after intracerebral inoculation. The SM strain (type 1) causes destruction of cells in tissue culture whereas TN does not do so. Both strains have been given to children in milk or in a capsule without any adverse result. These authors report that specific antibody formation was demonstrated in the majority of the children receiving the vaccine. Sabin[13, 14] has developed strains of all three types of polioviruses in tissue cultures which are non-pathogenic for monkeys when injected intracerebrally, although occasionally these strains have produced paralysis when injected intraspinally. Sabin has also isolated avirulent strains of types 2 and 3 from healthy children. In children after oral administration, and also after intramuscular inoculation, fæcal excretion of the virus occurs. In chimpanzees the attenuated strains of types 1 and 2 regained some virulence for monkeys. Recently, Sabin has reported further laboratory work which has suggested that there may have been a breeding out of virulent strains in the process of growth in the intestinal tract or on intramuscular injection.

Strains now being used appear to contain only attenuated virus. The question of safety of the attenuated or avirulent strains from the standpoint of their possible spread in the community

through excreta is receiving much attention. Reports of Dane and Dick[15, 16] of Belfast, Ireland, give grounds for concern. Employing strains TN and SM (Koprowski), these observers found that excretion of the virus in stools after the administration of the type 2 strain TN was irregular but that some individuals excreted virus for as long as a month and in high titre. The virus recovered from stools was pathogenic for monkeys when injected intracerebrally. More limited trials were made with SM virus. It was found that the virus recovered from vaccinated individuals was more virulent for monkeys than the vaccine strain, and was regularly present in the fæces, often in high titre and persisting for several weeks. From one individual, virus was isolated from the blood eight days after vaccination. In one family, infection of one child and possibly one adult was traced to contact in the home with a vaccinated child aged four years. It is possible that by improved laboratory procedures satisfactory avirulent strains may be developed. The method of pure culture of viruses developed by Dulbecco gives promise of important advances. Search is being made also for avirulent strains that may occur naturally. Another approach is an effort to breed harmless polioviruses in the laboratory by selective procedures. Cross-breeding of polioviruses is under study in an attempt to produce a single virus with the characteristics of the three known poliovirus types.

Improvements are being made in the preparation of the present vaccine. It is both difficult and costly to obtain the large number of monkeys required to provide the fresh kidney tissue used in propagating polioviruses for vaccine production. Dr. Salk recently announced that a strain of cells of monkey heart tissue, capable of continuous propagation, has been grown in his laboratory. These cells had remained susceptible to polioviruses and may prove to be satisfactory in the production of the polioviruses for vaccine. The use of this new cell strain would greatly reduce the number of monkeys required and also would remove the possibility that unknown viruses of monkey origin might be present in the vaccine.

PRESENT NEEDS

It is now known that vaccination protects against paralytic poliomyelitis but does not prevent intestinal infection with polioviruses. Vaccinated persons may still become carriers and may be the source of infection to others. The spread of infection of poliomyelitis would, therefore, be little affected by vaccination, and protection against paralytic poliomyelitis would be dependent on each individual's being vaccinated. In the control of diphtheria, however, through the use of diphtheria toxoid the disease disappears in communities when a sufficient number of children are protected, even though a considerable number remain unprotected.

When it is realized that approximately a quarter of all cases of paralytic poliomyelitis occur in the age group 20-40 years, the magnitude of the problem of poliomyelitis vaccination is appreciated. In Canada approximately 10,500,000 persons are included in the age group of infancy to 40 years; and since it is estimated that 4,000,000 persons have now received at least one dose of vaccine, there are 6,500,000 persons remaining to be given the opportunity of receiving vaccine. To meet this need the medical profession and the public health authorities should give leadership in a Canada-wide effort to provide vaccination. Every physician in his practice should urge vaccination of all persons under 40 years of age, emphasizing the safety, effectiveness and availability of the vaccine.

Another approach to this problem is the attempt to combine the present triple antigen (diphtheria, tetanus and whooping cough) with poliomyelitis vaccine. The advantages of such a quadruple vaccine are obvious. Because of the number of injections involved in giving protective vaccination against diphtheria, tetanus and whooping cough and against poliomyelitis, there is, already, a tendency to give only one series of inoculations and to omit either the triple vaccine or the poliomyelitis vaccine. The preparation of a quadruple vaccine was commenced in the Connaught Laboratories two years ago and the technical difficulties have been largely solved. The stability of the quadruple vaccine is now being determined, a procedure which requires extended testing and clinical trial. Similar work is in progress at the University of Michigan and at several other centres in the United States. A quadruple vaccine would be a most important contribution and would be welcomed by parents, physicians, and the administrative health authorities. Some physi-

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cians have given children both the triple vaccine and the poliomyelitis vaccine at each visit, injecting the triple vaccine and the poliomyelitis vaccine separately, in each arm. If the two antigens are mixed together in the syringe, injection should be made promptly, as the preservative present in the triple vaccine may reduce the antigenic value of the poliomyelitis vaccine.

SUMMARY

Polio vaccine in Canada has been established as entirely safe and studies confirm the findings that it is effective in reducing (75%) the incidence of paralytic poliomyelitis when three properly spaced injections are given. The recommended intervals are two to four weeks between the first and second doses and not less than seven months between the second and third doses. The indications are that recall doses will be necessary at intervals of several years.

Federal and provincial health authorities urge the vaccination of persons under 40 years of age, and all pregnant women.

Reactions due to the vaccine are uncommon and generally of a mild nature.

Adequate supplies of vaccine are available.

Vaccinated persons when exposed may harbour polioviruses in the intestinal tract and occasion widespread dissemination. Protection is dependent on each individual's being vaccinated.

Laboratory confirmation of diagnosis is urged in every case of poliomyelitis since a large number of non-paralytic cases are known to be caused by Coxsackie, ECHO and other viruses.

Although 4,000,000 persons in Canada have received at least one dose of vaccine, 6,500,000 persons under 40 years of age have not received any vaccine. To control paralytic poliomyelitis, the Canada-wide program of vaccination requires the support of every physician.

Encouraging progress is being made in the development of a quadruple vaccine (diphtheria, whooping cough, tetanus and poliomyelitis). Attenuated living virus vaccines continue to be the subject of important research.

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RÉSUMÉ

La vaccination contre la poliomyélite au Canada s'est révélée comme un procédé entièrement sûr. L'étude des résultats a démontré qu'une série de trois injections administrées à intervalles déterminés avait abaissé la fréquence de cette affection de 75%. Les intervalles recommandés sont de deux à quatre semaines entre la première et la seconde dose, et pas moins de sept mois entre la seconde et la troisième. Une dose de rappel deviendra probablement nécessaire après plusieurs années. Les autorités d'hygiène fédérale et provinciale recommendent la vaccination de toute personne âgée de moins de 40 ans ainsi que de toute femme enceinte. Les réactions qui suivent la vaccination sont rares et habituellement de peu d'importance. On possède maintenant des quantités de vaccin suffisantes pour les besoins de l'heure. Les sujets vaccinés lorsqu'ils sont exposés à la poliomyélite peuvent héberger dans leurs voies gastro-intestinales des virus qui pourraient répandre la contagion. Il est donc important que chaque individu soit vacciné. On doit obtenir la confirmation du diagnostic de la poliomyélite par des épreuves de laboratoire, car il est établi qu'un grand nombre d'infections non paralytiques peuvent être causées par les virus Coxsackie, ECHO et autres. Bien que quatre millions de personnes au Canada aient déjà reçu une dose de vaccin, six millions cinq cent mille autres personnes au dessous de 40 ans restent encore à vacciner. Afin de juguler les atteintes paralytiques de la poliomyélite, le programme de vaccination à travers le Canada exige l'appui de chaque médecin. Des progrès encourageants ont été réalisés dans le développement d'un vaccin quadruple (diphtérie, coqueluche, tétanos et polio), et des travaux importants sont en cours sur l'emploi de virus vivants mais atténués comme source d'immunité.

A STUDY OF DIAGNOSTIC ERRORS

Eleven hundred and six autopsies from one hospital, representing the period 1947 to 1953, were reviewed by Gruver *et al.* (*Ann. Int. Med.*, 47: 108, 1957), and an incidence of 6% incorrect clinical diagnoses was found. Infections, particularly pneumonia and meningitis, were the most commonly overlooked diagnoses. Other frequently missed diagnoses were neoplasms, especially of the liver and brain, surgical conditions of the abdomen, and cardiovascular catastrophes.

Forty-five per cent of the patients in this group were unable to give a history because of acute alcoholism, confusion or toxicity, shock, coma or aphasia.

Correctable diagnostic errors seemed to be due not so much to lack of medical knowledge as to deficiencies of medical judgment, alertness and thoroughness. These included failure to: (a) obtain routine screening tests; (b) investigate abnormal symptoms, signs or laboratory reports that did not fit in with the diagnostic impression; (c) pursue indicated procedures; (d) recognize new illnesses developing in the presence of a previously diagnosed chronic disease; (e) realize that x-ray examination occasionally may fail to disclose pathologic changes, and (f) periodically review the record in prolonged illnesses and repeat the physical examination.