both the age groups we have used—namely, under 2 years and between 2 and 5 years (Tables IV, V, VI, VII, and IX). The smaller number of positive cases in the higher age group is not necessarily due to any lowering of the risk as age advances, for it must be, in part if not wholly, a function of the frequency with which inoculations are carried out. That frequency is, we know, lower in the higher age group.

Similarly, our figures show that paralysis has certainly followed the injection both of A.P.T. and of the combined A.P.T. and pertussis vaccine; for the pertussis vaccine alone we have no convincing data, and presumably it was not being extensively used (Tables VI, VII, and VIII). As stated, we cannot with figures of this kind determine whether one vaccine is more prone to produce paralysis than another. On the present published evidence we can see little support for the belief that the pertussis and the combined antigens are more prone to do this than A.P.T.

It has naturally been suggested that the effect of a recent inoculation is merely to localize the paralysis in the limb of injection in a child already incubating poliomyelitis. In the absence of inoculation the paralysis would not have occurred necessarily in that limb, but it would have occurred in some limb. The comparison of our cases with their paired controls (Table IX) suggests that this argument may not be well founded. The excess of recently inoculated children in the poliomyelitis group—and the equality in other intervals—does, we think, indicate that the group includes cases which would not have been diagnosed as poliomyelitis at all if there had been no previous and recent inoculation. Such children may already have been cases of non-clinically recognizable poliomyelitis, but the data suggest that they have been brought by inoculation into the paralytic class.

Summary and Conclusions

An investigation has been made to determine speedily whether, in the epidemic of 1949 in England and Wales, cases of paralysis diagnosed as and indistinguishable from poliomyelitis were occurring in association with inoculation procedures.

Records of 410 patients aged under 5 years were collected from 33 administrative areas, and in 164 of these cases a record was obtained for a closely paired control child.

The distribution of the bodily sites of paralysis was quite abnormal in children who had been inoculated within the month preceding the onset of their illness. In this group paralysis in the arms was just as frequent as paralysis in the legs, and the left arm showed paralysis more often than the right; in children without recent injections the two arms were equally affected and the legs were affected two to three times as often as the arms. The distribution in the recently inoculated is in accordance with the customary inoculation procedure in this country—that is, use of the arms more than the legs, and predominantly the left arm.

In the recently inoculated children the limb of injection (arm or leg) was a site of paralysis much more frequently than was the case with children not recently inoculated.

There is no evidence whatever that inoculations carried out in the more distant past have any effect at all upon the incidence or localization of paralysis. These effects appear to be confined to injections given within about a month of the onset of poliomyelitis, and after that interval from inoculation has elapsed no risk need be envisaged.

It has been suggested elsewhere that the recent injection of an antigen merely localizes an already developing paralysis in that particular limb of the child. The contrast of the present poliomyelitis cases with their specially collected and paired control children indicates, however, that there may be present in the poliomyelitis group cases which would not have been

clinically diagnosed as poliomyelitis at all if their inoculation had not brought them into the paralytic group.

Paralysis in the limb of recent injection was observed to follow both inoculations with A.P.T. and inoculations with the combined A.P.T. and pertussis antigens. Few figures were available for pertussis vaccine, but one case of paralysis following a recent injection was recorded.

The intervals of time less than 28 days that elapsed between the last injection of an antigen and the recorded onset of symptoms of poliomyelitis lay mainly between 8 and 17 days.

The mode of inquiry was such as to give a rapid and sufficiently accurate answer to the problem at issue—were such cases, in fact, occurring more frequently than could be attributed to chance? From the data thus collected it is not possible to determine the *relative* risks of injections either at different ages or with different antigens. For that purpose another, and a very laborious, statistical investigation is required.

We have very gratefully to acknowledge the care and trouble taken by all the medical officers of health who supplied us with the basic data. We are also indebted to Dr. A. H. Gale, who readily gave us much assistance and advice, and to Sir Wilson Jameson, Chief Medical Officer to the Ministry of Health, who suggested that this was a subject upon which inquiry was obviously desirable and gave us encouragement throughout its course.

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CLINICAL POLIOMYELITIS IN ASSOCIATION WITH PERIPHERAL INOCULATION OF PROPHYLACTICS

BY

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Aetiological Investigations

Recent observers in Australia and England have drawn attention to the occurrence, in 1949 in particular, of paralytic poliomyelitis in children who had received prophylactic inoculations within the preceding month. The most striking feature was that the paralysis was either localized to the most recently inoculated limb, or at least was first noticed in that limb, usually the arm. In the article on page 1 Bradford Hill and Knowelden have made a statistical evaluation of data collected in England in 1949 and confirmed the occurrence of such cases in this country.

Without going into the history of paralysis of limbs in association with inoculations of vaccines and sera and with trauma, it may be mentioned that clinical opinion is that two types of syndrome may occur, one of which appears to be associated with a lesion in the anterior horn cells of the spinal cord and the other in peripheral nerves. Therefore it was considered essential to try to determine whether a poliomyelitis virus was associated with the cases occurring in England in 1949, which appeared to be due to a lesion in the anterior horn cells of the cord.

No material has been received from fatal cases in association with the "double event," so that it has not been possible to obtain a histological diagnosis in confirmation of virus studies. However, stools have been obtained less than 21 days after the onset of the illness in a number of children included in some of the recent observations, and the poliomyelitis virus has been isolated by monkey

inoculation from each of the five children whose stools have so far been tested. The rhesus monkeys used all developed a disease similar to experimental poliomyelitis, and lesions pathognomonic of the disease were found in the brain and cord at necropsy.

Case 1.—R. R., aged 10 years. June, 1949. Revaccinated with smallpox lymph with "mild take" 12 days previous to the onset of symptoms. Developed meningo-encephalitis with evidence of paresis of the seventh cranial nerve four days after onset. Stool collected on the sixth day of illness.

Case 2.—S. S., aged 9½ months. September, 1949. Combined diphtheria-pertussis vaccine injected 17 days previous to onset. Paralysis of both arms three days after onset. Stool collected on the fourth day of illness.

Case 3.—D. M., aged 1 year. October, 1949. A.P.T. vaccine injected nine days previous to onset of symptoms. Paralysis, localized to inoculated arm, 12 days after injection. Stool collected on the 14th day of illness.

Case 4.—J. R., aged 1 year. December, 1949. Pertussis vaccine injected four days previous to onset of "cold." Paralysis, confined to inoculated limb, seven days after onset of "cold." Stool collected on the tenth day of illness.

Case 5.—R. W., aged 1 year 7½ months. December, 1949. Pertussis vaccine injected five days previous to onset of symptoms. Could not swallow two days after onset, and paralysis of neck muscles occurred on the following day. Stool collected on the 20th day of illness.

Cases 3 and 4 appear to be examples of the "double event" under discussion. In Cases 1, 2, and 5 the association between inoculation and poliomyelitis-like illness was present, but paralysis was not confined to the inoculated limb.

Summary

Poliomyelitis virus has been isolated from the stools of two children who had paralysis of a limb inoculated 11 and 12 days previously with certain vaccines.

The virus has also been isolated from the stools of three children who developed poliomyelitis or encephalitis 5 to 17 days after receiving a prophylactic inoculation without localization of paralysis in the inoculated limb.

It is recognized that the poliomyelitis virus is widespread during epidemic times, and no suggestion is made here that the viruses isolated were necessarily responsible for the present illness of the patients. These strains will be used, however, for experimental investigation of the problem of the effect of peripheral trauma in precipitating poliomyelitis or localization of paralysis in patients infected with or carrying poliomyelitis viruses.

The National Insurance Advisory Committee has been asked to consider and report on the preliminary draft of regulations which would modify the time limits for giving notice of incapacity and claiming sickness benefit for persons in hospital and for those who have not claimed that benefit before under the National Insurance Act. The proposals in the draft regulations are that a person claiming sickness benefit for the first time would have 21 days to put in his claim and would not be disqualified for having failed to give notice of incapacity. Long-stay patients in hospital would be treated as having good cause for failure to claim sickness benefit within the normal time limits while they are in hospital up to a maximum of three months; for short-stay patients this period would instead be the time spent in hospital and the three weeks after discharge. Copies of the preliminary draft of these regulations (the National Insurance (Claims and Payments) Amendment (No. 2) Regulations, 1950) can be purchased from H.M.S.O. for 3d. or from any bookseller. The committee will consider written objections to them if sent before July 18 to the secretary, National Insurance Advisory Committee, 30, Euston Square, London, N.W.1.

ANTIMALARIAL DRUGS IN WEST AFRICA, WITH PARTICULAR REFERENCE TO PROGUANIL

RESULTS OF A SURVEY IN NIGERIA

BY

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The traditional bottle of quinine tablets disappeared from the breakfast table of every European resident of West Africa soon after the outbreak of the last war. Mepacrine ("quinacrine," "atebrin"), introduced in 1943 by the armed Forces and adopted of necessity by the non-African civilian population, reigned supreme during the war, to be succeeded soon after the end of it by proguanil ("paludrine").

The use of proguanil for the prevention and treatment of malaria in West Africa dates from 1946, but the general adoption of the new drug was not achieved until well into 1947. The originally advocated dosage of proguanil in West Africa was 0.1 g. twice a week for prophylaxis, and 3 g. in fractional doses over 10 days for a radical cure of infections with *Plasmodium falciparum*, the prevalent parasite species.

In consequence of reports of field trials from other parts of the world the officially advocated prophylactic dosage was soon raised to 0.1 g. three times a week. By the end of 1947 several medical officers in Nigeria expressed their concern about the value of proguanil taken in the above dosage for prevention of malaria. The slow curative action of proguanil caused a good deal of disappointment, especially in severe clinical cases which eventually responded to quinine or mepacrine. The early cautious reports on the value of proguanil in Nigeria were met with a good deal of disbelief.

An important investigation carried out during 1948 by Covell, Nicol, Shute, and Maryon (1949) on neurosyphilitic patients at Horton revealed that infections with the Lagos strain of *P. falciparum* are causally prevented by the prophylactic administration of proguanil in fractional doses varying between 0.3 and 0.7 g. a week. On the other hand, proguanil used alone for treatment of infections with this strain failed to effect a radical cure when given in total doses varying between 2.1 g. in seven days and 4.2 g. in 14 days. Yet Maegraith and Andrews (1949) were able to report constant radical cures with proguanil given in a total dose of 3 g. in 10 days. Their latest results did not materially differ from those obtained in 1945, when the first therapeutic trials of proguanil were being carried out in Liverpool.

Experimental data obtained by Covell and his associates tacitly implied that medical reports referring to the failure of proguanil in the prophylaxis of West African malaria were based on insufficient evidence. None the less, during 1948-9 several medical officers in tropical Africa continued to express their conflicting views on proguanil. While Walls (1948), Bostock (1949), and Abbott (1949) were on the whole satisfied with its prophylactic value, Best (1949), Davey and Smith (1949), Shearer (1949), and Jelliffe (1949) quoted cases of overt *P. falciparum* malaria in subjects taking regularly 0.1 g. of proguanil a day.