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Effect of immunizations on the susceptibility to poliomyeltis

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THE EFFECT OF IMMUNIZATIONS ON THE SUSCEPTIBILITY TO POLIOMYELITIS

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INTRODUCTION

The selection of my topic came about because of the great amount of attention in current literature and thought concerning the effect of immunizations on the susceptibility of poliomyelitis, particularly during the summer months. This problem raised considerable question in my mind as to the degree of danger involved especially in regard to the immunization programs among children. Since a great amount of work is being done in attempting to determine the etiological factors in poliomyelitis, I thought it would be interesting to try to compile present theories and attempt to discover if any relationships actually exist. There are several interesting questions before us. We should like to know what danger, if any, exists in the administration of prophylactic immunization procedures in children of all ages; and if a danger exists, to what degree is it present? Is there a measurable difference among the various antigens currently employed--either alone or in combination loads? What are the prime relationships? Is there a danger period following the administration of a prophylactic injection? If so, what is its duration? Does technique make a difference? These are questions to be answered and will largely determine the confines of this thesis.

It has been known for a number of years that a certain small percentage of patients develop certain neurological and paralytic syndromes following injections of various agents. This situation had arisen following a great variety of drugs injected. In many of these cases a neuritic type picture developed. However, only a small number probably presented true poliomyelitis. In this thesis, only those conditions representing true poliomyelitis will be considered, as determined by analysis of clinical and laboratory findings, using certain criteria to be discussed later.

The effect of the various immunizing agents aimed towards the purpose of prevention of the disease, such as the various viral suspensions and other agents, will be discussed only as problems of their use are incidental in the investigation of our main problem.

During the past 10 years, investigators have suggested that many conditions may influence the individual's resistance to paralytic poliomyelitis. Conditions such as fatigue, traumatic episodes, both accidentally conceived or due to surgical procedures, temporary changes in metabolism, such as we find with pregnancy, sudden changes in habits, and sudden exposure to adverse weather conditions have all been incriminated. Inoculations fall into this same broad category. Again, this thesis will be

limited to the effect of immunization procedures per se.

Many attempts have been made to perfect a vaccine against polio that would be effective. Our first hint that the inoculating needle may be attended by ill-consequences came in a report by the Medical Director of the U. S. Public Health Service, Dr. J. P. Leake, in 1935 (13). Dr. Leake reported 12 cases with 6 consequential deaths after vaccination by the subcutaneous or intracutaneous route for the prevention of poliomyelitis. Various investigators have noted cases presenting neuritis-like syndromes (Keim and Wakefield 1939) (12). Since spinal fluid findings were normal and clinical analysis did not present a polio-type picture, we may assume they were not polio cases. Spillane in 1943 reported several cases of brachial neuritis in which paralysis followed strictly a nerve and not a spinal chord distribution following injection (28). He likened the cause probably not to trauma, but to a hyper-sensitivity to the agent injected. In 1943 Brain (3) reported 3 cases of proven poliomyelitis following alum precipitated toxoid inoculations against diphtheria. Brain was the first one to suggest that a statistical analysis should be carried out in regard to the incidence of poliomyelitis following inoculation (3). However, he figured the incidence to be rare.

Hughes in 1944 (11) reported 6 cases with neurological complications following serum or vaccine therapy in military stations; and although these cases resembled neuritides rather than poliomyelitis involvement, Hughes suggested virus causation with possible syringe transmission, although he did not present any direct clinical evidence (11). About this time, other investigators one by one began to report isolated cases and small groups of cases that showed post-inoculation paralysis. Walshe (1945) had several (34). Parsonage and Turner in 1948 reported 1 case after TAB therapy for urethritis (25). This case was apparently not due to poliomyelitis.

In 1949 Russell in discussing various etiological factors in poliomyelitis listed 2 cases in which the injection site corresponded with the site of paralytic involvement. One was a TAB inoculation, the other a penicillin shot (27). It was not until 1950 that any large series of post-inoculation paralytic cases were found in the literature, but by the end of 1950, 8 investigators or investigator teams had reported series of their own or referred to other compiled series of cases. Among these workers were D. K. Martin, B. P. McCloskey working in Australia, D. H. Geffen in London, Hill and Knowelden in Wales and England with about 450

cases, Banks and Beal with one London hospital's records, 13 cases, Newcombe, Verjaal in the Netherlands, Bousfield, Dundon in Ireland, and Leake (18 19, 20, 8, 2, 24, 33, 4, 6, 14). Further reports have reached the literature in 1951 from McLeod (22) in Belfast, Northern Ireland, more complete studies by McCloskey (21), a good series by Anderson and Skaar, working at the University of Minnesota (1), a discussion by Lenard in Rome, Italy (15), and a joint report by a number of Swiss workers, Mooser et al (23). These gentlemen have all contributed a great deal to our knowledge of the present status of the effect of the various immunization and vaccination procedures on the possible increased susceptibility rate.

Recently a comprehensive report by Goerke of the City Health Department, Los Angeles, California, was made known (9).

CLINICAL INVESTIGATION

Let us now consider the clinical evidence that we have for post-inoculation poliomyelitis. First of all, let us discuss the incidence. Geffen in 1950 (8) considered the incidence to be about 1 case in 1800 or 1900 injections. If this figure approaches any degree

of accuracy, the incidence is not comparatively rare when we consider the incidence of paralytic poliomyelitis in the population as a whole. Poliomyelitis in itself is not a common disease. At first glance it might seem to be a comparatively easy proceeding to determine incidence of paralytic poliomyelitis among those previously receiving antigenic injections. However, if one considers the number of annual injections given in the different localities, it is immediately apparent that one cannot simply compare the number of post-injection cases versus the probable number of paralytic cases that would have occurred in spite of any previous injections. This would be especially difficult in comparing the results of different investigators because of different localities and different immunization practices particular to the locality, and the severity of the epidemic. Any figures presented, therefore, must be subject to a wide degree of tolerance, and must not be taken literally. A number of workers in 1950 and 1951 collectively have accumulated a goodly number of cases pertinent to our discussion. Martin (18) in his review in 1950 presented 17 cases of post-inoculation poliomyelitis. Geffen (8) had 182 polio cases which he reviewed. Banks and Beal had 111 cases, 12.6% of which had a

previous inoculation history. McCloskey (21) had 620 cases, Hill and Knowelden, 410 cases (10). Anderson and Skaar (1) reviewed 2,709 cases, and Goerke, 1,321 poliomyelitis cases (9). In actuality, the total number of cases presented by each individual worker does not represent a great amount of material, but when all taken together, quite a significant total number of cases have been reviewed. Moreover, we are able to study the conclusions and methods of analysis of each individual man or team to compare the results and conclusions of the various workers among themselves. By this method it is hoped that a logical conclusion may be approached.

D. H. Geffen, British health officer, working in the metropolitan borough of St. Pancras, in London during the 1939 polio epidemic found two cases of poliomyelitis in children, 10 months of age, both of whom had been immunized within the previous 3 week period with combined pertussis and diphtheria vaccine (8). This unusual happening led to an inquiry, and Geffen found that 6 polio cases had been reported in the borough in children who had been immunized within 22 days of the onset of their disease. Geffen also found that similar cases were being reported in other boroughs. He found that of 182 cases, to September

1949, 30 had been immunized within 4 weeks of the onset of their symptoms. This series of cases, however, only suggested a connection to Geffen that a definite relationship might exist. It is of interest to note, though not at all conclusive, that 16.48% of the polio patients that Geffen reviewed had received some sort of inoculation within one month. This large percentage, of course, may be due to the fact that a large percentage of the children were receiving immunization shots at this time.

During this same period, B. P. McCloskey (21) made a study of 620 cases in the Victorian epidemic in Australia in 1949 and found that 53 cases had received an injection within 3 months previously, giving an incidence of 8.54%. McCloskey surmised that the more recent the injection of any agent, the more likely its association with the onset of poliomyelitis. Interestingly, 41 of the 53 had received their inoculation within the previous month. McCloskey also reported an outbreak of poliomyelitis in a small isolated town remote from Melbourne (20). This outbreak, also in 1949, was the first since 1946 in this little town (Population 3,000). There were, in all, 8 cases, all paralytic in form; all occurring within 1 month of the initiation of the outbreak. Notable, however,

were 2 cases with immunization history. Case #1 was a male, 9 months of age, in which combined diphtheria-pertussis antigen was given 11 days previously. Case #2 was also a male, 11 months of age, in which combined diphtheria toxoid and pertussis vaccine were administered 14 days previously. Neither of these cases had any direct contact with other victims. The occurrence of 2 such cases in such a small isolated outbreak was considered distinctly unusual.

Then, Banks and Beal reviewed the cases of 111 patients with paralytic poliomyelitis between 1947 and 1949 in Park Hospital in London (2). There were 14 patients, or 12.6%, previously immunized.

Four hundred ten cases from wide spread areas in England and Wales, in children under 5 years of age, were reviewed by Hill and Knowelden (10). In each case, where possible, a questionaire was completed as to sex, date of birth, date of notification of poliomyelitis, date of onset of symptoms, amount of paralysis, site of paralysis, whether fatal or not, and as to the inoculation history from birth. The inoculation history included the date of each injection, the number of doses, the site, the technique (subcutaneous or intramuscular), and the nature of the vaccine and its origin. This latter data was confirmed where possible

by the attending physician. Then in order to see if poliomyelitis children had been recently inoculated more often than the general run of children, that is, whether inoculation was bringing them into the paralytic class, collecting officers paired a control child to each poliomyelitis case. These children were of the same age, from the same general area, and of like constitution if possible. These were either children whose birthdays closely coincided with the polio cases or were measles cases whose records could be more easily obtained. All in all, 164 closely paired control children were obtained. These workers found that 96 polio cases had been inoculated while 83 controls had been inoculated, and that 50 polio cases had not been inoculated while 67 controls had not been inoculated. In 18 polio cases it was not known whether or not the child had been immunized, and the same was true with 14 control children. In other words, about 58% of the poliomyelitis group had been previously immunized, to approximately 51% of the control group. Obviously this is a small difference. Of those patients who contracted polio within 1 month following injection, the proportion was 16 to 1 polio cases to their matched controls as to the proportion who had received prior injections. We must therefore conclude, though this is a small total

number of cases, that there seems to be definite evidence to indicate that the antigenic injections do have an effect on the incidence of polio where the relationship in time interval is less than 1 month.

After reviewing the work of the British and Australian workers, Anderson and Skaar (1) of the University of Minnesota came out with a study published in 1951 of 2,709 poliomyelitis cases in Minnesota during the polio epidemic of 1946. Of the 2,881 reported cases that year, 2,709 were questioned about injections, dates, name of physician, or the clinic giving the injection; and 2,677 gave a definite statement as to immunization. Thirty-three cases that were confirmed had received injections within the previous month before the attack. Seven cases were not confirmed. Eighty-five confirmed cases occurred within the 6 month period after an antigen injection. Twelve were confirmed in the second month previously, and 15 in the third month before onset. The unusual number of confirmed cases occurring within 1 month after antigen injection, that is, 33, a definitely higher concentration, suggested some relationship to the authors with antigen injected within the previous month. But the question arose that there might have been more

injections given to the population during that month. Although difficult to check, this was probably not the case since the authors did not find that a greater amount of antigen was sold in the state during this period. They found that the peak of immunization was in May, and that the peak of the 85 cases was in late July or early August which was the peak of the 1946 outbreak in Minnesota. Therefore, it was logical to assume that the number of immunizations, in itself, did not cause a large number of cases to contract poliomyelitis within a 1 month period following immunization. The authors found that the number of cases occurring among recently immunized children was actually small in spite of the large outbreak. They found also that there was a large number of children immunized in 1946. They further noted that there seemed to be no effect whatsoever of immunizations given more distant than 1 month previous to the onset of the illness.

In May of 1951, L. S. Goerke, of the City Health Department of Los Angeles, rendered a report including the records of 1,321 cases of poliomyelitis in Los Angeles in 1948 (9). Notation was made if the patient was vaccinated against small pox or received any other injections preceding the onset. In children under 12 years of age, Goerke found that the incidence of

poliomyelitis was slightly higher with those who had been previously injected. He found also that the incidence of paralysis was also slightly increased. However, the author concludes that the disparities were not considered statistically significant and that they were not wide enough to warrant withholding immunizations against other serious diseases in order to get a slight reduction in poliomyelitis.

On the other hand, an association between the site of inoculation and paralysis was not found after 6,250 inoculations of P.T.A.P. in children of the age group affected by the poliomyelitis epidemic compiled by McLeod in Belfast (22).

Grasset (23) found, that although in 1949 when compulsory small pox and diphtheria immunizations were instituted in Geneva, and there were 23 poliomyelitis cases, 4 of which were fatal, none of the patients had received injections during the previous year.

Hottinger (23) found that 22,000 children were immunized in the canton of Basle against diphtheria in the last 8 years, from 1942 to 1950. Two hundred thirty cases of polio occurred of which only 1 patient had taken ill 3 weeks after vaccination during a polio epidemic.

Gautier (23) found that poliomyelitis had no

relation to small pox, pertussia and diphtheria immunizations observed at the pediatric clinic of Geneva.

Payot (23) found that there was no evidence in the canton of Vand, in the last 6 years, with 5 to 6 thousand immunizations per annum in 6 to 8 month old children, compared with the previous year and with neighboring countries with non-immunized control groups.

Jaccottet (23) summarized 8 years' records of 168 polio cases in children to 1943, and found that 2 of 65 cases were immunized against diphtheria. Since 1944 when vaccination was made compulsory for diphtheria, 63 out of 103 poliomyelitis cases were immunized and 60 of this 63 were immunized 3 months or so previously--5 within 3 months. This author believes that there was little connection between vaccination and poliomyelitis; however, his reasons for thinking thusly are not clear.

Koller found that in 1943 in Zurich that there were 8,327 immunizations against diphtheria with only 4 cases of poliomyelitis. No prophylactic inoculations were performed in 1942, when there were 41 cases of poliomyelitis and in 1944, when there were 14 cases. Since 1943, 3,400 children were immunized against

diphtheria at a child health resort with no cases of poliomyelitis.

It remains highly apparent, therefore, that data concerning the exact incidence of poliomyelitis following various inoculation procedures is woefully lacking. Material gathered thus far only can be thought of as suggestive; and, according to Hill and Knowelden, it would take several years' study of carefully selected control groups in order that the problem might be settled conclusively one way or the other.

As far as sex is concerned, there is no difference from the general run of poliomyelitis cases. Males seem to be about twice as susceptible as females (1, 10). Twenty-four cases (73%) of the 33 first month cases were males, whereas only 31 (60%) of the 52, 2 to 6 month cases were males.

Neither does there seem to be any difference from the general distribution of poliomyelitis cases as far as age is concerned. The younger the patient, the greater is the susceptibility (1, 2, 8, 10, 18, 19, 20, 21). Of Anderson and Skaar's 33 first month cases, 19 of them, or 58%, were under 2 years of age, while of the 52, 2 to 6 month cases, only 19, or 37%, were under 2 years of age. The rest were spread out in a normal age distribution. It must be concluded, therefore,

from these figures, that the younger children seem to be more apt to have their subsequent reaction to polio virus altered by antigen than older children.

One of the factors that drew the attention of investigators to the problem of poliomyelitis following inoculations was the fact that in these cases the paralysis seemed to have a certain predilection or affinity for the previously inoculated site.

That the paralysis was frequently first present, more severe, and lasted longer in the injected extremity was clearly shown by McCloskey in his series of cases (19, 21). Not only was this fact true in McCloskey's large series, but in his investigation of the outbreak in the small isolated town (20). His 2 cases who had recently received diphtheria-pertussis antigens both showed flaccid paralysis of the left arm, the site of previous inoculation.

Banks and Beal found that with an average interval of from 9 to 14 days following inoculation, in their previously inoculated paralytic cases, that there appeared an unusual distribution of paralysis in those immunized in the previous 2 month period. Arms were paralyzed 12 to 3 over legs. Those having no inoculation history and those immunized 6 months or more before revealed the proportion of legs paralyzed over arms to

be considerably greater. In those patients inoculated within 2 months of the disease, all showed a correlation between the site of inoculation and the site of paralysis except one.

Carrying the investigation a little deeper, Hill and Knowelden (10) found that in children less than 2 years of age contracting poliomyelitis, those that were not inoculated showed an arm involvement in 23% of the cases and a 57% leg involvement. In those inoculated 3 months previously, approximately the same proportion occurred--23% arm involvement and 55% leg involvement. They concluded, therefore, that inoculation 3 months or longer previously showed no difference as to site of paralytic involvement. The same held for those inoculated from 1 to 3 months previously; arms were involved 30% of the time and legs 61%, about the same proportion. However, in those inoculated less than 1 month before the attack of the disease, arms were involved in 46%, while legs were involved in only 39%. Moreover, the right arm was only involved in 18%, while the left arm was involved in 23%--the left arm being the usual site of injection as was customary practice in the community. These authors had 101 total cases under 2 years of age. The percentage of this total number having paralysis at or including

the inoculation site was as follows: of the 0-1 month interval from inoculation to onset of the disease, 81% showed a site correlation. Of the 1-3 month interval, there were only 25%; of the 3-6 month interval, 25%; and of the 6 month plus interval, only 15%. Of the 149 total cases 2-5 years of age, much the same picture was presented. In the 0-1 month interval, 57% showed a site correlation; while 0% were present in the 1-3 month interval and the 3-6 month interval, and there was only a 10% occurrence in the 6 month plus interval. The authors deemed these findings technically significant. As to the interval between inoculation and paralysis, 26 of 33 cases were within 28 days in Hill and Knowelden's series. None were below 8 days, except in 2 cases where there was no site correlation.

As far as the correlation between the site of inoculation and the site of paralysis is concerned, the work of Geffen (8) confirms the findings of Banks and Beal, and Hill and Knowelden. Of Geffen's 182 cases, 30 had been immunized within 4 weeks of onset; and in these, paralysis affected more particularly the limb of injection. In 7 others immunized recently, paralysis did not affect the limb of injection.

The work of Anderson and Skaar (1) corroborates

the work of the other writers. Anderson and Skaar called cases correlated when the site of last injection coincided with localization of paralysis. In the first month group, 58% of the cases were correlated, where in the 2 to 6 month group, only 15% were correlated. The difference between these groups is significant, suggesting that there is a relationship between the site of injection and the localization of paralysis developing within the subsequent month. In children under 8 years of age, 20 children (61%) of the 33 immunized during the preceding month had arm involvement as contrasted with only 11 children (21%) of 52, immunized 2-6 months preceding. Nineteen percent of those immunized before 1946 had arm involvement, and 21% of those who had never been immunized had arm involvement.

Of the 19 correlated first month cases in this series, 7 showed involvement only of the injected extremities. Seven others had frank paralysis of the extremity in question, but some weakness in other parts of the body. Five showed definite paralysis in some other part. In analyzing the time interval involved of 33 cases, 17 developed in the 10-14 day interval, 20 in the 5-14 day interval, while the rest showed a considerable spread. Furthermore, figures

suggest a causal relationship since the correlated cases show a closer relationship; that is, 11 of 19 cases. Thus, an additional relationship between location of paralysis and injection site is suggested.

The work of these writers tends to indicate that there is no relationship to injections prior to 1 month before onset or to previous series of injections since 27% of the less than 1 month interval group had been given their first injection of any antigen, while in the 2 to 6 month interval group, 25% had been given their first injection. Since these percentages are nearly identical, and if we accept the previous anxiom that only injections given within the previous month show any relationship to the onset of poliomyelitis, we must therefore surmise that it must have made no difference whether the inoculation preceding the paralysis was the first injection of any antigen or the last in a large series of injections. Anderson and Skaar (1) statistically computed the probability of certain types of poliomyelitis occurring among cases having ever received various antigens. That is, they calculated the expected number of different kinds of involvement versus the actual number of cases. Statistical analysis proved no relationship to the injection as regards to the total number of cases, but

there was a definite suggestion of localization of the paralysis with prior injection in the 1 month interval group. However, the methods used to arrive at this conclusion and the statistical techniques involved are beyond the scope of this thesis.

A number of other authors have also reported post-inoculation cases with flaccid paralysis enveloping the previously inoculated site. J. K. Martin had a series of 17 cases with flaccid paralysis in one limb (18). These were all in cases in which inoculation had been performed fewer than 28 days previously. Dundon (16) reports a case in 1950 in which paralysis occurred first in the left arm, the same utilized for administration of pertussis vaccine five days earlier. Russell (27) in 1949 reported a similar circumstance after TAB inoculation. A. Verjaal (33) in 1950 reported 2 cases. One occurred in a 1 year old child and the other in a 35 year old man, 21 and 27 days respectively after vaccination against small pox, beginning in the vaccinated limb in both cases.

McLeod (22) in 1950 reported a series of 88 cases of poliomyelitis in Belfast that might contradict the work of the investigators who attempted to show that injections increased the percentage of arm involvement. In McLeod's series there was an unusual involvement of

upper extremities which was characteristic of the Belfast epidemic. On the other hand, arm involvement was not characteristic in the series reported by the other men.

Let us now turn our attention to this question. Is the severity of paralysis in inoculated cases increased over that in the non-inoculated cases? Let us again review the findings of the various investigators.

First of all, it might be said that since the work of various investigators tends to show that the usual pattern of paralysis is altered, it might be reasonable to assume that many patients would not otherwise show involvement at the injected site. Furthermore, in the case of those patients who showed involvement only of the injected extremity, those patients might otherwise have been in the non-paralytic group, and might have shown no involvement or paralysis at all if it had not been for the injected member. Hill and Knowelden (10) state that the excess of recently inoculated children in the poliomyelitis group and the equality in all other intervals would tend to indicate that this group includes cases which would not have been diagnosed as poliomyelitis at all if there had been no previous and recent inoculations. Anderson

and Skaar (1) conclude from their figures, as to the severity of paralysis in those children under 2 years of age, that there is a definite suggestion that the first month cases were more severe than the 2 to 6 month group. However, they emphasize that too great attention cannot be attached to the difference since as wide a variation exists in the non-immunized and those immunized before 1946 in their series. In their first month group, 17 were classed as severe cases and 1 was a mild case, giving a total of 18 cases in the first month group. Of the 2 to 6 month group, only 10 cases were classed as severe while 9 were classed as mild, giving a similar total of 19 cases. While in those immunized before 1946, 6 were classed as severe and 7 were classed as mild, making a total of 13. In the non-immunized patients, 21 were classed as severe and 5 were classed as mild, giving a total of 27.

Let us next turn to the types of antigens indicated. In his original report of 340 cases in Melbourne, B. P. McCloskey (19) suggested that pertussis vaccine was particularly striking. He goes on to state that the association with pertussis was statistically significant and certainly not to be dismissed as chance. Hill and Knowelden (10) found in comparing the different antigens employed, that in the one month post-

inoculation polio cases, with the use of alum precipitated toxoid, 6 out of 8, or 75%, in children under 2 years of age had a site correlation. Only 2 out of 9, or 22%, had a site correlation in the 1 to 3 month group, and only 5 out of 53, or 15%, had a site correlation in the 3 month plus group. While with the use of APT and pertussis vaccine combined, 22 out of 26, or 85%, of those under 2 years of age in the 1 month group showed a site correlation, only 30% of those in the 1-3 month and the 3 month plus group showed a site correlation. Hill and Knowelden disagreed with McCloskey, finding pertussis to appear to be no more offending than the other antigens. However, when McCloskey published his final report, a study of 620 cases in the Victorian epidemic of poliomyelitis in 1949 (21), he again stressed that pertussis or combined pertussis-diphtheria to be considerably more offending than diphtheria alone. He stated that the paralysis was more severe and more frequent in children under 3 years of age with pertussis used alone or in combination, and also that the localization was more frequent and that there was no evidence of localization with diphtheria used alone. He also states that Hill and Knowelden's figures coincide closely with his own incidence in the cases in which

the inoculation was administered one month previous to the attack of poliomyelitis. Of pertussis alone McCloskey had 7 cases; Hill and Knowelden, 5. With combined pertussis-diphtheria, McCloskey had 22 cases; Hill and Knowelden had 27 cases. Of diphtheria injections alone, McCloskey had 12 cases; Hill and Knowelden, 11 cases. The cases in the series of both men were proportionately the same. It is seen that of the total number of cases here, that the combined antigen shows the greatest total number. Diphtheria alone ranked second. McCloskey, however, points out that in England and Australia the number of subjects receiving pertussis alone was small. The author concludes that further evidence in the relationship between recent inoculation and the onset of poliomyelitis is presented, in particular, for pertussis alone or in combination. Evidence for diphtheria toxoid incrimination is less conclusive. In Geffen's series (8), 21 patients had had combined pertussis-diphtheria, only 8 had alum precipitated toxoid alone, and 1 had had pertussis alone. Geffen concluded that the combined injection with pertussis was of the most importance. However, it is extremely difficult to evaluate these figures because we have no way of knowing how many injections of each kind of antigen were given to the

children in the various localities.

Banks and Beal (2) found that combined pertussis-diphtheria, alum precipitated toxoid in 9 cases, pertussis alone in 1, and diphtheria alum precipitated toxoid alone in 4 cases. These figures seem to be in keeping with those of the other British writers.

Anderson and Skaar (1) studied the types of antigens in those cases in their series that were correlated. They found that of the 19 correlated first month cases, in 16 there was no history of small pox vaccination; in 7 no history of pertussis vaccination; in 7 no tetanus; and in 1 no diphtheria. These authors maintain that the reason for this proportion is that diphtheria toxoid is the most extensively used of the antigens. They further maintained that this explanation is borne out by the study of non-correlated cases and those in the 2 to 6 month group in which they supposed there was no connection with subsequently developing poliomyelitis. They state, therefore, that paralysis is probably not due to any one specific antigen but rather to a non-specific factor; possibly the presence of some irritant acting as a foreign body. They also state that in their series, all the antigens were alum precipitated except in one non-correlated small pox case occurring within the first month after

vaccination. These authors also found that in taking the records of all patients immunized from July through October, 1946, calculating the expected number of poliomyelitis cases and comparing them with the actual number, that there was little significant difference for each antigen; that is, for diphtheria, vaccinia and pertussis, etc. They conclude, therefore, that no single antigen may be singled out as being more offending than the others. They do not agree, therefore, with McCloskey or Geffen. They are in agreement with Hill and Knowelden. McLeod (22) suggests that PTAP antigen is the one of choice since there has been a noticeable reduction in the number of local reaction with this antigen and in his series no association between the site of inoculation and the site of paralysis after studying 6,250 children inoculated with PTAP, and in this large number only 6 cases of poliomyelitis were found, and only 1 case within one month of inoculation.

All of the various investigators do, however, seem to be in agreement that among their series of patients that there was absolutely no relation to any particular technique nor was the incidence higher; that is, the incidence of poliomyelitis cases following inoculation in any particular clinic or locality. However,

Bousfield (4) in 1950 suggested that the use of PTAP administered subcutaneously might be the answer to the current diphtheria immunization problem in regard to poliomyelitis after noting McLeod's series and noting that subcutaneous injection is attended with less reaction than intramuscular administration of the preparation.

EXPERIMENTAL INVESTIGATION

Let us look now to substantiating experimental evidence in the light of the previous clinical investigation. F. O. MacCallum in 1950 at the Virus Reference Laboratory of the Public Health Laboratory Service of London examined the stools of 4 cases in which recent inoculation had been associated with paralysis. Two of these were examples of the "double event", paralysis being confined to the inoculated limb and having occurred 11 and 12 days after intramuscular inoculation of APT and pertussis vaccine respectively. In the other 2 cases the paralysis was not confined to the inoculated limb. It occurred in 1 case 17 days after inoculation with combined APT and pertussis vaccine, and in the other case 8 days after inoculation with pertussis vaccine alone. From all these 4 cases poliomyelitis virus was isolated.

It was also isolated from another case, meningo-encephalitis with paresis of the 7th cranial nerve 4 days after onset. In this case 3 vaccinations with small pox lymph resulting in a mild "take" had been performed 12 days before the onset of symptoms. Thus we have confirming evidence of virus etiology in at least several of the cases from Hill and Knowelden's series (17).

As far back as 1934 J. A. Toomey found that poliomyelitis virus combined with colon filtrate, injected directly into the gut of monkeys, accelerated poliomyelitis (29). The purpose of Toomey's investigation was to determine if a possible synergistic effect existed between the poliomyelitis virus and various enteric organisms or their toxins. Toomey attempted to determine if there was any relationship between the enteric organisms and gastro-intestinal transmission of poliomyelitis. In 1935 Toomey (30) reported a small scale experiment. Six baby monkeys, divided into 3 experimental animals and 3 controls, were used to determine the effect of a standard poliomyelitis virus in monkeys previously given paratyphoid-colon filtrate and vaccine. Paratyphoid and colon bacilli were grown, autoclaved and filtered. The supernatant fluid was called the filtrate while the organisms themselves

were termed the vaccine. Eighteen injections in massive doses were given to the 3 experimental monkeys at 3 to 4 days intervals. These experimental monkeys were then given a 2 weeks rest period. Then 25 cc.s of a 1% suspension of poliomyelitis virus was given to 2 of the experimental animals and to 2 controls. The virus was injected subserosally at multiple points after laparotomy. Eighty cc.s of a 1% suspension of poliomyelitis virus was given to the third experimental animals and the remaining control.

Let us look at the results of this experiment. All of the 3 vaccine and filtrate animals died rather promptly. All 3 control animals developed localized paresis or paralysis, but none died. These animals were all autopsied and histopathologic studies were carefully made. In all 6 animals typical findings in agreement with anterior horned poliomyelitis were found, such as degeneration of anterior horn cells, inflammatory reaction accompanied by capillary dilatation, perivascular cuffing, neuronophagia, glial reactions, and total anihilation of cells in some sections. However, the experimental animals, particularly the ones in which the 80 cc.s of virus suspension was administered, showed a much greater reaction of anterior horn cell degeneration than did the control

animals in which the reaction tended to be spotty, segmental and less severe.

Curiously enough, in later screening experiments, Toomey found that the production of massive abscesses after subcutaneous injection of laboratory cultured staffloccoccus (1 animal with 1 control), with 2 successive subcutaneous injections given 2 days apart of the fifth immunizing dose of scarlet fever streptococcus toxin (Dick) (1 animal with 1 control), the presence of massive pulminary tuberculosis in 11 monkeys used over a 3 or 4 year period and the injection of vaccinia virus intradermally (1 animal with 1 control) did not accelerate the production of poliomyelitis in these animals when they were later given the disease experimentally. On the other hand, injections of massive doses of paratyphoid-colon bacillus filtrate and vaccine subcutaneously rendered the monkey less immune so that when poliomyelitis virus was later introduced by way of the gastrointestinal tract, the production of the disease was accelerated (30).

In 1943, Toomey and Tischer (31) re-duplicated their previous experiment with Macaca mulatta monkeys. Twelve healthy monkeys were used and were divided into groups of four. The results were the same as in the

previous experiment, and the author states that though the number of animals used was too small to allow them to state that such results would always be obtained, the results in their experiment were quite definite and contrasting with the use of paratyphoid and typhoid vaccine and other enteric organisms. Then again in 1948 Toomey, this time with Takacs (32), working with 11 baby monkeys, inoculated 3 subcutaneously with typhoid-paratyphoid AB every 5 days for 6 doses. Then 23, 24, and 25 days later these three monkeys were injected subserosally with poliomyelitis virus, while 4 monkeys not inoculated were injected subserosally with poliomyelitis virus to act as 1 control group. Four other controls were injected intracerebrally with poliomyelitis virus. Toomey and Takacs found that the previously injected animals showed accelerated symptoms of poliomyelitis within 3 to 5 days, while there was a minimum reaction in the non-inoculated control. The microscopic changes in the central nervous system were also more severe in the TAB injected animals. These experiments do tend to show that the injections of the products of the enteric organisms tend to increase the subsequent susceptibility to poliomyelitis, at least in monkeys. What the relationship is in humans, of course, is only

a matter of conjecture.

In 1950, Findlay and Howard (7) obtained experimental evidence that intravenous injection of TAB vaccine, diphtheria toxoid, or diphtheria toxoid plus pertussis vaccine in mice which had been injected intracerebrally with Lansing strain of poliomyelitis virus 2, 4 or 6 days prior to the inoculation of the vaccines caused a more rapid onset of paralysis and death. These men offered the explanation to the effect that it is possible that trauma, in particular, alters the rate of metabolism in neurones with nerve connections to that area, thereby liberating nucleotides in a form which permits their rapid use by virus particles. Thus the multiplication of virus in these particular cells is encouraged.

In working with the idea of non-specific factors, Levinson, Milzer and Lewin (16) in 1945 found that fatigue and chilling decrease the resistance to poliomyelitis in monkeys. However, when these workers externally traumatized various muscles and muscle groups with a rubber mallet under anesthesia, there was no correlation with the location of paralysis in monkeys developing poliomyelitis.

THEORETICAL CONSIDERATIONS

Let us then consider the cause of increased susceptibility due to the various antigens injected. A great number of investigators have listed non-specific shock as a factor in the development of poliomyelitis or in the production of clinical poliomyelitis from cases which might otherwise have not been diagnosed. Almost all types of trauma, surgical procedures such as tonsillectomy, and all types of injections have been cited. Reports have reached the literature in Europe in which, in addition to various kinds of prophylactic inoculations, penicillin, arsenicals, and gold salt injections have been reported as having been administered previous to paralytic complications. Some of these paralytic conditions were not poliomyelitis, as evidenced by the clinical picture (3, 11, 12, 13, 25, 28, 34). However, many true poliomyelitis cases have been reported. The exact pathogenesis and early multiplication of the virus of poliomyelitis in the body during the early stages of the disease is, as yet, unknown. The question of a viremia, in which the virus appears transiently in the blood stream of the host during the early stages of the disease, is a dubious one.

Russell in 1949 (27) after noting 2 cases of

paralysis at the site of previous inoculation, one with typhoid-para typhoid A and B inoculations, and the other following a penicillin injection, discounted the possibility that poliomyelitis virus follows the nerve from the injection site to the corresponding level of the spinal cord. He sites Hurst's work (1930) of injecting virus into the sciatic nerve with resultant paralysis only if the nerve was injured by the needle. He also sites the work of German and Trask in 1938, in which a denervated flap of tissue was injected in experimental animals, but paralysis nevertheless ensued, being more severe on the same side. This is evidenced against strict neuronal transmission. Russell suggests that the involvement of the segment of the spinal cord innervating the injected area is probably due to trauma modifying the physiology and increasing vulnerability of the spinal cord cells with which the traumatized area is an anatomical neuronal connection. This idea seems to be the most prevalent and the most plausible explanation for this phenomenon at the present time.

Cummings in 1950 rendered an etiological hypothesis (5). Cummings' theory is resolved essentially to the following facts: 1. poliomyelitis is an inoculation and not an auto-inoculation disease. 2. In order for

the virus to cause nervous system involvement, there must be a break in nerve continuity somewhere in the body; otherwise, the symptoms due to the virus are non-paralytic. 3. The site of nervous interruption may occur anywhere throughout the body, such as in the nasopharynx, oropharynx, and the g.i. tract. Assuming the author to be correct, it would be easy to see how the virus already present in muscle or fascial tissue might gain entrance to nervous tissue, or might work physiological changes in the anterior horn cells innervating the area, and thus gain entrance to the spinal cord at this level or segment.

As discussed previously, Leak in 1935 reported 12 cases, with 6 deaths occurring after vaccination for poliomyelitis by either the subcutaneous or intracutaneous route (13). In each case the level of the spinal cord first affected corresponded to the injected extremity. In 1950 Newcombe (24) reported an interesting case occurring in 1947 in a 21 year old female given 20,000 units of penicillin q. 3 h. alternately in both thighs for furunculosis, who developed flaccid paralysis of the hips bilaterally on the fourth day of therapy, which was still severe after three months. The spinal fluid findings in this case were characteristic of poliomyelitis. This author also suggests

that needle trauma was a predisposing factor to the paralysis of the limbs independent of the syringe content.

In 1951 Glanzmann (23) discussed 2 possible factors in the etiology of so-called "injection induced" poliomyelitis. He first spoke of a traumatic factor. He suggested that injection of the limbs may cause reflex hyperemia of the ganglion cells of the corresponding spinal segment where localization of the virus may be favored. Secondly, he discussed a toxic factor, stating that the Hemophilus pertussis endotoxin is neurotoxic, as is likewise typhoid and paratyphoid endotoxin. These neurotoxic endotoxins may cause a neuritis mimicing poliomyelitis, but in these cases recovery should be prompt. It is interesting to note at this point that at least one man, Pellew, in 1951 (26) reported a series of cases closely resembling poliomyelitis seen in Adelaide from 1949 to 1951 in which cerebrospinal fluid findings were essentially normal. However, it is rather unlikely that the diagnosis of poliomyelitis gives difficulty in the vast majority of cases.

All of the men who reported series of post-inoculation poliomyelitis cases rather universally denied the possibility of syringe transmission of the poliomyelitis virus. However, McCloskey stated in

1951 (20) in discussing 2 cases in the isolated community remote from Melbourne that syringe transmission could not be excluded since the sterilization of syringes was limited to the treatment in spiritus vini methylatus.

In 1944 Hughes suggested that virus might be introduced directly by the inoculation needle, but did not give any direct evidence in discussing a number of post-inoculation neuritis-like syndromes (11).

In 1951 Alexander Lenard of Rome, Italy, presented a dissertation in which he took exception to other authorities on the possibility of syringe transmission of poliomyelitis (15). Two cases of poliomyelitis occurring after prophylactic or theraupeutic injections in children in Rome prompted review of similar incidents by the author. He is of the opinion that there is evidence that the disease may be transmitted by syringes and needles which have not been autoclaved at least 1/2 hour immediately previous to administration of their contents. The first case was in a 23 month old white female immunized against diphtheria in the right buttock and in which paralysis developed in the left leg with hypersensitivity of the right lower extremity. One month later this patient had recovered somewhat, but still had an uncertain gait. Administration of the

toxoid had been by a male nurse who had used no special care in aseptic technique.

In the second case, penicillin had been given for "bronchitis" q. 6 h. alternately in each buttock in a 3 year old female child. She developed paralysis in both legs on the second day after therapy was commenced. On the evening of the same day the fever rose to 39.9° C. and the whole body was hyperesthetic. Injections were given by the son of a nurse living near by. The syringe and the needle belonged to the family and were used for its members for several years. The mother of the patient boiled the syringe for a short while. The author points out the prevalence of like cases in the recent literature in which the paralysis occurred in relation to the inoculation site, and he also cites a survey of poliomyelitis published in 1949 especially pointing out the poliomyelitis epidemic among British troops in Malta and India where almost no civilians were effected. As the soldiers received various types of vaccinations, no specific substance was assumed to contain the virus. (However, the author does not discuss the idea of non-specific shock causation.) The author goes on to discuss the similarities between the viruses of poliomyelitis and the virus of syringe-transmitted jaundice. He states that in the blood of about 3% or 4% of all healthy

persons there is a virus of the size of 10 to 15 millimicrons, which is capable of producing hepatitis, when transmitted to others. He states that the incubation period of this hepatitis virus is 1 to 6 months. It is transmitted not only by blood and plasma administration, but even by the use of syringes and needles which have been contaminated, regardless of the substance injected. He goes on to state that jaundice has been observed since the administration of arsphenamine and gold, because it was given to ambulatory patients, where a great number of injections was routinely carried out by means of the same instrument. The hepatitis virus by itself is resistant to ether, alcohol and other disinfectants. It resists storage in ice or in the exsiccated state for months, exposure to -20° C. for 4 months, inactivation by exposure to 56° C. for an hour, the effects of 0.5% phenol or 0.2% tricresol solution, ether extraction, and exposure to ultraviolet light (2,537 Angstrom units) for 1/2 hour. Thermoresistance is apparently that of spores and 10 minutes of ebullition is insufficient to destroy it. The comparatively mild methods used to disinfect syringes are unlikely to destroy the virus of hepatitis. The author then proceeds to make the comparison between the virus of hepatitis and the

poliomyelitis virus.

Both viruses seem to evidence the same size. Poliomyelitis virus can be preserved in 50% glycerin at 4° C. for 8 years. It is resistant to freezing, drying, x-rays, sonic vibration and protoplasmic poisons. It remains stable in a wide pH range, and in the presence of ether. Phenol, alcohol, hexylresorcinol have little effect on it. It is apparently a pure nucleoproteid, believed by some to be a non-living protein capable of repeated precipitation without loss of its infectivity. These are the reasons according to Lenard why concepts applicable to bacteria and their destruction do not apply to viruses. The author states that, though the thermoability of the poliomyelitis virus was asserted in 1930 to be some 45 to 50 degrees C., the hepatitis virus was also considered very thermolabile in the past, but is capable of transmission with methods commonly used to sterilize syringes in mass inoculation; that is, short boiling and placement in various aseptic solutions. The author states that epidemics of hepatitis disappeared when the "multiple dose per syringe technique" was abolished and when syringes and needles were sterilized by means of autoclaving or exposed to 160° C. of dry heat for an hour or more. In giving multiple doses per syringe,

when a syringe is filled with fluid and a drop is expressed at the tip of the needle, the drop is immediately sucked back when the needle is removed from the syringe and contaminates the next injection. Individual needles and disposable syringes obviate this situation.

Since diphtheria toxoid adheres tenaciously to glass, the chances of virus present to be transmitted are extremely great.

The possibility exists of contamination of the hypodermic needle with virus from the doctor's hands or the patient's skin, or with a syringe used to give, for example, penicillin to a child with an undiagnosed fever which was, in reality, a non-paralytic attack of poliomyelitis. The syringe might later be employed without adequate sterilization to give vaccine to another child. But it has also then to be assumed, either that a viremia occurs in non-paralytic cases, and that the injection of penicillin or another drug coincides with the viremia, or that the virus is present for a longer or shorter time in subcutaneous tissues. Local tissue damage caused by the needle and/or vaccine might favor the successful implantation of a very small dose of the virus.

Since in poliomyelitis there is no practical

method for the tracing of the virus, and since all portals of entry in humans have been considered, Lenard reasoned that when paralysis followed trauma (for example, vaccination, adenoidectomy, tonsillectomy, or skin wounds), it seemed to the author highly probable that the virus passed up the exposed afferent fibers to the psuedo-unipolar cells in the corresponding sensory cranial nerves or posterior spinal root ganglia and thence to neighboring motor neurones. Paralysis following inoculation of poliomyelitis "vaccine" has always appeared in the same or contralateral limb (Leake 1935) (13).

From the preceding evidence given, Lenard states that one should be justified to advance the hypothesis, that aside from ways which still cannot be explained, poliomyelitis can also be transmitted by means of insufficiently sterilized syringes. Further reasons given by the author are the following. Poliomyelitis has become more common since injections of all kinds have become widespread. Healthy carriers may represent the source of infection, as is the case with hepatitis. A decrease in poliomyelitis cases in consequence to these precautions would prove, according to the author, that we have to consider syringes an important factor in the transmission of poliomyelitis.

Although this author's statements are merely his own ideas, certainly lacking in agreement with other investigators, and certainly cannot be considered as based on any strict evidence, his explanation should certainly be considered in the light of future investtigation.

SUMMARY

In the last few years a number of workers have given attention to the problem of poliomyelitis following various prophylactic immunizations. Only McCloskey, Banks and Beal, Hill and Knowelden, Geffen, Martin, and Anderson and Skaar, and Goerke have compiled and analyzed any series of cases. These men are all in agreement that there is evidence that is highly suggestive, but not conclusive, that there is an association between certain cases of poliomyelitis and injections of various antigens given not earlier than 1 month previously. Hill and Knowelden suggest that a large controlled series of cases is needed in order to reach a definite conclusion as to the exact incidence. The investigators are pretty well in agreement that immunization procedures should be postponed during epidemics of poliomyelitis with the exception of Goerke, who appears to minimize the danger. Good evidence has

been presented as to the relation of the site of paralysis with the site of injection in those cases in which an injection was administered approximately 1 month or less before the onset of poliomyelitis. The severity of paralysis appears to be increased in those cases where there is time interval of less than 1 month from injection to disease onset. MacCallum offered proof of the etiology by isolating poliomyelitis virus from the stools of several of Hill and Knowelden's patients. The various investigators differ in opinion as to the importance of the various antigens employed in the production of poliomyelitis. McCloskey and Geffen placed emphasis on pertussis vaccine, either alone or in combination. Anderson and Skaar, and Hill and Knowelden saw no significant difference in the antigens used. There were very few reported cases following vaccination with small pox in which a different technique is employed. McLeod on the other hand found that with the use of P.T.A.P. antigen that there was no relation to poliomyelitis in over 6,000 cases that he had reviewed. McLeod and Bousfield suggest the use of P.T.A.P. antigen as a solution to this problem. There is general agreement that the technique, locality, or clinic giving the injection does not make a difference in the incidence of the disease. Lenard takes exception, suggesting virus

transmission through the syringe, but does not offer any direct evidence or proof. Experimental work with monkeys by Toomey et al showed that injections of enteric antigens increased the rapidity of onset and the severity of poliomyelitis, but found no relation to staphlococcus, streptococcus, vaccinia, or tubercular infections. Findlay and Howard found that there was increased susceptibility in mice with intravenous injection of typhoid, paratyphoid A and B, diphtheria, and diphtheria-pertussis combined antigens. Although there have been many attempts to explain the causal relationship between the injection and the onset of poliomyelitis, probably the most prevalent theory is that of non-specific shock causation. Since a number of cases have been recorded due to a variety of substances injected, it is thought that trauma due to disruption of the tissue by mechanical means or by the irritating influence of various foreign substances injected, makes the anterior horn cells innervating the area more susceptible to the virus of poliomyelitis. Lenard's conviction that the poliomyelitis virus is inoculated with needles and from contaminated syringes and other equipment finds little support among other authorities.

CONCLUSION

Although studies at the present time do not encompass a large enough number of cases for conclusive evidence, a relatively small number of cases of poliomyelitis probably do occur as the result of previous injections of the various antigens. Only those injections given within the previous month are of any consequence. It is likewise quite probable that paralytic cases have arisen following injections that would have otherwise remained non-paralytic virus infections. Evidence suggests that the severity of paralysis in those cases less than 1 month post-injection is increased, with particular involvement of the injected extremity. The bulk of opinion suggests that the type of antigen injected makes little difference, with the possible exception that P.T.A.P. antigen might be less irritating to tissue and therefore less likely to increase the susceptibility to poliomyelitis. The technique of injection is not likely a factor. Experimental evidence with monkeys and mice tends to substantiate clinical investigation. Injections by some mechanism, as yet unknown, probably produce some local change in the tissues which increases the susceptibility of motor neurones innervating the

same area and thus lends them to virus multiplication. Practical evidence for syringe transmission of the virus is lacking.

Since prophylactic immunizations are in most instances elective procedures, taking our present knowledge into consideration, they may more wisely be postponed during the months of greatest danger or during an epidemic.

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