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Genetic Susceptibility: A Forgotten Aspect of Poliomyelitis

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Abstract

There was evidence of genetic susceptibility to poliomyelitis, but in the mid 1930's that evidence and the idea of genetic susceptibility disappeared from the literature and the collective research psyche. Alternative hypotheses, not amenable to test, were adopted but seldom formulated. Subsequent evidence for genetic susceptibility was ignored. I suggest that the ill-fated vaccine trials in 1935 presented a psychological watershed for researchers. The later vaccines owed their success to unwritten and untested hypotheses: genetic susceptibility might have been an insuperable barrier to testing vaccines in children. Now that eradication is probable, new research suggests that many people may be susceptible to paralysis and that plans must be made for possible reappearance of the disease.

Keywords: Families; Genetic susceptibility; Lymphocytes; Poliomyelitis; Sibs

Introduction

Aycock, a public health officer in New England, assembled much evidence of genetic susceptibility to poliomyelitis. A collector of family trees, he traced polio in twins separated as small children and followed leads in several states. In the 1930's, genetic susceptibility was discussed in standard works, but in the mid 1930's that evidence and the idea of genetic susceptibility disappeared from the literature and the collective research psyche. Alternative hypotheses, not amenable to test, were adopted, but seldom formulated. Subsequent evidence for genetic susceptibility was published in genetics journals and was ignored.

I suggest that the ill-fated vaccine trials in 1935 presented a psychological watershed for researchers. The later vaccines owed their success to unwritten and untested hypotheses: genetic susceptibility would have been a barrier to testing vaccines in children and would have diverted resources and money to little purpose. Other findings have been consistently ignored: the 2% incidence in children and up to 24% in adults: the protection by antibodies: the role of lymphocytes in the disease: no evidence of infection of foetuses.

In epidemics caused by widespread infection with virulent poliovirus, few children contracted paralytic poliomyelitis. The widely quoted figure is 'only about 1% of infections result in illness with neurological involvement' [1]. A statistical theory of infection - small doses immunise while large doses result in paralysis - should lead to wide variations in rates in different circumstances. The seemingly constant rate quoted might suggest host susceptibility, perhaps genetic.

Families

In the 1920's and 1930's W.L. Aycock, a New England medical officer of health published papers on poliomyelitis which described genetic susceptibility [2]. Aycock noted cases of past polio among sibs, parents and relatives when he visited cases in their homes. He found that in Vermont, 52% of 157 cases had cases of paralysis in relatives other than members of the same household [2]: he had previously noted that in rural Vermont, intermarriage was common [3]. Aycock traced cases among twins, double first cousins and in parents and their children. Where both husband and wife had paralysis, they were close blood relatives. He cited many cases in the same family on separate occasions. One family had 6 attacks among 5 children on 3 separate occasions. Many pedigrees showed cases among relatives eg 4 cases among 5 children in 1917, father in 1873, father's cousin in 1871 [3]. In Vermont all 5 cases in 1922 occurred in 3 related families, and in Vermont-New Hampshire all 11 cases in 1923 were related [2]. In Vermont 1910 - 1916, eighty of 180 cases came from only 38 families [4] and Massachusetts was similar [5]. Aycock concluded that the large 'hereditable element in susceptibility to poliomyelitis rests not on the significance of the observations taken singly but on their cumulative frequency' [2]. These and other data [6] gave prima facia evidence of genetic susceptibility.

The 1932 compendium on polio [7] had a section 'The inheritance factor' with 10 references: 'simultaneous occurrence of the disease among siblings,' 'unusual incidence might have been due to a lack of previous exposure to the virus on the part of the older members, and consequent lack of immunity'. For families with a second attack after a long interval, this would 'suggest the possibility of a chronic carrier in the families so affected'. It might have been possible to test this hypothesis. Two examples of coincidence were given: twins with polio after adoption into different families and two brothers with polio in the same year although living apart in California and Texas. T.M. Rivers, the father of virology, in his seminal book of 1928, made no mention of genetic susceptibility [8]. In 1941 however, he gave the following under the heading 'Genetics and natural immunity': Genetic background. Several workers [2] particularly Aycock [3] have commented upon the fact that certain families are more susceptible to poliomyelitis than are others. This is not surprising, because it has been shown experimentally by Webster that mice can be bred in such a manner that some of them will be highly resistant to infectious disease while others are quite susceptible. In the case of human beings, even though observations indicate that genes play a role in susceptibility to

poliomyelitis, no evidence is at hand to associate the findings with one or more specific genes' [9].

There were 3 serious studies of genetic susceptibility. In 1942, Addair and Snyder published their study of cases of polio in one county of West Virginia - all 29 cases over the previous 50 years occurred in 25 related families [10]. In 1951 Herndon and Jennings published their study of polio in dizygotic and monozygotic twins [11]. Much later in 1957 Reedy published the pedigrees of 50 children with polio from Indiana - there was a previous history of polio in 26 families [12]. All three papers were published in genetics journals. The paper by Reedy brought a letter from a well known polio worker, rebutting the comparison with the general polio rate. Gelfand pointed out, correctly, that the sample should be compared with the relatives of control propositi matched for socio-economic factors [13]. The propositi were not themselves used in the calculations, it was the relatives who were compared and it was these, in the two samples which should have been matched. This was probably impossible as the study was of 6 000 relatives of the 50 polio cases, but was not mentioned by Gelfand. These studies were not assimilated into the polio literature yet their origin was impeccable. Snyder was later a president of the American Association for the Advancement of Science, the Genetic Society, the American Society for Human Genetics and others, and Herndon was later president of the American Eugenics Society, the American Society for Human Genetics and others. Clearly they considered the evidence was substantial.

In 1971 John R. Paul published his magnificent History of Poliomyelitis [14]. Paul was an influential and impartial figure in polio research from 1932 to his death: his work was important and fundamental. His book has 42 chapters, most beginning with a portrait and short biography of a key worker. He skillfully dovetailed the work of the scientist with other strands of related work. He devoted 13 pages - 2.65% of the book - to Aycock's autarcesis theory, yet failed to mention papers on genetic susceptibility. Paul at Yale must have known Aycock who was based in Boston and died in 1951. How is it possible that Paul avoided all mention of Aycock's theories and data on genetic susceptibility? I had the privilege of asking Paul this question and he could not explain it. He did however search his files and wrote to me that he had been instrumental in the rejection of Aycock's application for funding of his research on genetic susceptibility.

In 1955 the [Irish] Department of Health wrote: 'Acute anterior poliomyelitis. It has been established that for each paralytic case there are many other unrecognised cases. In general, the family contacts of a case of poliomyelitis are those most heavily infected with virus and in such cases they and their immediate contacts usually excrete large quantities of virus in their stools' [15]. Professor Seddon from Oxford said of the epidemic on Malta 'The only obvious explanation which fits these facts is that the virus has long been prevalent in these islands and that the almost complete immunity of the adolescent and adult population is the result of exposure to small doses of virus sufficient to confer immunity without producing more than an occasional case of definite paralysis' [16]. There was no evidence for these opinions, which were not testable.

Psychological clues

In 1948 there was an outbreak of polio in an isolated Inuit community, a virgin-soil epidemic in which no age group had immunity [17]. Among 53 children under 5 yr there were only 2 cases, but among those over 16 yr, the case-rate was 24% [18]. Sabin suggested that this was 'an isolated highly inbred population of special genetic susceptibility' [19]. Horstmann postulated a 'highly susceptible population where children are apt to have mild or inapparent infections' [20]. Horstmann gave a table of virgin-soil epidemics in Guam, Nauru, Saint Helena, the Eskimos, Nova Scotia and Maguse River showing that in all, the 0-5 yr were spared and that most of the cases, with high attack rates, occurred in the over 10 yr. She commented:

'When such populations, not hitherto exposed, are visited by poliomyelitis virus, one would expect that all age groups would have equal attack rates, if susceptibility to infection is more or less equal. It has been pointed out by Sabin that the populations in which these epidemics have occurred have suffered extraordinary high attack rates, that the populations were not only isolated but inbred, and that genetic factors might have contributed to the unusual susceptibility displayed' [20].

If one explains away an exceptional epidemic by postulating genetic susceptibility, it is surely logical to admit genetic susceptibility as a possibility or necessity in other epidemics? Horstmann and her co-workers found that in families with a clinical case of polio, the ratio of inapparent to apparent infection was 3:1 and 7:1 compared to 100:1 in the general population [21]. They related this to greater exposure and dosage, an attractive but untestable hypothesis. It has since become clear that in many cases, sibs are infected at the same time, not the paralysed sib infecting the other with a greater dose. The authors did not mention genetic susceptibility, but used the phrase 'paralytic poliomyelitis breeds [sic] paralytic poliomyelitis' in their discussion. Is the use of the word 'breeds' a Freudian slip? Sabin investigated intracerebral inoculation of yellow fever virus in two strains of mice and found a simple Mendelian inheritance of susceptibility, which was recessive. He wrote in the discussion: "These data provide a model which indicates how the viruses responsible for encephalitis and poliomyelitis may behave in populations of mixed or highly selected genetic constitution" [22]. Perhaps the most convincing illustration of genetic susceptibility is the response of immunodeficient children to OPV. Whereas these children are subject to repeated infections with other viruses, only 2%, the same as normal children, develop paralytic polio although with a high fatality of about 40% [23].

The epidemic among the Inuit can be explained if the Hardy-Weinberg ratio of 2% p+p+ refers to children, the 24% p+p- to adolescents and adults and 74% p-p- to those without paralysis [4]. These figures apply to many epidemics, showing that children quickly become susceptible, but that the heterozygotes become susceptible much more slowly [24]. Burnet in a lecture in America said that 'there is good reason to believe that paralytic polio and overt tuberculosis depend more on the presence of individual genetic susceptibility to an initial infection than to the virulence or dose of the infecting strain' [25]. No references were given in this paper, but the only source of this belief is likely to be mine in Medical Hypotheses where Burnet was prominently displayed as one of the five Advisory Board [18,25].

Genetic susceptibility

Were all cases of paralysis due to genetic factors or were there only some families in mostly isolated places? To find out would have required a massive investigation of relatives of polios. But then what? There was no test to see who might be susceptible and no idea of what such a test would be. If no protection, such as a vaccine, was available, there was no point in panicking anyone. Rivers became scientific adviser to the National Foundation after de Kruif left following the

vaccine fiasco, and proposed ten research projects to prepare the ground for eventual vaccines. The vaccines of Koproski, Salk and Sabin followed and were (with difficulties) successful in virtually eradicating polio in first world countries. Research on genetic susceptibility would have been a distraction of resources from the work on vaccines. Rivers, Paul, Sabin and the others were aware that one or possibly more genes might be involved, but ignored it, believing (correctly) that immunity by antibodies was more important.

From 1982 to 1987, with the approval and support of the Chief Government Medical Officer, I examined the notes of the Infectious Diseases Hospital in Malta. I found the original notes of 1,072 Maltese cases of poliomyelitis from 1909 to 1964. I traced their parents, grand-parents and great grand-parents, together with baptism matched controls, from the public parish birth and marriage records. I have traced more than 4,500 births and 16,000 marriages. The Vatican dispensations for consanguinities of marriages were noted. On the island of Malta, there were 956 polio cases of which 54% were related as sibs and first and second cousins (Wyatt, in preparation). On the smaller island of Gozo, which had a greater proportion of consanguinous marriages than Malta [27] (paper submitted), 67% of the 116 cases were related as sibs and first and second cousins (Wyatt, in preparation). There were 13 pairs of sibs in which both were paralysed and where the younger was born months or years after the elder was paralysed. This is evidence that there is widespread distribution of genetic susceptibility through a large population of about 300,000 at the time, not just in small isolated communities.

The future

Once poliovirus has reached the motor neurones, there is no treatment. However, paralytic poliomyelitis is possibly unique in that there is a proliferation of lymphocytes which invade the spinal cord. When I showed the pictures of sections from Wickman's monograph [6], to my immunology colleagues, they immediately recognised them as showing a host-versus-graft reaction – in this case an auto-allergic disease [26]. Since the understanding of cellular immunity has blossomed, there are now immuno-suppressive drugs that allow transplantation: they could be used to prevent lymphocyte proliferation in poliomyelitis.

When poliomyelitis is eradicated and there is ten years without a case of paralysis, immunisation will cease. After that time, two per cent of children without immunity will then be at risk should a virus reappear. But ten years after that, there will be cohorts of young people of whom up to 25% will be at risk of paralysis. Polio or similar viruses may escape from unsuspected sources in laboratories, may be deliberately manufactured, may mutate from other enteroviruses or may have lain dormant in the environment. It will be prudent to have stocks of vaccine available for an emergency, but the knowledge that so many people might be susceptible to paralysis demands that far larger stocks of vaccine than presently envisaged will be required. Genetic susceptibility for poliomyelitis has not been considered since the 1930's, but the familial cases and pairs of sibs with polio, provide ample evidence for it and the need for realistic planning for the post-eradication age. Medical research is not only a search for truth, but for solutions to suffering. Interpretation may be distorted by emotional and ethical issues relating to safety and awareness of human suffering.

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Note: I have arranged that all the clinical notes, cards, printouts etc will be deposited with the Melitensis Collection of the University of Malta where they will be available to those with permission from the Medical Ethics Committee.

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