The Puzzle of Pink Disease

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MEDICAL HISTORY

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Pink disease (acrodynia in North America) takes its name from the bright pink colour of the hands and feet, which are very painful. The condition usually affects children around the age of two. The child has photophobia, is intensely miserable and unresponsive, and is unwilling to move about. The condition may last for weeks or months, and in the early part of the twentieth century had a mortality of around 10%.

Pink disease has interested me since 1951 when I investigated the sweat losses in children with this condition in Wilfrid Payne's department at Great Ormond Street, and later, glucose tolerance curves in pink disease at the Kinderspital, Zürich, under Guido Fanconi. After reading Dally's review[1] of the social history of pink disease I was stimulated to look further into the history of this fascinating disease. For reasons which will become clear I discuss pink disease in Continental Europe separately from pink disease in the English-speaking countries.

PINK DISEASE IN CONTINENTAL EUROPE

In 1903 Selter[2], in the industrial city of Solingen in the Rheinland, used the term *Trophodermatoneurose* to describe eight cases which he had seen between 1898 and 1903. In 1923 Emil Feer[3], professor of paediatrics at the Kinderspital in Zürich, published a short report on six cases entitled 'An unrecognized clinical picture'. In the same year[4] he gave a full description of the same six cases which he had seen between 1911 and 1923. Feer was at that time unaware of Selter's work and the English-language publications on pink disease; he called his paper 'A peculiar neurosis of the vegetative nervous system'. He wrote 'This is a clinical picture which has not been previously described, but I hesitate to claim priority'. He attributed the condition to an increased tone of the sympathetic nervous system. In 1925, in a third paper[5], Feer added three more cases. Using the same title as in 1923 he added a subheading, 'Acrodynia, Erythrödem, Pink Disease' and reviewed work published in English, but he still did not mention Selter. In 1926 Selter[6] published another paper; he had now seen a total of thirty-eight cases, starting from 1898; the oldest child was seven and a half. By 1934 Selter[7] had seen fifty-five cases; he expressed surprise at the rarity of cases in Switzerland and did not believe that 'an outstanding clinician such as Feer' could have overlooked such a striking condition. In view of later evidence it is of interest that one of his patients relapsed three years after the original illness when her mother gave her a 'worm cure' after ascaris ova had been found in her stools. By 1942, however, pink disease (Feer's disease) was no longer a rarity in Switzerland; Feer[8] had seen one hundred cases in Zürich between 1920 and 1940.

Though the clinical picture of pink disease was now well established, Jenny[9] in 1930, in Aarau in Switzerland, described a condition which he called mercury exanthema in children who had received calomel (mercurous chloride), with or without the vermifuge santonin, for actual or suspected ascariasis between five and eight days previously. The children developed a dark red eruption on the face, trunk and limbs. Jenny thought this was due to a hypersensitivity to mercury. Though clearly distinct from pink disease, this condition has caused much confusion in English-language publications.

In 1947 Fanconi[10], who had now succeeded Feer at the Kinderspital in Zürich, used the term calomel disease in describing several cases resembling those in Jenny's paper. Fanconi and his colleagues likewise attributed the condition to a hypersensitivity to mercury and remarked on the similarity in the age incidences of calomel disease and pink disease. This led them to consider whether pink disease was also the result of treatment with calomel. They found that most of their pink disease patients had indeed been given calomel but that the period before the development of symptoms was often weeks or months, rather than days as in calomel disease. They suggested that pink disease was a 'delayed neuroallergic response to mercury'.

At the Fifth International Congress of Pediatrics in New York in 1947 Fanconi discussed his ideas with Warkany, from Cincinnati. Warkany had also considered calomel, in the form of teething powders, as a possible cause of pink disease and had found abnormally high concentrations of mercury in the urine in his cases. Returning to Zürich, Fanconi[11] in 1948 confirmed Warkany's findings. Warkany and Hubbard also published their results in 1948[12].

During the 1940s pink disease was still a common condition in the Kinderspital. Between 1946 and 1950 Zellweger and Wehrli[13] had seen fifty-four cases at the hospital. All the Swiss workers agreed that the maximum age incidence was between two and five years, with occasional patients as young as three or four months (breastfed) and as old as thirteen years. Fanconi *et al.*[10] had found that 30% of unaffected children had received a

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calomel 'worm cure' at some time in their lives, and it is clear that Swiss mothers were very much aware of the possibility of ascariasis, though the symptoms for which they gave *Wurmschokolade* and other calomel preparations were usually vague and non-specific. These preparations were not prescribed by doctors, who would probably have used santonin alone or oil of chenopodium, but were bought from chemists' shops. The usual single dose of calomel was between 150 mg and 500 mg[13], but this was often repeated. In no case was the calomel given for symptoms attributed to teething. In his monograph *Dental Problems in Paediatrics* Perabo[14] discussed teething but in his review of work published in German he found no references to the use of calomel or any other form of treatment.

Why was calomel given to Swiss children so frequently? In 1930 Matossi[15] reviewed the prevalence of ascariasis (as shown by the presence of ova in the stools) in eight countries and examined the stools of one thousand children up to the age of fifteen in Zürich and the surrounding area; he found that 34% had ascaris ova in their stool compared with 5.8% in the same city in 1908. The prevalence of ascariasis in Zürich in 1930 was only slightly less than in Armenia in 1926 and Morocco in 1927. Other European countries (Finland, France, Germany and Poland) had a prevalence of less than 10%. Matossi attributed the rise in prevalence in Zürich to an increased consumption of green vegetables which had been inadequately washed; in the 1930s it was the practice to spread untreated human faeces from septic tanks on the fields, and this almost certainly contaminated the vegetables. Swiss mothers therefore had good reason to be concerned about 'worms' in the early part of the twentieth century and this anxiety seems to have persisted into the 1940s and 1950s when (I assume) the risk of ascariasis had decreased. It seems probable, as Dally has suggested in relation to teething powders, that the pharmaceutical industry encouraged mothers, who were now more literate and susceptible to advertising, to buy products such as calomel for the treatment of suspected ascariasis. There is thus a reasonable explanation for the rise in the incidence of pink disease in Switzerland during the first half of the twentieth century. This is a more satisfactory explanation than the possibility that before the end of the nineteenth century (Selter's first cases) pink disease was a common condition but was not recognized. Feer had been working in a well-established children's hospital and would not have missed such an obvious condition.

In 1948 Fanconi and von Muralt[16] publicized the dangers of mercurial preparations in scientific articles and lectures. By 1951 only one child with pink disease was admitted to the Kinderspital compared with a peak of twenty-one cases in 1945.

The published work from the rest of Continental Europe is less complete. Most Western European countries reported cases, but the incidence seems to have been lower than in Switzerland. The first cases in France were reported by Haushalter[17] in 1925, who described nine cases seen from 1911 onwards. The oldest child was aged eight but the remainder were between twenty-one months and four years, a similar age distribution to that in Switzerland. Haushalter could find no previous reports of the condition, did not give it a name but described it as 'A peculiar condition in children consisting of psychic disturbances and neuro-vegetative disorders'. In three of his cases roundworms were passed before the onset of symptoms of pink disease and in one of these santonin and calomel had been given three weeks before the child was seen in the clinic. Haushalter discussed the possibility that ascariasis was responsible for the symptoms but concluded that it was not; he did not consider the treatment as a possible cause. Haushalter's description of the *altérations psychiques* is one of the best in the published work on pink disease.

Papers published in France and Germany[18,19] in the 1950s, after the recognition of the role of mercury, refer to the use of calomel for 'worms', but its use as a remedy for teething seems to have been negligible. Teething seems to have been an obsession of the Anglo-Saxons, who were conversely not worried about ascariasis.

PINK DISEASE IN THE ENGLISH-SPEAKING WORLD

In 1914, Swift[20] in Australia published a description of fourteen cases, the first reported in the English language; he called the condition 'Erythroedema'. Four years later *The Lancet* published an annotation[21] on erythroedema, based on a paper sent to the journal by Swift. This prompted a response from Doak[22] who wrote that he had seen several cases at the Infants' Hospital in Bradford. Thus, Doak was the first to have recognized pink disease in England. In the USA Byfield[23] in 1920 described several cases; Byfield used the term acrodynia for the first time. In England in 1922 Parkes Weber[24] described a case of 'erythroedema' and in an accompanying paper Thursfield and Paterson[25] described a similar case under the title of 'Dermato-polyneuritis'.

From the 1920s onwards numerous reports were published from America, Australia and England, all giving the maximum age incidence between nine months and two years. In 1949 Logan[26], using the Registrar General's returns for England and Wales, reported the deaths from pink disease (and other synonyms) between the years 1923 and 1947. Starting with one death in 1923 there was a steady rise to a peak of eighty cases in 1936, followed by a dip between 1940 and 1946 (possibly due to incomplete reporting during the war years) and a further peak of one hundred and three cases in 1947. 95% of the deaths were under the age of two years. In 1965 Dathan and Harvey[27]

published the results of a national survey of the deaths from pink disease between 1950 and 1962. In 1950 there were fifty-seven deaths, followed by a consistent decrease until in 1962 there were none. They also recorded the number of cases seen in the area of Rotherham and Mexborough, South Yorkshire, between 1948 and 1963. From a peak of twenty cases in 1951 there was a steady fall in the number, with one case in 1963. A similar decrease in cases was reported from other parts of England.

The reason for this decline is clear. In 1954 Dathan[28] reported two fatal cases of pink disease to the coroner in Stoke-on-Trent, who recorded the cause of death as chronic mercurial poisoning. The publicity arising from these cases caused one of the manufacturers of teething powders to withdraw calomel from their product, and medical officers of health removed old stocks from chemists' shops. In Australia in 1957 a number of states enacted legislation banning mercury in teething powders and in the USA the Food and Drug Administration finally achieved an effective ban in 1960.

Thus, the recognition of the role of mercury in the aetiology of pink disease resulted in a rapid fall in the incidence in England and other English-speaking countries which had inherited the custom of giving calomel for teething. Sporadic cases continued to be reported in the 1960s, caused by old stocks of teething powders or contact with metallic mercury.

What was the cause of the apparent rise in the incidence of pink disease in the English-speaking world in the first half of the twentieth century? Again, Dally's conjecture is probably correct. The increased literacy of mothers made them susceptible to advertisements urging them to treat the symptoms of teething with calomel preparations (Figure 1). It was reported at the time of Dathan's[28] cases that one manufacturer was producing thirty million powders annually. Leys[29], in 1949, found that 48% of children between the ages of one and two years had been given teething powders and 4% had been given 'grey powders' (metallic mercury mixed with chalk). The usual dose of calomel in proprietary preparations such as Steedman's and Parsons and Ashton's powders was 65 mg, but children were often given repeated doses.

We might wonder why there was such concern about teething. In the nineteenth century teething was regarded as a very dangerous, even lethal, condition. Charles West[30] in his *Diseases of Infancy and Childhood* (1852) found that teething was registered as the cause of death in London in 4.8% of children dying under the age of one year and in 7.3% of those who died between the ages of one and two years. He wrote, 'the time of teething, too, is in reality one of the more than ordinary perils of the child, though why it should be so is not always rightly understood'. However, in 1885 in his *Mother's Manual of Children's Diseases*[31] he wrote

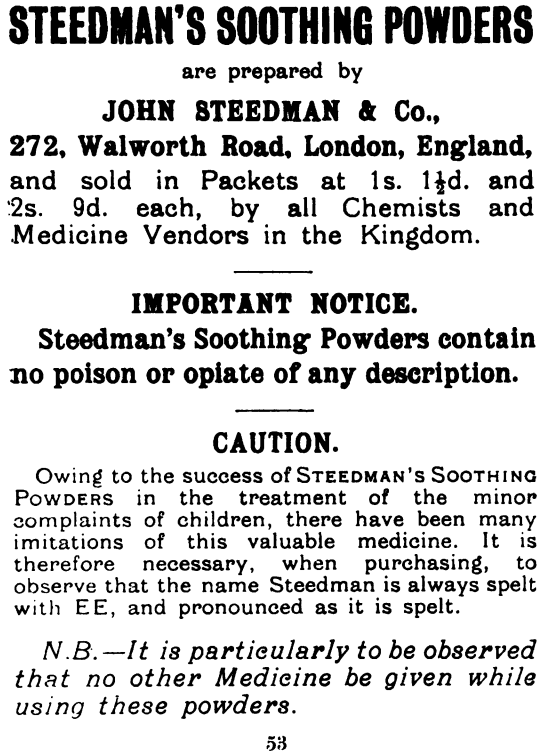

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Figure 1 **Advertisement from *Hints to Mothers on the Treatment of their Children*, published by Steedmans in 1914.** Reproduced by courtesy of the Wellcome Institute Library, London

that only once in 70 000 cases had teething given him cause for anxiety. Frederick Still[32] in *Common Disorders and Diseases of Childhood* (1915) devoted seven pages to teething but did not regard it as a serious condition. Neither author recommended calomel as a treatment. Thus, although paediatricians in the late nineteenth and early twentieth centuries no longer considered teething to be a dangerous condition, the tradition of treating symptoms attributed to teething seems to have persisted at a domestic level into the first half of the twentieth century.

CONCLUSION

It was surely not fortuitous that the rise of pink disease occurred at exactly the same period but for entirely different reasons in Continental Europe and in the English-speaking countries. The common factor seems to have been the pressure of advertising, which has already been discussed.

One further question remains unanswered. Why did only a small proportion of children who were given calomel develop pink disease? It was not a question of dosage—that is, straightforward poisoning—since some children who had received repeated doses remained unaffected. Warkany[33] estimated that 1 in 500 children given calomel (or other mercury-containing preparations) developed pink disease, but this is surely a gross overestimate, in view of the vast number of children who received worm cures and teething powders. There is no convincing proof, despite the occasional

family with two affected children, of any genetic predisposition to react idiosyncratically to mercury by developing pink disease. Cheek's[34,35] experimental work on rats showed that inorganic mercury enhances sympathetic stimulation and raises the concentration of plasma adrenaline, but we know of no additional factors which would act synergistically with mercury on the sympathetic nervous system or its effecters to produce the symptoms of pink disease.

Nearly fifty years elapsed before the connection between pink disease and the ingestion of an apparently harmless mercury salt was recognized. It is curious that while the question was being debated no one appreciated that powerful collateral confirmation of the role of mercury lay in the fact that the same condition was produced in children of two different age groups, treated for two different conditions, with calomel as the only common factor. When Selter and Feer wrote their first papers in 1903 and 1923 pink disease was regarded as uncommon; Selter had seen eight cases between 1898 and 1903 and Feer six cases from 1911 to 1923. By the first quarter of the twentieth century numerous cases had been reported in Continental Europe and the English-speaking countries and it must be concluded that this was because calomel was being given to children on a greater scale than previously. Calomel was not a new remedy and had been used for various conditions long before the advent of pink disease. However, it may be that the condition was such a rarity that it went undiagnosed. Commercial advertising directed at mothers is the only plausible explanation for the increased use of calomel during the first half of the twentieth century.

The almost complete disappearance of pink disease was undoubtedly due to the withdrawal of calomel from worm cures and teething powders. However, this still leaves the question why some children developed pink disease while others who had received a similar amount of calomel remained unaffected. No explanation has ever been advanced for this curious fact and pink disease remains the 'Peculiar neurosis of the vegetative nervous system' which Emil Feer described in 1923.

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