DOES THALIDOMIDE CAUSE SECOND GENERATION BIRTH DEFECTS?

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Abstract
The proposed association between thalidomide and second generation birth defects is an improbable hypotheses which lacks, so far, any credible scientific foundation. However, the media have chosen to give it extensive coverage. So much so that even the hard-headed scientist may start wondering if there is anything in it. However, there is no reason to suppose that people with birth defects caused by exposure to thalidomide during embryonic life have any greater or lesser chance of producing children with birth defects. This appears to be the case in practice. The question could be reworded to, ‘Can thalidomide be responsible for identical, or similar, birth defects in 2 generations of the same family?’

For such a phenomenon to be possible, a mechanism must be proposed and there appear to be only 2 possible candidates. The first is that the defects in the parent, originating during embryonic life, have somehow been transmitted to the next generation. The second is that thalidomide is a mutagen as well as a teratogen.

The first mechanism can be excluded, since Lamarckism has long since been abandoned by scientists. The hypotheses that thalidomide is a mutagen and might be responsible for birth defects in the children of thalidomide-damaged people is without any scientific foundation. Birth defects appear to be no more common amongst the children of thalidomide-affected parents than in the general population. It is important that thalidomide-affected adults are firmly reassured on this point. Most of them have now completed their own families, but they may still worry about their grandchildren.

Therefore, unless and until further supportive evidence is reported by a separate and independent source, the answer to the question, ‘Can thalidomide cause second generation defects?’ is a very definite ‘No.’

Perhaps we should start by reflecting on the fact that the editor of a reputable scientific journal requested a serious review of the proposed association between thalidomide and second generation birth defects, a wildly improbable hypothesis which lacks, so far, any credible scientific foundation. The reason, I suspect, is that although the scientific community has little time for this proposition, the

media have chosen to give it extensive coverage. After a series of claims and allegations in newspaper and magazine articles, and in radio and television programmes, even the hard-headed scientist may start wondering: ‘Could there possibly be anything in it?’ The known relationship between exposure to diethylstilbestrol in utero and ‘second generation’ vaginal carcinoma[1] lends slight credence to the idea.

Let us start by clarifying the question. There is no reason to suppose that people with birth defects caused by exposure to thalidomide during embryonic life have any greater or lesser chance of producing children with birth defects. This appears to be the case in practice. The question we are addressing could be reworded, ‘Can thalidomide be responsible for identical, or similar, birth defects in 2 generations of the same family?’ For such a phenomenon to be possible, a mechanism must be proposed. There appear to be only 2 possible candidates. The first is that the defects in the parent, originating during embryonic life, have somehow been transmitted to the next generation. The second is that thalidomide is a mutagen as well as a teratogen and that at the same time as inducing defects of the limbs or other organs, it was inducing mutations in the embryonic gonads which, a generation later, resulted in the birth of a child who is a phenocopy of the parent. Let us examine the first mechanism.

The theory of evolution by the inheritance of acquired characteristics was first proposed by the French naturalist, Jean-Baptiste Lamarck, in 1809. It is often referred to as ‘Lamarckism’. The underlying idea is simple: living creatures adapt to their environment, these adaptations influence their genetic make-up, and the adaptations are passed on to later generations. Lamarck made the extreme suggestion that if the left eyes of children were put out at birth and such children interbred, eventually a one-eyed race would develop. This experiment was never tried, but some years later Weismann, a professor of zoology, cut the tails off 22 successive generations of a family of mice. Some 1592 mice later, they had produced no tail-less offspring.

Lamarckism has long since been abandoned by scientists. The better we understand genetics, the more impossible Lamarckism becomes. It has been shown experimentally that acquired characteristics can be inherited in bacteria, but it is certainly not possible amongst higher organisms. We can therefore confidently exclude the first theoretically possible mechanism and turn to the possibility that thalidomide might be a human teratogen. Before doing so, however, it is appropriate to review the clinical cases which have been reported as illustrating possible second generation thalidomide defects.

McBride[2] reported on 2 families in which a parent and a child both had a limb defect. The affected parents in each family were accepted for legal purposes as thalidomide damaged. In Family 1, the father was born in 1960 with malformations of both hands and both legs. The defects in the child, a girl, are shown (not in detail) in a photograph, and x-rays of the limbs are reported to show ‘slight shortening and bowing of both tibiae with overgrowth of the fibula, probably resulting in dislocation of the ankle. Ossification was seen in a slightly

enlarged calcaneum, with one tarsal ossification centre and one metatarsal and a triphalangeal digit. Both hands show some ectrodactyly with two triphalangeal digits associated with two metacarpals'.

In Family 2, the father had bilateral malformations of the forearm and hand an left-sided deafness. His daughter also has malformations of both forearms and hands. No further details were given and the published photograph contributed little.

In an invited comment, Read[3] pointed out that if thalidomide had a mutagenic effect distinct from its teratogenic effect, there would be no reason why the limbs should be affected. He adds, 'I think that WG McBride and I agree that the two affected children probably have genetic syndromes'. I commented that the father's defects in Family 1 were quite atypical for thalidomide.4 (Indeed, I had examined him personally in childhood and reported that his defects 'in no way resemble those caused by thalidomide'). I also pointed out that about 350 children had been born to thalidomide-damaged people in the UK without any excess of limb defects.[4]

Tenconi et al.[5] reported on a child with amniotic band sequence limb defects, the illustration showing terminal toe amputations and constriction rings, born to a mother with bilateral upper limb defects attributed to thalidomide. Without going so far as to suggest 'second generation thalidomide defects', the authors raised the possibility that there could be some kind of link between the limb defects in parent and child.

It is important to appreciate that there is no specific test to determine who is and who is not thalidomide damaged. It is a matter of clinical judgement in every case. A clear history of thalidomide ingestion in early pregnancy clearly carries a lot of weight, but (i) the exact time of ingestion is difficult to determine in retrospect, and conversely, (ii) a negative history is encountered in about 50% of cases. As regards the birth defects, the more closely they conform to the recognised patterns, the more confidently they can be attributed to thalidomide.[6] In some cases, the distinction between thalidomide damage and genetic syndromes, such as Holt-Oram syndrome and isolated radial aplasia, may be impossible. By contrast, the defects of the father in McBride's Family 1 could not be attributed to thalidomide by anyone with much practical experience of the problem.

Turning to the possible teratogenicity of thalidomide, Ashby and Tinwell[7] reviewed the relevant literature and concluded that the bulk of the published evidence and their own work provided no evidence that the drug is mutagenic. They call attention to an article by MacKenzie in New Scientist, a popular science journal, which claimed, on the basis of unpublished work, that thalidomide is mutagenic to Salmonella and to mouse bone marrow. Ashby and Tinwell repeated this work, with negative (and unpublished) results.

Turning to animal experimental work, 2 papers have been published by Huang and McBride.[8,9]The first claimed to show that thalidomide could induce alteration in the secondary structure of rat embryonic DNA in vivo. The second claimed to show binding of the glutarimide part of the thalidomide molecule to rat embryonic DNA in vivo. This was severely criticised by Neubert[10]who concluded that 'the paper contains so many inadequacies that it is impossible to draw any conclusions'.

In summary, the hypothesis that thalidomide might be responsible for birth defects in the children of thalidomide-damaged people is without any scientific foundation. Birth defects appear to be no more common amongst the children of thalidomide-affected parents that in the general population. It is important that thalidomide-affected adults are firmly reassured on this point. Most of them have now completed their own families, but they may still worry about their grandchildren. Doubtless there will be further examples of 'thalidomide-affected people' having similarly affected children, but the logical conclusion must be that they are sharing a dominant gene. The clinical reports and experimental work which underlie claims of second generation defects originate effectively from a single research worker.[2,8,9]

Unless and until further supportive evidence is reported by a separate and independent source, the answer to the question, 'Can thalidomide cause second generation defects?' is a very definite 'No.'

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