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Thalidomide: was the tragedy preventable?

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Thalidomide, a sedative drug first synthesised in 1953, created one of the most dramatic disasters in the history of medicine. From 1958 the drug had been widely praised, advertised, and prescribed on the grounds that it was unusually safe—largely because it was almost impossible to commit suicide with it. Thalidomide was exceptionally effective in, among other conditions, the treatment of morning sickness in pregnancy. Then, in 1961–62, it was found to cause terrible malformations in unborn children. According to popular memory, both medical and lay, there had been no reason to doubt its safety. The tragedy was unlike anything that had gone before. It was, and still is, widely believed to have been unavoidable. Here, I shall examine this belief.

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Thomas Inglefield (1769), born without arms or legs
Kirby's Wonderful Musuem, 1804

Thalidomide was soon found to cause peripheral neuritis,[1] but little notice was taken of this discovery. Yet there was already evidence of its teratogenic potential, and extensive and increasing published work showed that fetuses could be deformed by external influences, including poisoning and therapeutic drugs,[2] infection,[3] X-rays,[4] and malnutrition.[5] One long pre-thalidomide review of evidence of the effects of drugs on the fetus contained 354 references, most of them about damage to the fetus and many of them published in influential and widely read journals.[2] Some of this evidence, particularly in relation to syphilis and rubella, had been accepted and acted upon by the medical profession (for example, in Wassermann tests for pregnant women and rubella parties for prepubertal girls), but most of it had been ignored. Pregnant women still had radiography; oestrogen was still given to pregnant women despite its known dangers; and drugs were still prescribed freely during pregnancy without thought for the fetus. Why had all this evidence been ignored?

Placenta as a perfect barrier

In 1941, the Australian obstetrician N M Gregg had shown that maternal rubella could damage a growing fetus.[3] Unlike most of the other evidence, this information became part of the medical profession's general belief or pool of knowledge, perhaps because it came from maternity units rather than laboratories, could be understood by everyone, and was soon reinforced by evidence from many parts of the world, which made it difficult to ignore. However, caution did not go further. For example, in 1943 an attempt to induce cretinism in animals failed but led to fetal skeletal deformities that were later shown to be due to riboflavin deficiency (eg, ref 6). This outcome was taken as being extreme and irrelevant rather than as a warning.

Alcohol is another example of the mass denial by the medical profession in the mid-20th century about the permeability of the placenta. The effects of alcohol on the fetus had been known throughout civilisation and had been described in the 19th century and earlier. Studies had shown the high incidence of fetal and perinatal death, prematurity, and low birthweight in association with maternal alcoholism.[7] In 1834, there had even been a House of Commons Select Committee which reported that the children of alcoholic mothers presented a starved, shrivelled, and imperfect appearance.[8] Yet by the mid-20th century this evidence seems to have been largely forgotten. It was no longer part of current medical thinking and the fetal alcohol syndrome was yet to be discovered. Medical students were taught that the human placenta gave perfect protection to the fetus and was impervious to toxic substances except in such large doses that they killed the mother (personal recollection). Antenatal care did not include advice about alcohol, drugs, or other chemicals. Routine testing of new drugs on pregnant animals was perfunctory or non-existent.

Those who knew the truth were teratologists, but they worked in laboratories on animals, published in specialist journals, seem not to have concerned themselves with human beings, and did not campaign or crusade. Editors of general medical journals showed little interest in teratological studies. The lack of comment and information easily available to most doctors was not conducive to new ways of thinking.

In December, 1961, the Australian obstetrician William McBride published a letter in *The Lancet* reporting an increase in the number of cases of congenital abnormalities associated with use of thalidomide.[9] However, he later claimed that he had submitted an article to *The Lancet* in June of that year, expressing his fears about the effects of thalidomide on the fetus, and giving supporting evidence. *The Lancet*, he told an investigative team of journalists from the *Sunday Times*, rejected it, and the assistant editor told him that the theory was interesting but pressure to publish important papers was such that there was no space to print it.[10] As proof, McBride claimed that he possessed a

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letter from *The Lancet,* but Ian Munro, the Editor, could find no evidence of the existence of such a letter; he was unable to elicit the letter either from McBride or from the *Sunday Times* team who used it in argument.[11] This confusion is typical of the many contradictions about thalidomide that circulated at the time.

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Margaret Vergh Gryffyth (1528–c 1588)
Welsh woman who exhibited herself with her 10 cm horn. Kirby's Wonderful Musuem, 1813

Denkstil

Why did the medical profession ignore the extensive existing evidence that teratogenic substances could cross the placenta? It might be thought that the drug companies were working to keep teratological information away from the medical public, but this does not seem to be so. There is evidence that, after the tragedy, Distillers, the manufacturer of thalidomide, along with the attorney-general, "were gagging the media",[12] as one would expect, but before the tragedy, drug companies had no reason to develop tests on pregnant animals because the medical profession thought them unnecessary. It is useful to look at what happened as part of a mind-set or style of thought (*Denkstil*[13])—a shared view of reality that controls, organises, and limits perception and understanding. We all tend to ignore what does not fit our theories and beliefs. What does not fit current belief tends to be downgraded or ignored until circumstances change or something happens that makes it impossible to continue to ignore it. In the mid-20th century the placenta was deemed to be impermeable to harmful substances and, as a result of this belief, counterevidence was ignored until something happened that was so startling, anomalous, and *public* that it could no longer be ignored. Only then was the belief challenged and changed. Damage by thalidomide was not compatible with a belief in an impermeable placenta. There *had* to be a substantial reappraisal.

Ignoring past beliefs

To some extent this rearrangement involved a return to past theories and beliefs, which raises the question of why they had ever been abandoned. The idea that maternal impressions can affect an unborn child for better or worse is old.[14] For instance, it was an ancient Jewish custom to put a beautiful child at the door of public baths to help women to "have children as fine as he".[15] In ancient Carthage, it is said that alcohol was forbidden to a bridal couple in case a conceptus was damaged by it.[16] Interest in "monsters" goes back at least to ancient Egypt.[17] For many centuries they were seen as warnings or divine omens and were often confused with mythological beings. Later they become objects of interest, to be collected and described. Most pathological museums still possess a collection of stillborn monsters, preserved in jars.

In the 18th century there was much interest in maternal impressions.[13] In the mid-19th century it was believed in the English-speaking world that heredity was not fixed but could be altered by external circumstances at any point between conception and weaning.[18] Physicians warned against sexual intercourse under the influence of drugs or alcohol because they believed that these substances could affect the constitution of a child. In 1870, the medical profession was criticised for its "prevalent belief" in the ability of maternal impressions to cause any degree of malformation.[18]

In the late 19th century this kind of belief was falling into disrepute. The idea of maternal impressions was linked with magic and "unscientific" thinking. Such a connection may be important in the way the idea was subsequently rejected and ignored. As medicine became more "scientific", magic became despised. The placenta was steeped in myth and mystery. Apart from a few people who worked with it "scientifically", the placenta seems to have remained in a kind of quasi-magical limbo and vulnerable to the social fantasies of the time.

Idealisation of the womb

Belief in the placenta as a perfect barrier against damaging influences in the environment was reinforced by the Victorian tendency to put "woman" on a pedestal, which led to idealisation of the womb as well as of the woman. Women's reproductive organs were regarded as special and also as the source of all women's symptoms and ills not visibly due to something else.[19] Only a few practising doctors disagreed. One of these practitioners was J W Ballantyne, a teratologist and lecturer in antenatal pathology in Edinburgh, who initiated many advances in antenatal care. In 1904 he listed "varieties of foetal morbid states", including transmitted diseases and toxicological states (eg, lead-poisoning, alcoholism, morphine-poisoning).[20] But few doctors took notice. Typically, as late as 1937, F J Browne, in his popular textbook of many editions, discussed the diagnosis of fetal abnormalities but not their causes.[21] In 1941, when the damaging effects of rubella were demonstrated, the peculiarity of the infection was emphasised but it was not taken as a general warning about the vulnerability of the fetus. Today one can still find examples of residual idealisation of the womb. For example, in 1990 an article in the *Sunday Times* on fetal surgery declared: "The womb is the perfect operating theatre and an ideal convalescent home".[22]

The expendable fetus

Another possible reason why little notice was taken of environmental dangers in pregnancy was that fetuses, stillborn babies, and newborn babies, were often regarded as expendable, or at least as not very important. Few doctors were interested in them for their own sakes.[23] They created danger for their mothers at a time when maternal mortality was high. 19th century accounts of obstetric cases seldom mention whether the infant lived, clearly regarding survival as trivial. All efforts were directed towards getting the baby out to save the mother. A deformed fetus was likely to arouse even less interest unless it had rare abnormalities, when it might be described in a medical or scientific journal. Victorian obstetricians who wrote articles or published papers showed no desire to save infants who were badly

deformed; and they aroused no criticism.[23] By the 1930s, maternal mortality was falling, birth control was spreading, families were smaller, and there was greater interest in infants and their survival. Also, decline in mortality from infection and improved antenatal care meant that congenital defects became more prominent as a cause of morbidity and mortality. In 1954, William Gilliatt wrote:[24] "In every series of neonatal deaths congenital malformations appear as an important cause. As the neonatal death rate is reduced, so deaths from malformations, which are unpreventable and often intractable, will become a greater proportion of the whole rate . . . The cause of malformations is unknown . . .". The text goes no further than to mention heredity, diabetes, and rubella as causing malformation and maternal age as a cause of "mongolism". The 1958 British Perinatal Mortality Survey brought fetuses into prominence and provided a background and a context for future fetal studies.[25]

The rise of teratology

Teratology, the study of congenital malformations, was an increasingly thriving science, particularly in France. It was practised mostly on lower animals since it was not considered relevant to mammals until the 1930s. In 1744, Trembley produced multiheaded monstrous hydras by cutting through the upper part of the organism.[2] In 1749, Watson was the first to study the permeability of the placenta (to smallpox),[26] which is probably the first mention of the idea that fetal disease could occur in utero. During the early 19th century, emphasis shifted from the role of monsters in generation and development to the study of species.[27] Étienne Geoffroy St Hilaire (1772–1844) attributed embryonic aberrations to physicochemical changes in the fetal environment, believing that new species arose in this way. His son continued the work and coined the word "teratology".[27] Teratological work continued throughout the 19th century, mostly on non-mammalian species, and published results were descriptive rather than analytical. Similarly, the medical published work of the period contains many descriptions of different and unusual fetal malformations but little attempt to analyse the phenomenon. Teratological work on mammalian fetuses did not begin seriously until the 1930s. It may have been delayed by the belief in the impermeability of the human placenta. Research was also hampered by the enormous variability between animal species: what is highly teratogenic to one species may have little or no effect on another, which complicated or invalidated many tests. Moreover, teratologists had a different and non-medical attitude in that they were trying to *produce* fetal malformations, and their publications frequently reveal their understandable enthusiasm for highly teratogenic substances. For instance (the italics are mine), one referred to thalidomide as "*an almost perfect example* . . .".[28] Another wrote: "*We succeeded in inducing abnormalities* . . ."[29] and "*we failed to produce endemic cretinism but found something much better* in the skeletal malformations induced by riboflavin deficiency".[30] Clearly, teratologists were working in a different mind-set. Moreover, they published their work in journals with a limited, specialist readership, and the articles were not reported in general medical journals, as tends to happen to evidence that does not fit current beliefs.

Conclusion

An analysis of the historical context of the thalidomide disaster suggests that there was more to the story than the "out of the blue" theory suggests. An analysis in terms of current medical beliefs can reveal some of the possible reasons why this occurred and why it has been misinterpreted ever since. In particular, there seems to have been an attitude of mind that idealised the womb and placenta and ignored most of the extensive existing evidence of fetal damage through environmental influences.

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