

# Bendectin

---

## **How a Commonly Used Drug Caused Birth Defects - Part Two**

by Betty Mekdeci Executive Director Birth Defect Research for Children

The other active ingredient in Bendectin is Decapryn (doxylamine succinate), an antihistamine which belongs to a group called ethanolamines, the most potent and highly sedative of the antihistamines. In fact, doxylamine succinate is marketed as an over-the-counter sleeping aid called Unisom. (This product carries a warning. "Do not take if pregnant".) It is also an ingredient of numerous over-the-counter products for colds and coughs including Nyquil and Vick's Formula 44 Cough Syrup.

Doxylamine is structurally similar to another ethanolamine, Benadryl. Both of these antihistamines affect the central nervous system and have anticholinergic properties like Bentyl. There have been reports of patients having facial dyskinesia, a nervous disorder causing involuntary repetitive movements of the face and mouth, after short term use of doxylamine and Benadryl. 29'30'31 In light of new research on the importance of the nervous system to fetal development, this facial dyskinesia may be an early warning signal of potential teratogenic problems much as peripheral neuritis was in thalidomide patients

In fact, Benadryl was associated with an increase in oral clefts in an epidemiological study published in The Lancet in 1974.<sup>32</sup> Comparable malformations were also noted in the offspring of test animals exposed to Benadryl in a 1977 study published in the Archives of Pharmacology and Toxicology.<sup>33</sup>

An unpublished survey of 50,282 pregnancies in the Collaborative Perinatal Project showed a statistically significant increase in diaphragmatic defects in infants whose mothers were exposed to the ethanolamines, doxylamine and diphenhydramine (Benadryl) during the first three months of pregnancy. 34

Research dating back to 1971 (Kahison and Rosengren) has shown that elevated levels of histamine can be detected in tissue undergoing rapid growth or repair such as healing wounds or developing embryonic tissue. Inhibition of histamine arrests fetal development in test animals.

Since ethanolamine antihistamines have both histamine and cholinergic-blocking action, 35 their use during pregnancy has the potential to disrupt the levels of these chemicals that are necessary for normal growth at different stages of fetal development.

In addition to Bentyl and Decapryn, ingredients that interact and have the potential for serious adverse effects together and individually, Bendectin also contained pyridoxine, vitamin B-6. Pyridoxine was thought to be beneficial in alleviating the symptoms of morning sickness although the evidence on this is scanty.

Bendectin was promoted in nineteen countries as a safe and effective remedy for morning sickness. Product sales soared. By the late '70's, Bendectin ranked as the 91st most prescribed drug in the United States. It has been estimated that over 33 million women worldwide received Bendectin.

Despite the drug's enormous popularity, questions about Bendectin's safety continued to trickle in to the company and drug regulatory agencies around the world. The company's standard reply to physicians reporting cases of malformation was to assure them that no other cases had been reported, or that such reports were extremely rare. The doctors would also receive copies of the Bunde and Bowles Study to reassure them about Bendectin's safety.

Some FDA medical officers were not so convinced. After reviewing the safety data on Bendectin, they asked the company to undertake additional animal teratology studies. Merrell responded by producing tests of the individual ingredients, but no new tests of the combination product.

In 1969, Dr Donald Patterson stirred up a new flurry of concern about Bendectin's safety. He wrote a letter to the Canadian Medical Journal reporting several cases of limb defects in children whose mothers had taken Bendectin.<sup>36</sup> That same year the German government held hearings on the safety of Bendectin, but the company was able to convince the authorities that there was no problem.<sup>37</sup>

The reports of congenital malformation kept coming in. Over half the cases involved absent or partially missing limbs. Merrell dismissed this unusual skewing toward limb defects as an increased tendency to report any limb malformation after the thalidomide episode.

Then in 1972, the company got a shock. Dr William McBride, who had first linked thalidomide to limb defects, reported to the authorities that he thought Bendectin was responsible for the births of three limbless babies in Sydney. This confidential report somehow leaked to the press and made headlines in Australia. <sup>38</sup><sup>39</sup><sup>40</sup> Soon Merrell was rushing to put out brushfires of suspicion about Bendectin's safety in other parts of the world as well.

On February 5, 1972, a woman in Milan gave birth to a daughter with a phocomelic arm. This prominent Italian family arranged for a well-known research institute to test all the medicine the mother had been given during early pregnancy. As a result of these tests, the family's attorney wrote to Merrell.

"The test of your product has given such an alarming result ... to determine the necessity of an immediate intervention...the existence of this danger being clearly certified, it is hardly believable that this product can be commercialized as a specified treatment for pregnancy nausea..." <sup>41</sup>

The company responded immediately that their scientists would meet with the researchers from the Italian institute at any time, any place in the world. The outcome of that meeting has never been made public. The government of Japan requested additional studies with Bendectin. Instead of complying with the request, the company voluntarily withdrew the product from the Japanese market in 1974. <sup>42</sup>

Since 1976, Bendectin has been the subject of continued controversy and litigation in the United States and abroad. After the first large award to the plaintiff in a 1983 Bendectin case, Merrell announced that they would no longer manufacture Bendectin. They cited the increasing costs of litigation as the motivating factor in the unprecedented move.

What are the facts? Does Bendectin cause birth defects or are the large jury awards in some Bendectin cases just the result of kind-hearted juries who feel sorry for deformed children. The proof lies in the evidence presented to these juries. Four different types of data are required to prove that a drug is teratogenic. These include:

1. Animal studies
2. In-vitro or cell culture studies
3. Human data, including epidemiological studies
4. Structural activity relationship
5. The scientific community considers information derived from all four of these methods when determining whether a drug causes birth defects in the developing embryo and fetus.

## **Animal studies**

All drugs on the market today were first tested for safety in animals. Different animals have different levels of sensitivity to different drugs. For instance, humans are 700 times more sensitive to the teratogenic effects of thalidomide than hamsters. Since a researcher cannot predict beforehand which test animal may be sensitive to a particular drug, several species of animals must be tested at varying dose levels.

Animal tests are used to predict the possibility of an adverse reaction in even one in 10,000 or one in 100,000 people exposed to a drug. It is not economically feasible to test a drug in 10,000 rats or rabbits, so researchers test animals at much higher doses of a drug than humans would ordinarily be exposed to. In this way, they have a better chance of predicting whether a particular drug may cause cancer, birth defects or other toxic effects in even a small percentage of human exposures.<sup>43</sup>

All drugs known to cause birth defects in humans have produced birth defects in at least one species of rodent. In addition to rats and rabbits, Bendectin and/or its ingredients has been tested in chickens, mice and four kinds of monkeys. Independent studies were performed at the National Center for Toxicological Research. As result of these studies, the National Toxicological Program now lists Bendectin as a developmental toxicant. <sup>44</sup>

## **Bendectin Animal Teratology Studies**

- 1963 Staples Merrell 3-part Bendectin rabbits Clubbed limbs, sternal defects. Kinked tail, abnormal head
- 1966 Merrell doxylamine rabbits Malformations in 40% of litters at highest dose
- 1966 Merrell dicyclomine rabbits 67% resorption at highest dose
- 1975 Merrell dox + B-6 rats Cleft palate, hematoma, dilated kidney, pelvis, agnathia

- 1981 McBride dicyclomine chicks Shortened limbs, exencephaly, gastroschisis
- 1981 McClure doxylamine rhesus monkeys Growth retardation
- 1982 Roll/Matthiaschk doxylamine rats Wavy ribs, diaphragmatic hernia
- 1984 McBride doxylamine rabbits Shortened limbs, microphthalmia, urogenital defects
- 1984 NCTR doxylamine rats Delayed bone formation-skeleton especially, metacarpals
- 1985 Hendricks, doxylamine macaque monkeys, rhesus monkeys, baboon, Ventricular septal heart defects, one baboon with multiple heart defects and limb reduction.
- 1985 McBride-doxylamine marmosets, Bowel and limb malformation

### **In-vitro or cell culture studies**

Dr John Hassell from the National Institute of Health studied the effect of doxylamine on chondrogenesis in mouse limb bud cells. Chondrogenesis is the ability of limb bud cells to differentiate and form cartilage, the precursor of bone. When doxylamine was applied directly to these cells, it interfered with the proper growth and differentiation of the mouse limb bud. 45

### **Human data, including epidemiological studies and individual case reports**

Epidemiology is the field of medicine which tries to determine the cause(s) of birth defects, cancer and other diseases by recording and comparing incidence rates and possible etiological factors in different human populations. Mathematical formulas have been devised that turn these comparisons into an estimated risk of certain etiological factors being associated with specific adverse outcomes.

In recent years, epidemiological studies have been considered one of the most important tools for assessing a drug's potential to cause birth defects. This reliance on epidemiology is questionable since scientific experts have acknowledged that even thalidomide's association with birth defects could not be clearly demonstrated using these same techniques.

Three factors must be taken into account in evaluating the reliability of an epidemiology study. One: Who paid for the study? Industry financed studies tend to agree with the corporate view of the product's safety. Two: How were the raw data collected? A study is no better than the raw data on which it is based. If there are discrepancies in any of the data, the outcome of the entire study may be subject to reinterpretation.

Three: What was the purpose of the study? A study should be specifically designed to answer a particular question. Reanalysis of old data from studies designed to answer different questions may not yield valid results.

Despite the difficulties of the epidemiological approach, Bendectin has been associated with malformations in both government and company sponsored studies. In some cases, these associations became apparent when experts reanalyzed the original raw data from the studies.

### **Bendectin Epidemiological Studies**

Bunde/Bowes: Reanalysis of raw data indicates up to 80% risk of BDN exposed baby having birth defect

CDC: Statistically significant association with amniotic band limb defects and encephalocele.

Heinonen: Data consistent for association of BDN with musculoskeletal defects.

Jick: Data consistent with modest teratogenic effect on limbs, BDN exposure increases risk of limb defect 120%

Michaelis: 36% increased risk of malformations in BDN exposed babies

Mitchell: 50% increased risk of limb defects in BDN exposed babies

Rothman: Statistically significant association with heart defects

Golding: Statistically significant association with oral clefts

Eskanaiz/Bracken: Statistically significant association with pyloric stenosis

Smithells: 36% increased risk of malformation in BDN exposed babies

Bass: 11-fold increase diaphragmatic hernia in BDN exposed babies

Maynard: Increase in diaphragmatic hernia in BDN exposed babies in analysis of 5 cohort studies

Most human teratogens were not discovered through animal studies or epidemiology. The disastrous effects of the rubella virus, thalidomide, anti-convulsive medications and excessive alcohol consumption during pregnancy were first reported by alert practitioners. Physicians noticed a pattern of malformations occurring in their patients and searched for a common etiological factor.

Since the early 1960's the pattern of birth defects reported for Bendectin has been heavily skewed toward limb reduction defects, part or all of a limb or limbs missing. A review of case reports of malformations in the Bendectin files at Merrell and the FDA reveal an extraordinarily high percentage (one-half or more) of the total defects reported are limb defects. A 1972 interdepartment memorandum from Merrell's Research Director, Dr Carl Bunde comments that in a review of Bendectin reports... "the type of abnormality reported is weighted very heavily to skeletal types involving the extremities." 46

Dr. Alan Kimball Done, former Special Assistant to the Director of the Bureau of Drugs at the FDA, testified in court that "one cannot find the same kind of reporting anywhere in the literature or anywhere else of the kinds of incidence we are talking about... with any drug other than Bendectin."

Dr. William McBride reported that he was aware of 77 cases of children born with limb reduction deformities or malformations of the external ear whose mothers had proof they had taken Bendectin during the first 7 weeks of pregnancy, the critical time of formation for these structures.<sup>47</sup>

In 1983, the Association of Birth Defect Children reviewed some 500 cases of Bendectin associated birth defects reported to the organization. One-half of these reports were limb defects.

A teratogen which can affect the limbs frequently causes defective development of the heart as well since these structures are formed at almost the same time. Thalidomide caused 14 different kinds of heart defects in addition to phocomelic limbs. Bendectin reports also reveal an excess of heart defects. In a review of over 3,000 cases of pediatric cardiac defects at Boston Children's Hospital, as many as 1,000 cases listed a prenatal exposure to Bendectin. The probability that Bendectin causes heart defects is increased by the results of monkey studies showing an excess of ventricular septal defects in Bendectin exposed offspring and birth defects monitoring data which report that the incidence of ventricular septal defects nearly tripled from the mid 1970's to 1981, years when sales of Bendectin were at their highest.

Although most teratogens are identified by a particular pattern of birth defects, they may also produce malformations of almost any part of the body depending on the time of exposure and the genetic susceptibility of the fetus. According to a report in the British Medical Journal in 1973, thalidomide defects could be single or multiple involving almost any system in the body; limb defects; defects of the eyes and ears; malformations of internal organs including the heart, kidneys and gastrointestinal tract.

45

It may be years before the full spectrum of Bendectin related birth defects is known. To date, studies and clusters of reports show an association between Bendectin and the following malformations: limb defects, heart malformations, defects of the eyes and ears, gastrointestinal malformations, urogenital defects, oral clefts and certain kinds of central nervous system defects.

### **Structural activity relationship**

In the years since thalidomide, researchers have tried to determine how the drug caused such tragic deformities. In 1971, Dr William McBride was awarded a \$40,000 international prize for his discovery that thalidomide caused birth defects. He used the award money to set up Foundation 41, a research institution that studies the first 40 weeks of life in the womb and the first seven days outside the womb. Much of the research at Foundation 41 focused on investigating how thalidomide produced birth defects.

McBride and his team hypothesized that thalidomide damaged embryonic nerve cells that are essential for the proper development of the limbs and other organs. This theory has had support in the medical literature since the turn of the century. In 1900, Schlesinger, a German researcher, suggested that a combination of a limb and muscle defects might be caused by an injury to the nerve supply rather than to the tissues themselves. 49

In 1966, Gordon suggested a neural basis for thalidomide malformations. He postulated that thalidomide had a toxic effect on initial nerve impulses to muscles in the organogenetic phase of development. He went on to correlate birth defects in thalidomide babies with the peripheral nerve damage seen in adults who took prolonged doses of the drug. 50

McBride's work on nerve injury preceding limb malformations included research on Bendectin. Both active ingredients of Bendectin, dicyclomine and doxylamine, have anticholinergic effects which are potentiated when the drugs are combined. Anti-cholinergic or atropinic drugs block the passage of nerve impulses through the parasympathetic nerves. In overdose, these drugs can cause the same effect as curare, paralysis of muscles and the respiratory tract.

The effects of anticholinergics on morphogenesis have been studied since the early 1900's. New data suggest that cholinergic nerves may be involved in the phenomena of embryonic growth and differentiation particularly of the muscles and limbs. Atropinic drugs have been shown to block embryonic development in echinoderms, amphibia, chicks and ducks.<sup>51</sup> McBride also performed more experiments with atropine, hyoscine and dicyclomine in chicks and rabbits which resulted in abnormal fetal development.<sup>52</sup>

One ingredient of Bendectin was shown to cause nerve injury in premarketing tests. In 1951, Crescitelli and Geissman applied the antihistamine doxylamine succinate to frog nerve fibers. The drug prevented the transmission of nervous impulses and caused irreparable damage to the nerve fiber.<sup>53</sup> Many researchers believe embryonic cells are highly vulnerable to the effects of drugs that can block nerve impulse transmission.

## **Summary**

The proof that Bendectin causes birth defects is based on a composite of evidence taken from animal studies, cell culture studies, human epidemiology, case reports and studies of the drug's structure and activities in the body. However, one important question is left unanswered even by these methods. If Bendectin has the potential to cause birth defects, why doesn't it cause malformations in every baby whose mother took the drug? The Merrell Dow Company reminds the public in every press release that over 33 million women worldwide have taken the drug.

Thalidomide, the most potent human teratogen known, caused birth defects in approximately 20% of the babies exposed to the drug in early pregnancy. In animal tests with thalidomide, some of the offspring would have typical limb malformations while their litter mates would be normal. Although scientists do not have all the answers yet, the most current research suggests the following three factors may determine this difference in susceptibility to teratogens:

The fetus exposed to the drug must be susceptible to its harmful effects. Because of differences in genetic makeup, one baby may be harmed by a drug while another shows no ill effects. It has been shown in animal tests that one genetic strain of rodent will be far more susceptible to the teratogenic effects of the drug than another.<sup>54</sup>

The drug must be taken at the critical time of fetal development. The baby's organs and skeleton develop during the first 60 days of pregnancy. This is the time when a drug exposure can cause major structural defects. Although the most serious birth defects occur during the early part of fetal development, toxic exposures can have adverse effects on such things as the child's neurological development throughout the entire nine months of pregnancy.

Some drugs may exert harmful effects only after they have reached the fetus in sufficient doses. The amount of a drug that can cause a birth defect may vary. The metabolism of a drug may be affected by a woman's height, weight, general health and nutritional status.

At the present time, scientists do not have the technology to determine which babies are potentially at risk from any drug or chemical. Many drugs and chemicals have structural and pharmacological activity similar to the ingredients of Bendectin and theoretically would have the same potential to injure the developing fetus. The safest course for a pregnant woman is to avoid all unnecessary exposure to drugs and chemicals, including smoking and alcohol, during the entire nine months of pregnancy.

## FOOTNOTES

29. Favis, Gregory R., "Facial Dyskinesia Related to Antihistamine", *New England Journal of Medicine*, 294:730, 1976.
30. Brait, K.A. Zagerman, A.J., "Dyskinesias After Antihistamine Use", *New England Journal of Medicine*, 296:111, 1977.
31. Lavenstein, B.L., Cantor F.K., "Acute Dystonia: An Unusual Reaction to Diphenhydramine", *JAMA* 236:291, 1976
32. Saxen, Irma, "Cleft Palate and Maternal Diphenhydramine Intake", *Lancet*, March 9, 1974, pp. 407-8.
33. Alia, F.M., Herranz, J.M., "Study on the Teratogenicity of Benadryl in Rats", *Arch de Farmacol y Toxicol* 1977. 111:2. 157.
34. Rosa F., "Antihistamine Exposure in 30 Diaphragmatic Defects Among 50, 282 Outcomes in the Collaborative Perinatal Project", FDA memo 3/15/82
35. Patterson, D.C., Letter to the Editor, *C Med Assn. Journal*, 101:175-61969.
36. "Sickness Pill May Cause Deformity", *Perth Daily News*, April 19, 1972.
37. Westhoff, Justin. Transcript of testimony during proceeding reviewing Bendectin in West Germany. 10/7/80.
38. "Sickness Pill May Cause Deformity", *Perth Daily News*, April 19, 1972.
39. "Health Dept. Won't Talk On Limbless Baby Drug", *Canberra News*, April 19, 1972.
40. "Another Birth Drug Suspect", *Sydney Morning Herald*, April 19, 1972.
41. Auletta, A.M., letter to Richardson-Merrell, Inc., February 8, 1973.
42. Richardson-Merrell's answer to interrogatory #101, *Mekdeci vs. Richardson-Merrell*, 1977.
43. Epstein, S.S., transcript of presentation on risk assessment for environmental hazards, Case Western Reserve U. Med. School, p. 218
44. Schwetz, B.A., "Chemicals identified as Reproductive and Developmental Toxicants", memo to Director NIEHS, Dept. HHS, February 19, 1987, p.2..
45. Hassell, J., Horigan E., "Chondrogenesis: A Model Developmental System for Measuring Teratogenic Potential of Compounds", Laboratory of Developmental Biology and Anomalies, National Institute of Dental Research, NIH.
46. Bunde, C., Interdepartment memo, Richardson-Merrell, 1972.
47. McBride, W.G., Affidavit to federal court, *Mekdeci vs. Richardson-Merrell*, July 1980.

48. Smithellis, R.W., "Defects and Disabilities of Thalidomide Children", *British Medical Journal*, Feb 3, 1973, pp. 269-272.
49. Schlesinger, H., "Zur Lehre vom Angeborenen Pectoralis-Rippendefect und dem Hoch Stande der Scapula", *Wien Klinische Wochenschrift*, 13:25-31, 1900.
50. Gordon, G., *Develop. Med. Child Neurol.* 8:761-767, 1966.
51. Karczmar, A.G., Srinivasan, R., Bennisohn, J., *Cholinergic Function in the Developing Fetus*, *Fetal Pharmacology*, Raven Press, New York 1973, pp. 127-162
52. McBride, W.G. "The Effects of Anticholinergic Drugs on the Development of the Chick Embryo", *IRCS Medical Science*, 8, 537, 1980.
53. Crescitelli, F., Geisman, T.A., "Certain Effects of Antihistamines and Related Compounds on Frog Nerve Fibers", *Amer. J. Physiol.*, 164:509-19.
54. Saxen, L., Rapola, J., "Congenital Defects", Holt, Rinehart and Winston, New York, 1969, pp. 46-57. Dr" .