

## DES Researchers Begin Three Year Studies

**O**n September 30 the National Cancer Institute awarded five 3-year research contracts, totalling nearly \$3 million, for "Continuation of Follow-up of DES-exposed Cohorts." We are very excited by this breakthrough, which has followed years of work and the mobilization of thousands of DES-exposed people and their allies.

The chart shows the information we have obtained on the research contracts.

The main focus of this three-year project is to assemble a large and stable group of DES-exposed individuals and unexposed "controls" who can then be followed over the course of many years. There will be a strong emphasis on locating and securing the cooperation of as many people who meet the study criteria as possible. Only those for whom documentation of DES exposure is available will be included. (For more on study criteria see the article in this issue

### Research Institution

### Amount Awarded

1) University of Massachusetts Medical Center Principal investigator: Kenneth L. Noller, M.D.	\$933,385
2) University of Chicago Principal investigator: Arthur L. Herbst, M.D.	\$633,547
3) Boston University School of Public Health Principal investigator: Theodore Colton, Sc.D.	\$618,553
4) Baylor College of Medicine Principal investigator: Raymond H. Kaufman, M.D.	\$420,179
5) Dartmouth Medical School Principal investigator: E. Robert Greenberg, M.D.	\$288,833

on Selection Bias).

DES daughters, DES sons and DES mothers will all be surveyed via mail in three separate questionnaires. Although the DESAD study has surveyed DES daughters for about 15 years, and there have been small studies of DES mothers and DES sons, this is the first attempt to assemble large groups of sons and mothers for surveys of a range of health effects. DES offspring will be questioned on such subjects as

cancers, reproductive changes, immune system effects, genitourinary tract changes, sexual history, and others. Areas of inquiry to DES mothers will include all causes of mortality and all cancers.

In total, the cohorts add up to nearly 19,000 participants (estimates; figures may change). See the chart below for estimated number of each cohort.

Many DES-exposed people are

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### Cohort

### Number

DES Daughters	about 5,000-5,200
Unexposed control daughters	about 1,800-2,000
DES Sons (target figure)	about 2,500
Unexposed control sons	about 1,500
DES Mothers	about 4,000
Unexposed control mothers	about 4,000

*All figures are estimates and may change.*

## DES Action Affiliates

Each group was created and nurtured by volunteers. Write them if you want information on their activities or can volunteer.

<b>DES Action/USA National Offices</b> 1615 Broadway, Suite 510 Oakland, CA 94612 L.I.J. Medical Center New Hyde Park, NY 11040 <b>California</b> c/o Dr. Wingard Community Medicine M-007 Univ. of Calif-S.D. La Jolla, CA 92093 Box 661653 Los Angeles, CA 90066 417 Avenida Abetos San Jose, CA 95123 Box 4826 Fresno, CA 93744 <b>Colorado</b> P.O. Box 2645 Colorado Springs, CO 80901 <b>Connecticut</b> Box 8027 New Haven, CT 06530 <b>Georgia</b> Box 566067 Atlanta, GA 30356 <b>Indiana</b> Box 3158 Carmel, IN 46032 <b>Louisiana</b> P.O. Box 804 Chalmette, LA 70044 <b>Massachusetts</b> P.O. Box 126 Stoughton, MA 02072 <b>Michigan</b> P.O. Box 2692 Ann Arbor, MI 48106 2205 Rosewood SE Grand Rapids, MI 49506 <b>Minnesota</b> Box 3102 Butler Quarter Station Minneapolis, MN 55403 <b>Missouri</b> 7647 Carswold Clayton, MO 63105 <b>New Jersey</b> Box 762 Fort Lee, NJ 07024	<b>New York</b> 268 11th Street Brooklyn, NY 11215 <b>Ohio</b> Box 21625 Cleveland, OH 44121 <b>Oklahoma</b> 3155 East 68th Street Tulsa, OK 74136 <b>Oregon</b> 2700 NE Studio Road, #3 Bend, OR 97701 <b>Pennsylvania</b> Box 286 Nescopech, PA 18635 <b>Rhode Island</b> 144 Columbia Avenue Cranston, RI 02905 <b>Texas</b> 8230 Shadowwood Drive Waco, TX 76712 <b>Washington, D.C. Area</b> 12494 Alexander Cornell Drive Fairfax, VA 22033 <b>Washington</b> 719-15th Ave. East Seattle, WA 98112 <b>Wisconsin</b> P.O. Box 17102 Milwaukee, WI 53217 <b>DES Cancer Network</b> P.O. Box 10185 Rochester, NY 14610 <b>DES Sons Network</b> Michael Freilick 104 Sleepy Hollow Place Cherry Hill, NJ 08003 <b>3rd Generation Network</b> Box 328 Mahwah, NJ 07430 <b>DES Action/Canada National Office</b> 5890 Monkland, Suite 203 Montreal, Quebec H4A 1G2 <b>Alberta</b> 1303 A Rosehill Drive N.W. Calgary, Alberta T2K 1M3 <b>Newfoundland</b> Box 104 Port Aux Basques Newfoundland A0M 1C0	<b>Nova Scotia</b> Box 25007 Halifax, N.S. B3M 4H4 <b>NW Ontario</b> 4-A South Ct., #17 Thunder Bay, Ont. P7B 2W4 <b>Ottawa</b> 644 Wavell Avenue Ottawa, Ont. K2A 3B1 <b>Prince Edward Island</b> 45 York Lane Charlottetown, PEI C1A 2A5 <b>Saskatchewan</b> 41 Knowles Crescent Regina, Sask. S4S 4N9 <b>Toronto</b> Box 1004, Station A Toronto, Ont. M5W1G5 <b>Vancouver</b> 926 Clements Ave. N. Vancouver, B.C. V7R 2K7 <b>Winnipeg</b> c/o Women's Health Clinic 419 Graham, 3rd Floor Winnipeg, Man. R3C 0H3 <b>DES Action/Australia</b> P.O. Box 282 Camberwell, Victoria 3124 <b>DES Action/Britain</b> c/o Women's Health 52 Featherstone Street London EC1 Y 8RT <b>DES Action/France</b> Info DES/France 9 Allee de Guignegault 45800 St. Jean de Braye <b>DES Action/Ireland</b> Council for Status of Women 64 Lower Mount Street Dublin 2 <b>DES Action/Italia</b> Centro Simonetta Tosi Casa Intern Donna Via della Lungara 19 00165 Roma <b>DES Action/Netherlands</b> DES-Aktiegroep Wilhelminapark 25 3581 NE Utrecht
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## letters to the editor

I just saw Jean Kasem on a talk show speaking of her DES exposure.

She described feelings I have had for so long when she said, "DES did to our insides what thalidomide did to the outside of the children whose mothers took it." That may not be verbatim—but I was so moved by hearing her.

The fertility issue aside, it is so hard to vocalize the feelings of what has been done to us.

I would like to thank Jean for so eloquently expressing how so many of us feel.

Robyn Levesque  
Biddeford, Maine



## Tribute Gift Program

You can honor a friend or relative for an anniversary, a birthday, as a memorial donation, or for any important occasion, by giving to DES Action in your honoree's name.

If you would like to receive our Tribute Gift cards, please send us a note or call to let us know how many you would like.

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1615 Broadway, # 510  
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(510) 465-4011

**Executive Director:**  
Nora Cody  
**Board Officers**  
President:  
Karen Fernandes  
VP: Andrea Goldstein  
Secretary: Pat Cody  
Treasurer: Libby Saks

**Contributors:**  
Nora Cody  
Pat Cody  
Ellen t'Hoen  
Elizabeth Kronisch  
Judy Turiel

**Design and Layout:**  
Kristin Prentice &  
Sphinx Graphics  
Berkeley, CA  
**Printing:**  
Inkworks,  
Berkeley, CA



## Notes From Nora DES Cohorts And "Selection Bias"

**W**e have heard from many DES-exposed people over the years who are frustrated that no one is studying them and want to enroll in a study. We agree that many more DES-exposed people should be studied. Last year DES Action collaborated with Boston University's Slone Epidemiology Unit on a "Health History Survey" of our members, with the intention that the information learned be shared with other scientists.

At the same time, we are aware that our survey has limited application because of the problem of "selection bias." Selection bias excludes our members as well as those individuals who want to enroll themselves in a study.

What is selection bias? Basically, this is the bias that occurs when study participants (or "subjects") are not randomly selected but are, in this case, self-selected. DES Action's membership is a self-selected group, and our members tend to have a higher incidence of DES-related health problems than would a random group of DES-exposed people. This is what motivates many (although not all) to join and to remain members.

In the book *DES Update* (Kenneth L. Noller, MD, ed., Elsevier Science Publishing Co., 1992) a chapter on "Selection Bias in Observational Studies" illustrates some of the consequences of selection bias, in this case in the DESAD study. The authors compared three groups in evalu-

(VEC), a clinical finding related to DES exposure. The three groups were DES daughters assembled from:

- (1) prenatal record review (i.e. randomly selected);
- (2) clinic walk-ins (self-selected);
- (3) physician referred patients.

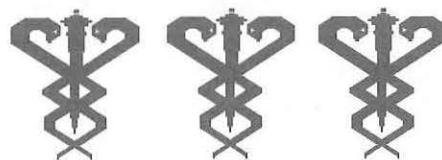
They found VEC in 34% of the first group, 59% of the second and 65% of the third group. They also found that while 42.1% of the mothers of the record review group had a history of miscarriage, the average for the walk-ins was 55.1% and for the physician-referred, 57.6%. This finding suggests that the DES mothers'



experience influenced their daughters' participation in the second and third groups.

The authors concluded

that "the DESAD Project provides a dramatic example of the hazards of interpreting data from self-selected cohorts."



## DES Action Elects New Officers and Board Members

**D**ES Action has new officers. We welcome President Karen Fernandes, board member from Texas. Our former president Andrea Goldstein replaces Karen as the new Vice President. And Pat Cody, staff program director, takes over as Secretary. Libby Saks remains in her position as the Treasurer.

Three new members were welcomed to DES Action's Board of Directors at their fall meeting. The three bring a wide range of talent and diversity of experience which will serve the organization well in the years to come. Carol Allen, a DES daughter and clear cell adenocarcinoma survivor, joins the Board following years of activism in DES Action Canada and the DES Cancer Network. Shirley Simand also hails from our sister group in Canada. A DES mother, Shirley previously served on DES Action's board but had taken a required one year off between her terms. And we are also grateful for the addition of Sally Esposito, a DES daughter and a leader in DES Action Connecticut and in her field of disability advocacy.

The Board also said goodbye to two members who have left the board: Maureen Rafael and Margaret Lee Braun, each of whom has devoted years to helping DES-exposed individuals across the country. Earlier in the year Linda Dozoretz resigned from the board. We extend our thanks to all of these volunteers for their time and talents.

# Ritodrine in Pregnancy

by Judy Turiel, Ph.D.

Last July the *New England Journal of Medicine* (NEJM) published a study questioning the effectiveness and safety of ritodrine, the one medication with FDA approval for use in stopping preterm labor (doctors do often prescribe similar medications such as terbutaline). Of all people, DES daughters hesitate to take medications during pregnancy. The irony, of course, is that these women have an increased risk of preterm labor and delivery as one long-term effect of their prenatal DES exposure. The recent medical report reinforces concerns about ritodrine-type medications: do they delay delivery long enough to improve a baby's health? Can prenatal ritodrine exposure harm the baby it is supposed to "save"? How risky is this treatment for the pregnant woman?

Deciding whether to take ritodrine requires consultation with experienced medical professionals. We summarize here main findings of clinical studies and some key questions about ritodrine/terbutaline that can help individuals weigh risks and benefits in their particular case.

Unlike DES, ritodrine has been shown to provide *some* benefit in *some* pregnancies. Researchers agree that ritodrine can successfully postpone delivery for up to 48 hours. After that time, however, several studies show no significant differences overall in delay of delivery or incidence of preterm birth (before 37 weeks) between treated and untreated pregnancies, nor in

certain health outcomes for the newborn. Authors of the recent NEJM study suggest that clinicians could better use the 48 hours to administer lung-maturation drugs and, if needed, to transfer the woman before delivery to a hospital with a newborn intensive care unit. They also note greater benefits within the subgroup initially treated between 24 and 27 weeks rather than later in pregnancy. They suggest that future studies should focus on determining benefits of administering ritodrine before 28 weeks gestation.

Outcomes measured in newborns are primarily mortality (death rates), incidence of respiratory distress syndrome, and birth weight (up to 2500 grams). These measures are not significantly better with ritodrine treatment. While important, these are not the only outcomes needing attention, and, it is important to consider subgroups rather than look only at the overall results which include later gestational ages and higher birth weights (where treatment benefits will be low).

The NEJM study suggested trends (not statistically significant) needing further study with greater numbers of pregnancies. These trends were in the direction of improved outcomes with ritodrine, compared to placebo: lower perinatal mortality when preterm labor was diagnosed between 24 and 27 weeks gestation; slightly improved score on Bayley Psychomotor Development Assessment in offspring at

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18 months of age; less incidence of cerebral palsy.

Obstetricians who do administer ritodrine for extended lengths of time (several weeks is common) question whether preterm labor has been detected early enough to allow effective treatment in studies showing no significant benefits after 48 hours. They also note the importance of monitoring the pregnant woman regularly after contractions are stopped, to catch any recurrence and adjust treatment (oral or intravenous medication, bedrest, etc.). Uterine monitoring for contractions can be done at home.

These obstetricians do acknowledge, however, that they are probably *overtreating* in as many as 25-30% of cases in which they administer ritodrine type drugs. That is, by attempting to catch preterm labor in its earliest stages in order to prevent preterm birth, many women whose contractions would have stopped without treatment are

given these medications and/or stay on them for a longer amount of time. In the view of these practitioners, greater risks come from undertreatment—missing signs of preterm labor, resulting in the delivery of a baby with serious health problems related to prematurity. As with most medications, over-prescribing also results from the pharmaceutical industry's influence on doctors, and from the desire to "do something" even when doing nothing is the more appropriate medical course. In treatment of preterm labor, however, there is the very real trade-off between attempting to catch early signs and missing the chance to prevent preterm birth, a perplexing dilemma for doctors and patients alike.

☛ What are the risks? For the pregnant woman, ritodrine-type medications bring considerable side effects that were not adequately documented during the FDA approval process. Of greatest concern are increased heart rate, irregular heart beat, chest pain, pulmonary edema (a dangerous build-up of fluid in the lungs). Maternal deaths from pulmonary edema, and in women with undetected heart problems, have occurred. We cannot stress enough the importance of close monitoring during treatment by medical professionals experienced in use of these medications and in managing any side effects.

During treatment, the fetal heart rate also increases; some metabolic effects (e.g., abnormal blood sugar levels) are seen at delivery, but soon return to normal. No long-term health consequences are reported in the medical literature. However, as

with other reproductive interventions, no adequate follow-up studies exist to determine the health of older offspring. Target organs that could theoretically be affected include the heart and smooth muscle tissue. Unlike DES, these medications are not hormonal, and are not administered early in pregnancy, the time of greatest risk to fetal development. To the extent that ritodrine does prolong pregnancy, prenatal exposure must be weighed against risks faced by the more premature newborns from illnesses and treatments administered after birth, particularly if intensive care is required.

☛ A DES daughter writes to ask whether her children's medical behavioral or learning problems were caused by their prenatal exposure to ritodrine. No one knows the answer to that question. Tracing the cause of such problems would be difficult because of other factors that could be involved. For example, if a pregnant woman is also on bedrest, physical inactivity could affect fetal development. If a DES daughter has a very small uterus, there could be effects as the fetus

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grows. If the babies were premature, there may be long-term consequences that are hard to separate from effects of ritodrine.

Though pinpointing causes might be difficult, however, it is crucial to know whether ritodrine/terbutaline exposed offspring (as well as those exposed to IVF and other reproductive therapies) will be at risk for health or developmental problems. Serious questions remain about the original approval of ritodrine, the adequacy of tests for safety and effectiveness, the expense of this one approved drug compared with other similar substances, the lack of attention to less invasive or risky alternatives. However, faced with preterm labor now, DES daughters and other pregnant women must reach decisions about available options in order to safeguard their own health and the health of their children.

Registries should be established for long-term follow-up of such pregnancies. As a start, individuals can share anecdotal experiences to see whether any hints or patterns merit more systematic study. DES Action member Cheryl Roth of 10 Peach Drive, Roslyn, NY 11576, has written:

"I would be interested in learning if other readers of the *Voice* who have taken ritodrine during pregnancy have experienced any significant medical, behavioral, learning or other difficulties with their children. I would be happy to receive any communications from readers."

**Note:** *The NEJM in its 10 Dec issue has a number of letters about their July article. You may be able to find this journal in your local library or medical center library.*

# Major Victory in Dutch Law Courts

by Ellen 't Hoen

**F**riday, October 9, 1992 will be remembered as a very important day by thousands of Dutch women who have followed the DES law suit for six years. On that day the Supreme Court in the Netherlands paved the way for liability suits against the manufacturers of DES. In a landmark decision it took away the main obstacle for the Dutch DES daughters: the fact that many women cannot identify the manufacturer who produced the pills their mothers took. In the opinion of the lower courts the companies could therefore not be held liable for the damage caused by their products. The Supreme Court called the result of the lower court's reasoning unacceptable and overruled it, stating that each of these companies can be held liable for the complete damage these women

*"The Supreme Court in the Netherlands (has) paved the way for liability suits against the manufacturers of DES."*

have suffered. After this victory, thousands of women have called DES Action, interested in claiming compensation.

## **"No" to market share**

DES has been marketed in The Netherlands by over 20 different companies. As in the U.S., many women do not know the brand name or the manufacturer of the drug they were exposed to. This has always been a serious obstacle for compensation for which

solutions such as market share liability have been developed. The Dutch Attorney General saw grounds for market share liability in this case (see the last issue of the Voice).

The Supreme Court rejected market share liability because the DES daughters would not receive compensation from companies which had become insolvent or were impossible to trace. The DES daughters would have to bring suit against many companies involving complicated procedures to determine the size of the market share. According to the Court there is no need for market share liability since each of the companies is in principle liable for the whole of the damage caused by DES products.

## **Not the end yet**

Although the main obstacle

## **RESEARCH from page 1...**

concerned about their children and grandchildren, the "third generation" of the DES experience, and whether harmful effects from the drug have been passed on to them. The National Cancer Institute has instructed researchers to investigate the feasibility of establishing and studying a group of third generation children for future studies. They are consulting various experts to determine such criteria as size of cohort and age ranges needed for reliable research projects.

What can we expect from this three-year project? Each participating institution will be free to publish data on their findings,

and we will certainly keep you informed about any research news. All the researchers will combine their cohorts into one large database which can be surveyed every year or every two years, and which will provide a base for testing hypotheses about the effects of DES exposure. Our hope is that this project will provide some confirming evidence about the many unknowns in the range of health effects from DES, and will give us all tools we can use to best protect our health.

These studies have an importance beyond their help to the DES-exposed. Scientists will learn in detail about the possible effects of a powerful synthetic hormone on pregnant women and their

offspring. These are lessons that may protect current and future generations from other "wonder" drugs.

The "DES Education and Research Amendments of 1992," which President Bush signed into law on October 13, *separately* establishes a three-year program of education, outreach, and research through the National Institutes of Health. Congress has allocated \$1.5 million for the first year of this program. In January DES Action representatives will meet with NIH officials to discuss their plans for the implementation of this legislation, as well as their ongoing DES research.

has been taken away by the Supreme Court, this does not mean that the procedure has come to an end. The questions of negligence, foreseeability and causation have to be dealt with. The case is now referred to the Hague Court of Appeals which will probably rule within a year. The costs of the appeal will have to be paid by the drug companies.

### Industry response

The companies responded through a press release from a public affairs bureau. According to a Dutch newspaper: "They refuse to communicate on this case in any other way." In this press release they state that this decision puts The Netherlands in an exceptional position compared to the rest of Europe and that even in the U.S. such far-reaching liability has not been accepted by any court. This is not true, according to attorney Sybil Shainwald who happened to be in The Netherlands at the time of decision, and who is involved in many DES lawsuits. In several

states in the U.S., courts have accepted similar liability based on the "concert of action" theory which also leads to full compensation for DES daughters.

### Limitation period

The Supreme Court decision has not only removed the obstacles to the case in question, but also makes individual suits possible. Because of the introduction of the new Civil Code in the Netherlands, the limitation period in which one can claim compensation has been set at five years after the damage becomes apparent. DES exposed people who wish to keep the right to claim for compensation in the future had until the end of 1992 to make this known. Immediately

*"(The) decision has not only removed the obstacles to the case in question, but also makes individual suits possible."*

after the Supreme Court decision, DES Action started a public campaign to encourage DES exposed people to send in their names and addresses. This campaign received a lot of support from the media. DES Action has been able to repeat the call on national television, in many radio programs, and in practically every newspaper available in the country.

The telephones at the Utrecht office have not been quiet for one moment since October 9th. More than ten thousand DES daughters have responded to the call and many are still trying to get through. Volunteers are assisting the DES Action staff. Surrounded by piles of letters and postcards, they deal with mailings, process the many responses, and answer requests for information. According to Dietske van der Brugge from DES Action, this has been the largest public campaign DES Action has ever had. "Sometimes we do not know whether to laugh or to cry when the postman brings another load of letters and registration forms." 🐣



## Join DES Action!



**Yes** - I want to get the answers about DES. Enclosed is my membership.

- ☐ Benefactor: \$1000 and above    ☐ Friend: \$75  
☐ Sustainer: \$500    ☐ Subscriber: \$50-\$25 (sliding scale)  
☐ Associate: \$200    ☐ Low Income: \$10  
☐ Supporter: \$100

All members receive **The DES Action Voice** quarterly. Those at the \$75 level and above receive additional annual reports on DES Action's work and progress.

- ☐ I am enclosing my annual payment of \$ \_\_\_\_\_.  
☐ I would like to donate through the **Pledge Program** with ☐ quarterly or ☐ semi-annual payments totalling \$ \_\_\_\_\_.  
☐ Check enclosed (please make payable to: **DES Action**).  
 I am a: ☐ DES Daughter ☐ DES Son ☐ DES Mother ☐ Other

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address \_\_\_\_\_

city \_\_\_\_\_

state \_\_\_\_\_

zip \_\_\_\_\_

phone ( ) \_\_\_\_\_

DES Action USA  
1615 Broadway, Suite 510  
Oakland, CA 94612  
(510) 465-4011 #55

## Locating Pharmacy and Medical Records for DES Litigation

by Elizabeth Kronisch, Esq.

**I**n DES cases, where exposure to the drug took place many years ago, pharmacy records are often unavailable. However, on the chance that they do exist, some suggestions may be helpful in locating them.


If the pharmacy is no longer in existence, try to locate the pharmacist or his family. The State Board of Pharmacy may be able to put you in touch with the pharmacist if he is still alive. If not, try to locate the person who may have bought the business from the original pharmacist.

Pharmacists are often wary of talking to people about DES because they fear that they will be sued. If there was a prescription for DES from your treating

physician and the prescription was properly filled, there is no liability on the part of the pharmacist. Assuming this to be true, please assure whomever you contact that he will not be sued.

It would be helpful for you to try to remember what the pill looked like. The color, shape, size, coating (if any) and any scoring or writing are characteristics that may help to identify the manufacturer. Some mothers are able to "feel" the pill between their fingers or "see" the pill as they are about to put it in their mouth. Did you tend to keep the vial or bottle on your nightstand, in the bathroom, on the kitchen table or the counter above the sink? Did you take the pills one,

two, three or four times a day? Did you take them with food? Did they tend to upset your stomach? Did anyone see you taking the pill who might remember what they looked like?

Obstetrical records are also important. The County Medical Board may be helpful in tracking down your treating doctor. If you are unable to locate records from your treating physician, another source may be the hospital where you gave birth. Doctors usually sent the prenatal records to the hospital prior to the date of delivery and those records became part of the hospital chart. These may be difficult to locate, but as with all the records we are looking for, persistence often pays off. 

## DES Action USA

West Coast Office  
1615 Broadway, Suite 510  
Oakland, CA 94612

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