Fetal Exposition to Synthetic Sex Hormones

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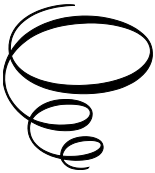
Their Nature and Impact on Human Health

Edited by

Marie-Odile Soyer-Gobillard
and Charles Sultan

Cambridge Scholars Publishing



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PREFACE

Pr Jean-Marc LOBACCARO, PH.D., Distinguished Professor of Molecular Physiology, Université Clermont Auvergne, Director Institute of Life, Heath, Agronomy, Environment Sciences, Co-leader of the research team Nuclear Receptors and Pathophysiology.

1.Ephebe in a complicated world. MOG-S, 2012. Patinated bronze.

> *...And he said to the human race, "The fear of the Lord—that is wisdom, and to shun evil is understanding" ...*
> —Job 28:28

Job was a God-fearing man. This fear of God governed his whole life, and made him an upright man, who shunned evil. He was a wealthy man with a blessed large family. However, he lost everything because of a bet between God and the Satan. Despite everything, he never gave up. The Book of Job is definitively a poetic book; however, it somehow tells us a lot about the history of endocrine disruptors. Initially synthesized to improve human health, they were widely distributed. Of course, toxicity tests had been carried out but history will reveal that these were completely insufficient. What may seem confusing, even despairing, is ultimately that the health disaster of diethylstilbestrol will not have helped much. Despite families devastated by what should have been a benefic hormone replacement treatment, few systems have been put in place to study the real long-term effects of the new molecules, in the treated person but also on their offspring. *Primum non nocere* that means "first, do no harm" is one of the most important points defended by bioethics, in all medical schools and shared by all the pharmacist and medical students. Even not present per se, this concept is present in the Hippocratic Oath. Once again, it seems that profits are brushing aside this proverb. So, should we sink into the deepest despair, like Job at the beginning of the book that tells his story?

In reality, this book gives us the inside story of synthetic steroids. With its double side, like Aesop's tong or the story of Doctor Jekyll and Mister Hide. A positive side and a dark side. Indeed, we must remember that these synthetic steroids were given to different patients to improve their symptoms, without any intention of causing harm. Beyond the known effects on the genital area, which are reported in a second part, this book first describes the neurodevelopmental effects of synthetic steroids. Beyond the sum of articles, this book also gives us the story of a woman, that of the Doctor Marie-Odile SOYER-GOBILLARD, hardly hit in her family by the story of DES. Thanks to her, and with the help of Professor Charles SULTAN, and that of his research team, who devoted his career as pediatric endocrinologist for understanding the anomalies of genital development in children, this entire story is now available in a single volume, for as many people as possible.

On the over side, the optimistic aspect of this book is that the molecular mechanisms leading to the deleterious effects are also brought together.

Even if we thought that the effects of these endocrine disruptors are irreversible because they are developmental, we can only remain optimistic about the possibility of one day identifying molecular targets which could perhaps become pharmacological targets in order to reduce the side effects of treatments. In any case, all data is available to everyone. Can we still say: we didn't know?

Jean-Marc A. LOBACCARO

FOREWORD

Pfr Terence PRESTON, PH.D. University College London, Honorary Associate Professor, Research Department of Genetics, Evolution & Environnement Division.

2. Body of a young girl. MOG-S, 2019. Raku ceramics.

The truth is rarely pure and never simple.
—('The Importance of Being Earnest.' Oscar Wilde)

This book recounts the story of a scientific journey concerning drug toxicity: a journey with a beginning, yet more than 80 years later, no end. The tale begins in 1938 with the synthesis of a diphenol demonstrating powerful oestrogenic properties - diethylstilbestrol (DES). At the time it was trumpeted as an advance of singular importance in the treatment of pregnant women with a propensity to miscarry. Unpatented, this drug was manufactured by numerous enterprises and used globally by millions of women. However, by the 1960's it became apparent that DES had been launched on a false prospectus since the "hormonal cause" hypothesis for foetal abortion was erroneous. If DES had proven to be no more effective than a placebo, its story would have been consigned to history.

Tragically, there was a darker side to the use of DES in human medicine since it could traverse the placenta gaining access to the embryo. The transformation of the fertilised egg to neonate in the privileged sanctuary of the womb is like an ultra-complex 4-dimensional cellular ballet involving a myriad of time-sensitive interactions, perturbations of which may prove disruptive to normal development, or indeed fatal. Whereas the use of any drug is not without risk, it transpired that in a certain number of cases offspring exposed *in utero* to DES exhibited malformation to their urinogenital systems. Furthermore, significantly higher instances were reported of cases of clear cell adenocarcinoma of the cervix or vagina in adolescent girls thus exposed. DES therefore could act as a teratogen and carcinogen in humans, as had been found previously in laboratory animals. Consequently in 1971 the prescription of DES for pregnant women was banned in the USA: France followed suit in 1977. It is now known that its toxicity depends on binding to, and activation of the oestrogen receptor; thus, it is an endocrine-disrupting chemical.

With the passing of time, despite the ban, further late acting effects of the historic use of the drug became apparent. In France in 1998, resulting from a survey among a group of "DES" afflicted families, a picture emerged of a different type of harm sustained by *in utero* exposure to this drug, namely psychological disturbance. This was manifested in the form of behavioural damage appearing in such children during adolescence on a spectrum of severity that included suicide. By serendipity this news caught the attention of one of this book's authors (Marie-Odile Soyer-Gobillard) a distinguished

cell biologist, and herself a DES mother. Directly affected as she was by the recent loss of both her psychologically harmed children by suicide, she set out to establish a scientific link between *in utero* exposure to DES and subsequent behavioural disturbance in the resulting offspring. She became the driving force behind the setting up of a comprehensive medical database of the testimonies of more than 1,300 DES families associated with the now called HHORAGES support group. An English translation of the harrowing, personal account of her experience with DES (together with those of several other affected families in this support group) and her resilient, courageous response to it was published recently*.

Data mining of this HHORAGES resource would come to play a major part in linking xenohormone (DES, ethinylestradiol, progestins - each an endocrine-disruptor) exposure *in utero* with medical (somatic & psychological) disorders not only in the initial offspring but also in their children, *i.e.* multigenerational effects of these synthetic hormones. In collaboration with her co-author (Charles Sultan), an eminent endocrinologist and specialist in environmental endocrine disruptors, she has worked tirelessly and with immense resilience testing the proposition that DES (and other synthetic hormones) act as psychological disruptors; an hypothesis yet to be accepted by all in the scientific and pharmaceutical community. Positive steps have been made at the molecular level in cleaving this Gordian knot as this book relates, but the journey is far from over. In 2021, in recognition of the strength of her scientific enterprise and fight for social justice for the hapless HHorages families, Marie-Odile Soyer-Gobillard was decorated with France's highest honour – Chevalier de la Légion d'Honneur.

The prescription of DES in pregnancy has left, and continues to leave, many innocent victims in its trail, not all of whom have received adequate support or financial compensation. It is no consolation that this failure in the duty of care by healthcare groups on a spectrum of causes, from ineluctable human weakness to the defensive action of financially vested interests, is not unique.

Terence M. Preston
London, July 29, 2024

*Marie-Odile Soyer-Gobillard (2022) "Resilience: *A scientist's campaign against synthetic hormones*". Nombre 7, Collection Hippocrate.

PREAMBULES

3.Thinking. MOG-S 2020. Patinated bronze.

WHY THIS BOOK?

Dr Marie-Odile Soyer-Gobillard, PH.D., DR Emeritus Honorary, CNRS, Sorbonne Université, 75005 Paris, France, Association HHORAGES-France, 66100 Perpignan, France

This book, which brings together most of our publications since 2011 to 2024, is the culmination of many years of observations and research on the disorders observed among a very specific group of people consisting of mothers treated during their pregnancy(ies) by synthetic hormones, estrogens and/or progestogens, administered alone or in cocktails, as well as the psychological and/or somatic disorders of their children and their grandchildren. These people gathered within the HHORAGES-France Association have made it possible, thanks to their testimonies, not only to highlight the link between *in utero* exposure of children to these xeno-hormones (Diethylstilbestrol, Ethinylestradiol, Progestins) and psychiatric and autistic disorders but to also focus on the multigenerational effects of these endocrine disruptors. Diethylstilbestrol (DES) is a xenoestrogen considered by the scientific community as the model for studying the impact of endocrine disruptors in animals and humans. Furthermore, as early as 2011, SKINNER et al. have suggested that the multigenerational transmission of the deleterious effect of endocrine disruptors occurs through alteration of the epigenome.

From the 1950s to the late 1980s, millions of women worldwide took diethylstilbestrol (DES) during pregnancy to prevent miscarriage and premature birth, to inhibit lactation after childbirth, or to treat infertility, primary or secondary amenorrhea, dysmenorrhea and other gynecological disorders. Despite various warnings published as early as 1938 [LACASSAGNE, 1938] it appeared that exposure to DES is associated not only with somatic effects, (notably female genital anomalies, vaginal cancers and male urogenital disorders [TOURNAIRE et al. 2014], hypospadias for the second and third generations [KALFA et al., 2011], as well as endometriosis at the multigenerational level (GASPARI et al., 2021]), but also with the neurological development of the unborn child. From the latter issued psychiatric disorders in the second generation such as schizophrenia, bipolar disorders, anxiety, numerous suicides and suicide attempts, deep depression, behavioral disorders, eating disorders [SOYER-GOBILLARD et al., 2015], demonstrated neurodevelopmental deficits (ADHD) on the

third generation [KIOUMOURZOGLU et al., 2018] or autism [SOYER-GOBILLARD et al., 2021, 2022].

Founded in 2002, the HHORAGES Association brings together the testimonies of more than 1,300 families, collected from a detailed questionnaire, established by scientific specialists and doctors and representing more than 2,000 children exposed *in utero* to synthetic hormones. In certain of these informative families there were eldest siblings that had not been so exposed and thus served as internal controls in this database. Our cohort is registered in the Epidemiological Portal of INSERM and AVIESAN (National Alliance for Life and Health Sciences) (epidemiologiefrance.aviesan.fr).

In addition to *in utero* exposure to Diethylstilbestrol, we also studied the effects of Ethinylestradiol (EE), a synthetic estrogen, whose deleterious effects on rat pups exposed in utero were studied by J. CASTON† and his team [2001, 2005]. This compound was banned in 1980 in Europe for pregnant women, but continues to be marketed with synthetic progesterones (progestins), administered after the ban on DES in France [1977/1982] and often given in cocktails previously. We were the first to demonstrate the harmfulness of synthetic progestins in terms of psychiatric disorders in children exposed *in utero* [SOYER-GOBILLARD et al., 2019] while P. YAO and his team had demonstrated its effects on the occurrence of autistic disorders [2017, 2018]. Our cohort also allowed the team of M-O. KREBS (Sainte Anne Hospital in Paris) to highlight at the molecular level the mechanism of action of these hormones which is of the epigenetic type. This involves hypermethylation at the level of two genes involved in neurodevelopment and the control of morphogenesis of the sexual organs [RIVOLLIER et al., 2017]. This epigenetic mechanism represents a significant risk for future generations via its multi- and trans-generational effects. We are currently in the fourth generation impacted, that of the great-grandchildren of women who took these hormones during pregnancy. Finally, the HHORAGES-FRANCE cohort made it possible to study the impact of these hormones which increase prematurity as well as the birth weight of exposed children [GASPARI et al. 2023] and to partially elucidate the biological mechanisms underlying the effect of these endocrine disruptors (SOYER-GOBILLARD et al., 2023). In addition, the results of a study within our cohort of several cases of gender dysphoria [Male (XY) to Female] have just been published that demonstrate an increased incidence in this disorder following from *in utero* exposure to DES [GASPARI et al., 2024].

This book also aims to be a wake-up call for doctors and other health professionals.: After this particular disaster, what precautionary principle should we take with regard to these endocrine disruptors?

Synthetic hormones owe their toxicity to their action on the functioning of certain genes involved in neurodevelopment (epigenetics) and also to the fact that their degradation in the human body is different from that of natural hormones: for example, Ethinylestradiol (EE) blocks the functioning of the P450 detoxification enzymes which no longer act in the liver; the artificial hormone, lipophilic, then attaches to the mother's fat and is then released to the fetus during pregnancy by crossing the placental barrier. More or less degraded, these hormones or their metabolites will then impact areas of the developing fetus's brain while disrupting its hormonal system and contaminating its gametes, therefore its germline, without forgetting the contamination of the mothers themselves. In addition to the deleterious effects with demonstrated multigenerational impact of these products, Progestins and EE are the major components of the contraceptive pill: the exponential increase in cases of autism in the world could be attributed to them [STRIFERT, 2015] as well as the drastic increase in cases of developmental disorders (ADHD, ADD and DYS disorders), and gender dysphoria of which there are more and more reports, cast a potential shadow over the use of these social phenomena, the birth control pill or the hormonal IUD.

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Perpignan (France, Occitanie) 28/07/2024.

4. Mother Courage. MOG-S, 2005. Patinated bronze.

DES (DIETHYLSTILBESTROL): A PROTOTYPE FOR EVALUATING XENOESTROGEN ACTION, A CLINICAL "EXPERIMENTAL" MODEL FOR ANALYZING EARLY, LATE AND MULTIGENERATIONAL EFFECTS OF FETAL CONTAMINATION BY ENDOCRINE DISRUPTORS

Charles Sultan[a], Laura Gaspari[a], Marie-Odile Soyer-Gobillard[b,c]

[a] Unité d'Endocrinologie-Gynécologie Pédiatrique, CHU Montpellier, University Montpellier, 34090 Montpellier, France.
[b] Sorbonne University, CNRS, 75000 Paris, France.
[c]Association HHORAGES-France, 66100 Perpignan, France.

Endocrine Disruptor Chemicals (EDCs) are man-made chemicals that interfere with hormone production, secretion and action in target cells. Fetal contamination by EDCs increases the risk of early and long-term adverse outcome, including genital malformations, neurodevelopmental defects, immune system disorders, metabolic alterations, obesity and various cancers. Diethylstilbestrol (DES) is a synthetic xenoestrogen prescribed to millions of pregnant women that was reported 50 years ago to induce vaginal cancers at adolescence, reproductive tracts malformations in male and female patients as well as several psychological, neurological, psychiatric, metabolic and reproductive disorders in adulthood.

A critical lesion from DES experience was that the exposition of this xenoestrogen during fetal development could increase risk for adverse effects in the adulthood, supporting the hypothesis of developmental origin of adult diseases (DOHAD). DES thus provided a foundation for risk assessment, an universal framework for identification of long-term effects of EDCs. This observation was a key-issue for elaborating the concept of EDC, raised some years ago, and confirmed by animal studies and epidemiological data.

Key characteristics of EDC are now well established. Molecular aspect of DES action, such as interaction with estrogen receptors, alteration of

estrogen receptor expression, variation of signal transduction and epigenetic modulation have been confirmed for several EDCs. Besides, DES alters miRNA profile, leading to up or down gene expression, as well as DNA methylation. Epigenetic modulation reported for DES has been extrapolated for several EDCs.

Actually, the deleterious consequences induced by DES impact prenatally exposed children, but also grandchildren, suggesting a multi- and trans-generational transmission.

In conclusion, during the last years, DES appeared to be a clinical and "experimental" model for analyzing early, late and transgenerational effects of EDCs, a prototype for identifying xenoestrogen action and a bellwether for EDCs contamination in humans.

Montpellier (France, Occitanie) 10-10-2024

CHAPTER I

AS AN INTRODUCTION

ENDOCRINE DISRUPTERS AND BEHAVIOURAL DISORDERS: NO, WE HAVE NOT AS YET LEARNED THE LESSONS OF THE DES STORY

M.-O. SOYER-GOBILLARD [a,b,c]

[a]UMR CNRS 7628, Université Pierre-et-Marie-Curie, 18, avenue Fontaulé, 66650, Banyuls-sur-mer, France
[b]Association HHORAGES-FRANCE[1] (Halte aux HORmones Artificielles pour les GrossessES), [c]78, avenue Georges-Guynemer, 66100 Perpignan, France; email : mog66@orange.fr;
[1]http://www.HHORAGES-FRANCE.com, HHORAGES-FRANCEfrance@yahoo.fr.
[*]Article from the Symposium "Endocrine Disruptors", organized by the "Réseau Environnement Santé (RES), September 14, 2010, Paris.

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SOYER-GOBILLARD, M.O. Endocrine disrupters and effects on behavioural disorders: No, we have not as yet learnt all the lessons of the DES story. *Médecine et Longévité* (Elsevier), © 2011, 3, 67-74. published by Elsevier Masson SAS. All rights reserved. Courtesy of Elsevier Masson France. (English translation from the original French article : «Perturbateurs endocriniens et troubles du comportement : Non, nous n'avons pas encore tiré toutes les leçons de l'histoire du Distilbène® (DES). » *Médecine et Longévité* (Elsevier), © 2011, 3, 67-74. Courtesy of Elsevier.

Summary

Synthetic oestrogens such as diethylstilbestrol (DES) or 17-α-ethinylestradiol (EE) prescribed to pregnant women from the 1950s through the 1970s have been shown to be responsible for devastating effects in their offspring. As far as behavioural disorders are concerned, work on animals (mice and rats) shows that these xeno-hormones have effects even at very low doses the foetal exposure period being crucial. There has been less work on human subjects but the recent analysis of a spontaneous cohort compiled by HHORAGES-FRANCE provides demonstrative data. The animal-