

CHAPTER 19

To Cell From Environment

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7. What we cannot speak about we must pass over in silence.

—Ludwig Wittgenstein, *Tractatus Logico-Philosophicus*

INTRODUCTION

Hormone means impulse, assault. An assault on the micro level of a cell attacked by foreign molecules has a parallel on the macro level of a society when chemical products are moved into social life and usage. Both processes reach out through time and space and trigger change—one deals with the individual cell and its immediate environment; the other deals with people and their immediate environment.

The world—as Ludwig Wittgenstein wrote—is the totality of facts, not of things. It is determined by the totality of facts and understood by us through our partial knowledge of these facts as we reproduce and transform them. Our continuous construction of hypotheses and beliefs is something we continuously test by fact collection and fact selection and by comparing the facts we find with expectations, both our own, more or less rigorously elaborated, and those of others, more or less easily perceived. One test is against nature as we have learnt to observe and measure it. The other test is against the social world in which we live and where we wish to be approved and recognized. Both tests influence our conclusions about the nature of the world. Both can be severe, especially if our findings are at variance with preconceived ideas, dominant beliefs, and vested interests.

To construct testable assumptions we condense and simplify. We always select only a limited number of variables—often only two, the binary set

that seems such a dominant pattern in any biological organism of a certain degree of complexity. These few variables, observed during a limited time period, are what we base generalizations on. It is natural, then, that our knowledge is partial and limited: To establish any lineage between causes and effects, asceticism in the choice of variables is rigorously required. And in order not to detract attention from the thinkable—as distinguished from the possible—paths between causes and effects, the selective assumptions themselves acquire a symbolical significance. Even long after the study or the experiment is completed, they continue to dominate in the ways we view, think of, and explain the phenomenon that was studied. We construct our own mind traps in order to figure out reality. The limitations that were necessary for the scientific reconstruction of a causal process lead us to repress and forget that which was outside the experiment, as if these facts were irrelevant, “outliers” that could contribute nothing to the understanding of the mainstream cause-and-effect trajectory. The limitations capture the mind and often inhibit us from placing the problem under study in its context. We search where the light falls for the lost key to the closed door.

What has this philosophical preamble to do with the knowledge of environmental carcinogens and with hormonal carcinogens in particular? Quite a bit. The study of the action of hormonal carcinogens on the cell in its environmental context requires viewing this environmental context as shaped both by nature and by individual and social expectations. One set of hormones—estrogens sold in the marketplace—will serve as an example of how the knowledge about the carcinogenicity of hormones on the level of the cell is part of a social construction and how the competition over the rights to define the “correct” knowledge about the relationship between cell and environment is manifested. Since an essential property of things is that they are possible constituents of states of affairs (Wittgenstein, *Tractatus* 2.011), estrogens in the marketplace will be viewed as a possible constituent of environmental hormonal carcinogenesis. “If a thing *can* occur in a state of affairs, the possibility of the state of affairs must be written into the thing itself” (Wittgenstein, *Tractatus* 2.012). I will use some of Ludwig Wittgenstein’s sentences in *Tractatus Logico-Philosophicus* as flags to remind us that the knowledge about tumors may have its origins not only in the organism where the tumors appear but in the interaction between human beings.

“2.014 OBJECTS CONTAIN THE POSSIBILITY OF ALL SITUATIONS”

Estrogenic substances have a role in hormonal carcinogenesis (IARC, 1987). Their carcinogenic potential has been the subject of numerous scientific investigations since the early 1930s. Two scientists engaged in the early experimentation with synthetic estrogens announced in 1933:

We have found oestrus-exciting activity to be possessed by the two most potent hydrocarbons yet known. . . . We confess that this last result was entirely unexpected; it is very striking that both types of biological activity should be shown by one and the same compound.

—(Cook and Dodds, 1933)

In animal experiments during the following years the carcinogenic potential of estrogens was observed repeatedly. (Lacassagne, 1936, 1938).

Estrogens were a technology with a market. They were already used in medical treatment, primarily of women in and after menopause as a compensation for the decrease of the menopausal women's endogenous estrogen production. The estrogen market began to boom after the synthesis of estrogenic substances, of which the best known is diethylstilbestrol (DES) (Dodds et al., 1938). These were substances that were based on cheap raw materials, easy to produce, not protected by patents, and possible to give to patients in the form of tablets instead of injections. Within a few months after the publication of the synthesis of DES, production started, as well as the marketing and the adoption of DES in clinical practice. No long-term toxicity tests had been done (Dodds, 1957, 1965). Already before 1940 both U.S. and European companies in the budding pharmaceutical industry were presenting DES products to the medical community, recommending it for an astoundingly wide variety of purposes. When the U.S. Federal *Food, Drug, and Cosmetics Act* was amended in 1938 for better control of the safety of drugs, DES was the first substance that was presented for approval in a joint application from drug firms all over the United States that wanted to engage in producing and marketing DES (Fenichell and Chaarfoos, 1981: 32–36).

All along there were warnings of the risks of estrogens, not least of the new synthetic compounds. Animal experiments repeatedly confirmed that estrogenic compounds stimulated malignant tissue growth. Early experiments with DES on patients also indicated toxic reactions: nausea, vomiting, skin reactions, and possibly liver damage. Many physicians in both the United States and Europe, and also the prestigious Council on Pharmacy and Chemistry of the American Medical Association, warned that DES was so potent and possibly harmful that it should not be recognized for general use until its functions were better understood (Shorr et al., 1939; American Medical Association, 1939).

However, others saw estrogens as substances that contained the possibility of many happy situations. Since the early decades of this century the powerful marketing of estrogenic products for medical and veterinary purposes has been impregnated with wishful thinking about control over life, youth, aging, and death. The benefits of estrogens in medical practice have been praised from the times of fuzzy ideas about how glands formed personality, through ideas about how estrogens could control fertility, pregnancy, sexual identity, cancer growth, and prevent the symptoms of natural aging,

to the present forceful marketing of estrogens for the maintenance of health, youthfulness, and sexual attraction in the baby boom generation of women during and after menopause and as a prophylaxis against osteoporosis, cardiovascular disease, and certain types of cancer. Estrogens are now commonly used in the current practice of medicine to control menstrual disorders, fertility, and complaints during and after the menopause.

An overview of the uses of estrogens as reported in the *Journal of the American Medical Association (JAMA)* from 1938 to 1987 indicates that estrogens have been given to patients for nearly 200 different indications in a giant trial-and-error process of experimentation. They have been a means to control pregnancy and childbirth: to improve fertility; for pregnancy testing; to control toxemia and bleeding during pregnancy; to induce abortion and to prevent abortion, pre-eclampsia and eclampsia, and stillbirth; to suppress postpartum lactation; and, more recently, to facilitate transplantation of human embryos. In skin treatment estrogens have been used in cosmetics as well as in the medical treatment of wrinkles, acne, scalp ringworm, sunlight dermatitis, and pigment changes. Estrogens have been used to mould sexuality in particular ways in men and women: to induce puberal changes in young women; to prevent them from growing too tall; to induce growth of a small vagina, a small uterus, and small breasts; and to treat disorders of sexual function in women, including lack of libido, frigidity, cervical hostility, uterine inertia postpartum, psychosexual disorders, fear of pregnancy, sexual infantilism, eunuchoidism, androgenicity, and oversecretion of androgens in young women. In men they have been employed to modify homosexuality, transvestism, nocturnal and morning erections, and hypersexuality in criminals and to facilitate transsexual feminization. They have been prescribed for mental conditions: melancholia, depression in general, premenstrual and postmenstrual depression, migraine, nervousness, fatigue, forgetfulness, and irritability. Estrogens have been believed to prevent aging and to treat psychogenic disorders in the elderly. Moreover, they have been tried in a wide variety of cancer treatments: as prophylaxis and in the treatment of breast cancer and in the treatment of genital cancers, cancer of the uterus, cancer of cervix, cancer of prostate, cancer of esophagus, bronchial carcinoma, pulmonary metastases, skeletal metastases, oral cancer, and leukemia (Palmlund, 1990; 363–374, 1991). Most of the patients who have received estrogens have been women and children. Men have been given estrogens mainly in the treatment of prostate cancer. The youngest patients were prematurely born babies given estrogens to increase survival chances, on the principle that the smaller the baby the larger the dose that should be given to compensate for the estrogen that the baby would have been exposed to if it had remained in utero (Brochier and Contamin, 1937). A list of the indications for prescribing DES around 1950 as medication for women before they reached menopause in the USA is given in Table 1.

In the early 1960s, oral contraceptives were launched on world markets after trials on a very limited number of women during a limited number of

TABLE 1. The Use of Diethylstilbestrol (DES) as Medication for Women Before Menopause in the United States ca 1950^a

To treat vulvovaginitis in little girls
To girls at puberty to control "flooding" and menstrual irregularities
In adult women to treat sterility and to control dysfunctional uterine bleeding, endometriosis, amenorrhea, hypomenorrhea, oligomenorrhea, and dysmenorrhea, menstrual migraine headaches, and other gynecologic endocrine disorders associated with ovarian deficiency
To pregnant women as diagnostic aid for ectopic pregnancy, as a pregnancy test, to stop nausea and vomiting, for missed abortion, against threatened abortion, bleeding from incomplete abortion, in connection with operations, to prevent abortion, for toxemia, diabetes, hypertension, excess saliva, large myomas, and to control premature labor and late accidents of pregnancy
To women after childbirth to eliminate painful engorgement of the breast and severe bleeding 2 weeks or more after delivery.

^a Data are from Karnaky (1948) and Bertling and Burwell (1950).

months—the first time in human history that a medication was introduced for consumption by healthy individuals for month after month, year after year during the long fertile period of their lives. The enormous market, partly supported by government purchases of these hormonal products for distribution via family planning programs in both developed and developing countries, was carried by a celebration of benefits.

The 1960s was also an epoch when a parade of full-page, vivid advertisements in medical journals persuasively argued that women needed replacement for something they had lost in order to function properly in family and social life. If they were to remain "endocrine rich and cancer poor" throughout their lives women should be given estrogen medication "from puberty to grave" (Wilson, 1962; Wilson and Wilson, 1963). Simultaneously books and articles in women's magazines, many of them by authors who received financial support from the major suppliers of estrogen drugs, carried a powerful message to middle-class and upper-middle-class women in mid-life: estrogen replacement therapy was needed so that women could remain feminine forever and escape the horrors of natural aging and "living decay" (Wilson, 1966; 43).

In a gradual response to observations of the actual efficacy and safety of estrogens *in manu medici*, the dosage of estrogens that patients have been given has decreased over the years, first by a factor of 10, later by a factor of 100. Since the 1930s estrogens have been administered to patients by injection, in tablets to be taken by mouth and implanted subcutaneously, in ointments, creams, and lotions to be applied on the skin, intravaginally, intranasally, and as intrauterine suppositories (Palmlund, 1991). We may never know how the indiscriminate use of estrogen medication some decades ago is reflected in the rising incidence of breast cancer in women and in

other malignant cell developments where estrogens are known to have a role. However, the marketing campaign for estrogen replacement therapy during the 1960s and 1970s has been traced as a major cause of the wave of increase in the incidence of endometrial cancer that followed (IARC, 1987).

Estrogens have also reached humans by the food chain, since they, in particular DES and related substances, have been widely used as growth promotants in animals. They make slaughter animals, from chickens to sheep and cattle, grow quicker for less feed to the appropriate slaughter weight. The use has been extremely controversial in industrialized countries, not least because of the suspected carcinogenic effects for those who ate the "hormone-cured" meat (Wade, 1972; Palmlund, 1990; 169–199). In 1957 Representative J. Delaney in the U.S. Congress charged that DES was a carcinogen, and in 1958 Congress passed the so-called Delaney amendment to the *Federal Food, Drug, and Cosmetics Act*, which still is used as a protective shield against environmental carcinogens: "No additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found after tests which are appropriate for the evaluation of the safety of food additives to induce cancer in man or animal" (U.S. Congress, Committee on Labor and Public Welfare, Subcommittee on Health, 1972; 2).

The use of DES in raising poultry was finally forbidden in the United States in 1966 (*Bell v Goddard*) after media attention to a restaurant worker who in the early 1950s had developed gynecomastia after eating chicken necks (Lawless, 1977; 72). Thirty years later, reports in *The Lancet* linked symptoms of premature puberty in little children in Mexico to meat from poultry raised with DES-supplemented food (Comas, 1982; Saenz de Rodriguez and Toro-Sola, 1982). Similar incidents have been reported from other countries.

The use of DES as growth promotant in slaughter cattle was made illegal in the United States from November 1979 after a long battle where the cancer risks for the meat consumers in the general public had been at the center of the controversy. Animal studies had repeatedly shown DES to be carcinogenic to male and female mice and rats, even at very low levels of exposure (Gass et al., 1964, 1974). A series of hearings in the U.S. Congress and pressure from people organizing around demands for a ban of hormones as growth promotants in slaughter animals created a political necessity to curtail the use of DES as a growth promotant, based on the Delaney Clause. The decision was made in spite of the strong resistance from the cattle-raising industry and firms producing pharmaceutical products for veterinary use (U.S. DHHS 1979a,b). However, other hormones, including estrogens, a few years later were allowed as substitutes (U.S. DHHS 1984, 1986). In some countries in Europe the use of hormones as growth promotants in animals was already forbidden in the 1950s. In the European Community a ban went into effect in 1989 by *European Community Directive 85/649*, a decision that started a minor trade war as U.S. meat exporters fought to

keep access to the important European market (Dickson, 1988). Several U.S. meat manufacturers announced that Mexico and Japan would be the attractive new markets for the hormone-cured meat banned from the European market (McGill, 1989).

Among the early reports on the observed toxicity of estrogens in humans were reports from the factories where DES was processed. Male workers engaged in the early manufacture of DES in Great Britain developed enlarged breasts and other female characteristics; the change was accompanied by complete impotence (Dodds, 1957). The occupational hazards of estrogens have been reported repeatedly and from many countries (Fitzsimons, 1944; Goldzieher and Goldzieher, 1949; Fisk, 1950; Pagani, 1953; Katzenellenbogen, 1956; Watrous and Olsen, 1959; Kneidel, 1963; Pacynski et al., 1971; Burton and Shmunes, 1973; Willems, 1981; Taskinen et al., 1986). As an occupational hazard, DES has also been known to afflict the children of workers (Budzynska et al., 1967).

Thus, estrogens as a technology celebrated in the marketplace was adopted in professional practices and used for over 50 years on a scale that has made us aware and conscious of them as carcinogens in the environment.

"2 WHAT IS THE CASE— A FACT—IS THE EXISTENCE OF STATES OF AFFAIRS"

It is part of the state of affairs in human society that groups elaborate a set of values or a worldview that they organize around, promote, and defend. An axiom for social scientists is that there is not a group without its interest. An interest is the equivalent of a group. Once a group is formed it is like a molecule—what binds its constituents to each other becomes more important for its subsistence than the single components. Within the group the members' knowledge and values merge. The group's knowledge and values align it with other groups. In this social ordering, knowledge and beliefs make the binding and bonding. It shapes domains of solidarity—just as energy may order molecules into domains where all point in the same direction. In the social bonding, not least in the scientific and professional domains, the competitive and the bonding transactions may lock us into worldviews more tightly than we like to know.

The history of the carcinogenic impact of estrogens on humans provides several examples of how our social bonding makes for states of affairs that affect our perception of reality. Here, the risk evaluation of DES given to pregnant women will be used to illustrate how our social conditioning serves as a cognitive filter on what we see.

It is now well established that DES and related substances are carcinogenic in both animals and humans. As mentioned, already on the basis of the early animal experiments with these substances the researchers warned that one

characteristic of the new compounds was their estrogenic and carcinogenic properties. Later we have come to understand that if they are given to a pregnant woman or animal they may trigger a biological response through two generations and even more than two if both carcinogenic and noncarcinogenic effects are taken into account.

In many countries around the world DES was given for decades to pregnant women to prevent spontaneous abortion and to ensure that bigger bouncier babies would be born (Smith et al., 1946; Direcks et al., 1991). The practice was in 1971 linked to the development of vaginal and cervical clear cell adenocarcinoma among the daughters born to the women who were given DES (Herbst et al., 1971). Many subsequent studies have since then verified that the cells in the fetus are at risk when a pregnant woman is given DES. DES is recognized as a transplacental carcinogen (IARC, 1987) and also as a teratogen (Kaufman et al., 1984; Herbst et al., 1981; Linn et al., 1988). Not only do 1 in 1,000 young women exposed to DES in utero run the risk of developing vaginal or cervical clear cell carcinoma (CCAC) (Melnick et al., 1987), but when many of those exposed to DES in utero reach the age when they themselves want to get pregnant and bear children, they may suffer primary infertility (Herbst et al., 1981). Moreover, these women are 2.7 times as likely as other women to have a pregnancy outcome other than a full-term, live birth (Swan, 1992). Sons exposed to DES in utero have been observed to have an elevated risk of testicular cancer (IARC, 1987), and the women who received DES when they were pregnant are at increased risk of developing breast cancer (IARC, 1987). Among other harmful effects of DES exposure in utero are neurological impacts (Vessey et al., 1983).

The image of DES as an environmental assault on a group of human beings when they are especially vulnerable and in need of care easily presents itself. Indeed, the assault was conscious, in the form of a technology applied for care, a technology application guided by medical *placebo*: I will please. Doctors wishing to save patients from spontaneous abortion responded to women's pleas for help. It is tragic that the means that the physicians resorted to had the effects of *nocebo*: I will harm. The exposure to DES as pregnancy medication occurred again and again in a social setting, where one characteristic is the asymmetry in knowledge, power, and decision-making ability between a prescribing physician approached by a patient. Asymmetry in knowledge and power seems to be a characteristic of many of the social situations in which humans are exposed to environmental carcinogens. It also seems to be part of the social attention to risk.

The social dimensions of the carcinogenicity of DES as pregnancy medication can be further illustrated by the fact that the exposed women in the United States—not in countries where medical services are freely available to anyone—primarily belonged to the middle- and upper-class strata of society (Apfel and Fisher, 1984; 25); expectant U.S. mothers among the lower socio-economic groups received little or no prenatal care in the 1950s and 1960s (Jacobson and Reid, 1964). In the United States it was also mainly women

from upper- and middle-class strata, active in the women's health and consumers' advocacy movements, who raised and kept the risks of DES and estrogen medication as an issue on the agenda of national politics.

DES medication for pregnant women has become an emblem for the carcinogenicity associated with estrogens in the environment. DES was celebrated as beneficial for pregnancy maintenance by authorities in medical teaching in many countries, in the United States by George Van Siclen Smith, an obstetrician/gynecologist at the Harvard Medical School-affiliated Boston Lying-In Hospital in which his wife Olive W. Smith was a biochemist in the Fearing Laboratory (Smith et al., 1946); in the Netherlands by Professor Dr. W.P. Plate (Plate, 1954), the Dutch Queen's gynecologist; and in other countries by other authorities in obstetrics and gynecology. Their belief in the beneficial potentials of estrogens for pregnant women and of DES in particular was strong.

It is sad that, in retrospect, the cancer effects from DES as pregnancy medication were utterly unnecessary and could have been avoided. Not only was DES a suspected carcinogen from very early in the history of its manufacture and use, but the giving of DES to pregnant women was also based on two controversial, flawed scientific theories: one concerning the function of estrogens during pregnancy and the other concerning the causes of "habitual" spontaneous abortion. The supporters of these theories recommended that massive doses of estrogens given during early and mid-pregnancy would forestall abortions (Karnaky, 1942; Smith et al., 1946; Smith, 1948). The assumption that deficiencies in the mother's secretion of hormones harmed the fetus was criticized as changes in hormone levels during pregnancy were shown to be a consequence rather than the cause of fetal suffering and when critics could not observe the purported effects of DES (Davis and Fugo, 1948; Somerville et al., 1949; Llusià, 1957). The value of DES may have been as a placebo only (Stallworthy, 1959; Jacobson and Reid, 1964).

Early in the history of DES use in pregnancy maintenance DES was shown to be ineffective by W.J. Dieckmann and collaborators (1953) at the University of Chicago in an epidemiological study conducted with a rigor that was unusual at the time. Dieckmann and his team had hesitated to draw the conclusions that their data actually led them to: that DES given to pregnant women actually raised the risk of spontaneous abortion, neonatal death of the fetus, and premature birth (Brackbill and Berendes, 1978). One can only speculate over the social climate surrounding this early critical study and those observations made by others who went against the wind. It is interesting to observe how, at the meeting of obstetricians and gynecologists when Dieckmann and collaborators presented their results, one voice in the audience expressed social allegiance as a reason for believing in the benefits of DES given to pregnant women: "As a former Bostonian I would be entirely lacking in civic loyalty if I had not used stilbestrol in my private office . . ." (discussion in Dieckmann et al., 1953; 1080).

Most of the investigations of the carcinogenicity of DES have been conducted with stringent scientific discipline in order to pin down a causal relationship between the environmental factor DES and cell changes. In the first epidemiological study of the association between DES given to pregnant women and the development of vaginal and cervical clear cell adenocarcinoma in some of these women's daughters, Herbst et al. (1971) meticulously reconstructed the prenatal history of the young women with cancer and closely matched controls. In the process they also imposed restrictions on the causal chain—medication with DES, tablet form, 25 mg dosage, verification of the prescription by control of medical records—in order to make the proposition that transplacental carcinogenesis was possible. These restrictions, so necessary in a scientific reconstruction of a causal relationship, have come to function as a cognitive boundary that maybe has excluded the perception of other possible causes of *in utero* exposure to DES: exposure by injections, implants, suppositories, ointments, and so forth, in medical practice (Palmlund, work in progress), exposure via the food chain because of the use of DES as growth promotant in slaughter animals, direct or indirect occupational exposure, or exposure via cosmetics, skin creams, skin lotions, hair shampoo, and hair tonic with DES (Anonymous, 1938; Nemecskay and Korpasy, 1953; Etienne-Martin et al., 1954; Stoppelman and van Valkenburg, 1955). Is it the case that these forms of assaults on cells from environment may have taken place in pregnant women as they have in some other individuals according to the reports in the medical literature? Is it the case that they may have been the cause of some of the incidences of vaginal and cervical clear cell adenocarcinoma that cannot be accounted for in the epidemiological studies of the effects of DES as medication for pregnant women? We will probably never know. We see what the spotlight captures before our eyes. The ascetic limitations necessary in scientific work bind our vision. As recent reports again highlight links between estrogen exposure *in utero* and tumor development (Ekbom et al., 1991; Hsieh et al., 1992), we may want to reflect on how we impose cognitive boundaries around our thinking regarding the relations between cell and environment.

The only thing we can know with certainty is the existence of some states of affairs: pharmaceutical manufacturers producing an array of products containing DES and related substances and promoting them for a variety of purposes; scientists investigating the effects of DES in animals; physicians prescribing DES to patients; physicians observing patients with cancer and malformations of the reproductive organs; physicians and scientists investigating the possible causes of these biological anomalies; and patients organizing to protect their interests in preventing further damage and recuperating some compensation for harm. The experience of the carcinogenicity of DES as pregnancy medication has also showed us that physicians respond to iatrogenic tumors with little overt guilt or self-blame. In countries where DES was in common use as a pregnancy medication, relatively few physicians spontaneously contacted patients to find out if the medication they had

prescribed had caused cancer (Nash et al., 1983; Apfel and Fisher, 1984; 107–125); some patients were, in effect, refused access to their medical records (Palmlund, work in progress). Thus, repression and denial also form the picture of hormonal carcinogenesis.

"4.06 A PROPOSITION CAN BE TRUE OR FALSE ONLY IN VIRTUE OF BEING A PICTURE OF REALITY"

Then, what is the truth? The French sociologist Pierre Bourdieu in a major study of *Homo academicus* stresses how, in scientific work, there is competition about the right way to define reality as well as an ever ongoing labor to find intellectual unity, a *communis doctorum opinio*, a common learned opinion "that imposes itself with more strength the more uncertain the proper scientific coherence and the greater the social responsibility of the corps of investigators" (Bourdieu, 1984; 91). Thomas Kuhn describes the same phenomenon in terms of an ongoing formation of paradigms of knowledge, patterns of shared views that are formed by the scientific community concerning how a problem should be defined and the proper methods to investigate it (Kuhn, 1970).

In the history of the evaluation of the risks of cancer originating in exposure to hormones, one cannot avoid seeing a competition in the many propositions that claim that a specific picture of reality is true and, consequently, that others are false. A review of all the entries regarding estrogens in *JAMA* during 50 years, from 1938 to 1987, revealed a dialectical pattern that seemed as two paradigms competing over time, as if the effects of estrogens were part of bullish or bearish business trends (Palmlund, 1990; 384–403, 1991). All the entries were classified after the dominant message regarding the benefits and the risks of estrogens that they expressed: promotional (that is, more or less strongly advising doctors to use estrogen medication in the treatment of this or that symptom or disease), neutral (that is, saying "on the one hand . . . , on the other hand"), or focusing risk (that is, warning of the risks based either on intuition and general experience or on observations of harmful effects). It was striking that in these data, viewed as a variable over time, the neutral tone never dominated. It appeared as if, at least as far as the presentation in *JAMA* of the effects of estrogens are concerned, there are many one-armed scientists in the biomedical field. The presentations in *JAMA* through these 50 years contained two steady, "classic" issues of contention: the benefits and risks of estrogen replacement therapy for women over 40 and the benefits and risks of oral contraceptives.

During the first period, 1938 to about 1962, the tone was bullish: Entries with a promotional tone were in a majority. The development of hormonal pharmaceutical products seemed to be regarded as part of humanity's great stride of technological progress that aimed at conquering the universe.

In the early 1960s a bearish phase commenced. The tragic experience of

how a drug given to pregnant women, thalidomide, had provoked malformations among the babies exposed in utero to it drew medical and popular attention throughout the Western world to the risks of medication. During the 1960s and 1970s the entries on risks dominated numerically in the presentations of the effects of estrogens. The bad news regarding harmful effects of oral contraceptives kept dropping in: After the news of elevated risks of blood clotting and stroke (Platt et al., 1967) came reports of elevated risks of cancer in different organs based on observations in humans (Melamed et al., 1969; Arthes et al., 1971; Baum et al., 1973; Boston Collaborative Drug Surveillance Program, 1973; Vessey et al., 1975; Fasal and Paffenbarger, 1975). In the literature one can see how several of these claims were met with resistance when publication first was attempted and how they incited counterclaims. Scientists involved in cancer research were pointing to the risks of harmful effects of oral contraceptives (Hertz and Bailar, 1966; Hertz, 1969), but other voices claimed that animals were different from humans and that analogies should not be drawn. In 1971 the linking of vaginal and cervical cancer among young women to DES given as a pregnancy drug to their mothers (Herbst et al., 1971) reminded both the medical community and the general public of the thalidomide tragedies. Three epidemiological studies relating elevated risks of endometrial cancer to estrogen use were fuel on the fire (Smith et al., 1975; Ziel and Finkle, 1975; Mack et al., 1976).

Those who warned of the risks did so in opposition to the forceful promotion of hormone products, sometimes at their own peril. The fate of whistleblowers is that of the messenger carrying the bad news, evoking a collective instinct, as it were, to kill—symbolically in our times—the messenger because the news runs counter to what the listener wishes to hear. The safeguards for whistleblowers in the biomedical field are notoriously weak (Swazey and Scher, 1981; Nelkin, 1984), a strong indication of the importance of the social loyalties in the scientific work in the field.

The risks of hormone drugs became a theme year after year in U.S. Congressional hearings during the 1970s, not least in response to people's fear of the cancer risks, and restrictions for the marketing of estrogens were demanded. There were social reactions also to the overblown promotion of estrogen drugs for women in and after menopause. In the history of the risks of estrogens as a political issue in the United States it can be seen time and again how a sequential pattern of reactions to the marketing of estrogens emerges: first one or several scientific reports announcing that estrogens increase the risk of a particular type of disease, often a specific type of cancer; then political action by consumers' and women's advocates; then scheduled hearings in Congress; and finally a regulation issued by the FDA, placing restrictions on the labeling of estrogen drugs and requiring that drug companies supply information about harmful effects as well as about benefits. The emergence of a women's liberation movement formed in opposition to male repression, partly in reaction to the symbolic violence in unwarranted medication for purported deficiencies in women's bodies, established, for a time, a boundary for the promotion of this type of hormone medication.

Safeguards for estrogen consumers were introduced during the 1970s in the form of mandatory package inserts both for estrogen drugs and for oral contraceptives, in order to enable consumers to read about what was known about adverse effects. For a while, in the mid-1970s, the sales of estrogen drugs fell, but they picked up again after some years (Morris, 1980). As long as the cancer risks of hormone drugs was a theme year after year in U.S. Congressional hearings during the 1970s, protection against these risks remained a matter on the agenda of national politics.

In *JAMA* the attention to the risks of estrogens stayed strong through the 1970s into the early 1980s, when a new bullish phase seems to begin. After 1983 the promotional tone again dominates in the entries on estrogens in the journal. One can only speculate over the relationship between the presentations of benefits and risks of estrogens and the shift in the political climate in the United States that was heralded by the election of President Reagan. The control of pharmaceuticals was one of the first targets for the deregulation policies of the new regime, as the Food and Drug Administration was ordered first informally and then formally to support the pharmaceutical industry in getting new drugs on the market rather than demanding detailed data from animal experiments and clinical trials (Claybrook et al., 1984; 51–53; U.S. DHHS, 1985). Regulations that required improved information to be given to patients regarding prescription drugs that had been instituted shortly before were quickly revoked (U.S. DHHS, 1982). Research funds regarding the carcinogenicity of certain hormones dried up. Consumer advocates have characterized the era as one of a “retreat from safety” (Claybrook et al., 1984).

The early 1980s was also a time when a new discourse began, aiming at discounting previous reports on the carcinogenicity of estrogens. There was a subtle shift in focus: Instead of investigating environmental factors that might be carcinogenic, many researchers turned their gaze to the bodies of the victims and their way of life (Efron, 1984; Ames et al., 1987). The rising incidence of breast cancer in the Western world was attributed to the fatty diets of the cancer-stricken women. Findings from a large prospective study that indicated that fatty diets had nothing to do with cancer risks largely were ignored for reasons that the researchers interpreted as “perhaps it swam against the ‘medically politically correct view’” (Marshall, 1993; 620). The blame-the-victim strategy was manifested also in the domain of the carcinogenic effects of estrogen medication for pregnant women; a new group of medical scientists argued that the elevated risks of cancer among those exposed to DES in utero originated in the cancer-stricken women’s bodies rather than in their prenatal exposure to DES. That rejection of the evidence from many different, rigorously controlled studies called forth an immediate rebuttal by several of those who had actively contributed to collecting the evidence on the transplacental carcinogenesis of DES (McFarlane et al., 1986, with subsequent correspondence to the editor from Bern et al., Swan, and Herbst).

The competition over the “true” picture of reality of estrogen-induced

breast cancer is particularly striking. A listing of the epidemiological studies of the relationship between oral contraceptives and breast cancer registered in the database Cancerlit from 1980 to 1987 yielded 43 references to mostly retrospective studies. The conclusions in the listed references and abstracts regarding relative risks and benefits were classified according to a scale from +3 (= safe; relative risk [if given], >1; strong statement of safety in continued use) through 0 (= no evaluation of hazard or safety in the reference or abstract) to -3 (= hazardous; relative risk [if given], >1; strong statement of hazard). In this material there were more positive signals that estrogens are not hazardous and may even protect patients against breast cancer than there were negative signals that estrogens might induce breast cancer. Of the 43 studies, 22 had a positive statement of benefits; among those 9 fell into the +3 category. Of all 43 references, 6 had no clear statement of benefit or hazard. In 15 of the listed studies the reference or abstract contained a statement of hazard; only two of these fell into the -3 category (Palmlund, 1990; 398–403). The outcome of that ministudy raises many questions about the engineered filtering of scientific knowledge as well as the cognitive patterns among both producers and consumers of epidemiological evidence. It reveals how the celebration of oral contraceptives as a socially desirable technology is opposed by concerns for its socially damaging effects. Many of these epidemiological studies were not only descriptive, but prescriptive. Some of them were truer pictures of reality than others. The dialogue in the medical field over the retrospective epidemiological evidence on the carcinogenicity of estrogens can be interpreted as a manifestation of the eternal battle over the control of history writing, conducted in the medical context with extreme sophistication.

It is also a battle over future markets. During the 1980s and into the 1990s the promotion of hormone drugs for women over 40 has again gained strength as the baby boom generation of women, well-trained consumers, many of them with incomes of their own, edged into the age when women's endogenous estrogen production decreases. The sales promotion began again to have not only prescribing physicians as a target group but also presumptive consumers. The argumentation regarding the benefits of estrogens seemed to sweep away, out of sight for potential consumers, all knowledge of risks.

“5.6 THE LIMITS OF MY LANGUAGE MEAN THE LIMITS OF MY WORLD”

The economic forces in the market in the form of the successful pharmaceutical industry and prescribing physicians are part of the nonbiological causes of cancer induced by exogenous hormones. Among those women and men who developed hormone-induced cancer, in how many cases were the economic reasons stronger than the biological ones for their hormone consumption? We will never know, because this is not a subject for conventional

scientific study. What we do know, however, is that some groups of women may by now have been exposed to hormone medication at several stages of their lives: in utero, by hormone drugs taken for contraceptive purposes, and by hormones taken as estrogen replacement therapy during and after menopause.

The increase in cancer disease and cancer deaths to some extent has to do with the aging of populations. In the Western world, persons who previously would have died at a younger age from other causes now live to an age where tumors start developing in their bodies. But the assaults on human bodies from the environment have also changed. During the last 50 years we have increased the anthropogenic assaults on the human organism immensely by adopting a wide range of known and new chemicals in use on a scale that humanity has never before experienced. There is already sufficient evidence that the use of hormones in medication and in other ways has added to the potential of abnormal cell development that we carry in our genes. It is perhaps too early to know what changes the increased exposure to chemicals will trigger in the biological evolution of the human species. The increased rates of cancer disease may be one indicator. Another may be the increased sensitivity to chemicals that is manifested in the increase of allergy type symptoms and neurological change (Ashford and Miller, 1991). Is it unreasonable to assume that the added chemical sensitivity also means a decreased ability to resist hormonal assaults from the environment?

The aim of scientific work is to formulate propositions about the nature of reality. Then, how true or false are the pictures of reality that we produce in social interactions, trade in social transactions, and reproduce in teaching? If we all lived in separate ivory towers, the relationships between scientific propositions and reality would hardly matter—but when hypotheses, beliefs, and scientific propositions are used to legitimate social practices where people are placed at risk, the test against reality is not a harmless experiment.

The cancer risks of estrogen use are in a way a matter of knowledge. Before they were shown to exist, they could be disregarded in the literal sense of the word. In communities where they are not known, they are not heeded. Although in countries such as the United States high estrogen dosage oral contraceptives were withdrawn early from the market because of risks, they continued to be marketed, for a time, in other countries. Although the links between DES as pregnancy medication and cancer in the offspring of women who took it during pregnancy led to restrictions in the United States in 1971, the use continued longer in other countries. In fact, as late as in the mid-1980s DES was used as pregnancy medication in many Third World countries (Dirrecks and 't Hoen, 1986). Single reports revealed its use in countries as far apart as Uganda, Mexico, and Poland in the early 1990s.

The discourses over how hormones affect human cells is conducted in social settings that have a bearing on their contents. As Wittgenstein said: “*The riddle does not exist. If a question can be framed at all, it is also possible to answer it.*” (Wittgenstein, *Tractatus* 6.5). The methodological

tools, the logic, the empirical material, and the language—all the necessities are available for those who want to create and present to the world as true a picture as possible of how hormones in the human environment affect the cells in the human body. Their answers are important for those who want to create a safe life for us living and for the generations to come.

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