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# About the Phenomenon of Iatrogenic Endocrine Disruption in the Female Pig's Reproductive Endocrine System

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**Abstract**

Endocrine disruptors have been present in our environment since the tide of stable, man-made chemicals of the Industrial Age arose. As it has turned out, one of the medicaments used in my studies, diethylstilboestrol (DES), is also a very potent endocrine disruptor.

These field trials took place a long time ago, in the 1960s, when the use of this kind of treatment was still authorized in the veterinary medical practice in order to hormonally castrate fattening female pigs instead of the traditional surgical intervention. Diethylstilboestrol (DES) was then suggested to be administered to pigs for this purpose. However, now DES must not be administered to food animals at all. The result of the hormonal treatment of pigs was then believed to be a consequence of a negative feedback reaction. Nevertheless, thorough investigations found that the induced reaction was not a negative, but on the contrary, a positive feedback reaction. In the meantime it came to light that the medicament DES itself is a most potent endocrine disruptor. Later it became clear that this positive feedback reaction could be regarded as the manifestation of the significant protective effect of the corpus luteum function, the organism's own, natural shield aimed at preventing certain disrupting factors. This seems to be a promising domain worthy of doing research on.

**Keywords:** Ovary; Corpora lutea; Progesterone; Gonadotropin; Pig

## Abbreviations

DES: Diethylstilbestrol; GnRH: Gonadotropin Releasing Hormone; hCG: Human Chorionic Gonadotropin Hormone; IU: International Unit

## Introduction

In the 1950s an international ambition emerged in the veterinary medical practice in order to initiate the hormonal sterilisation of fattening female pigs, instead of the traditional surgical intervention. Diethylstilboestrol (DES) injection in a dose of 0.5mg/kg body weight was suggested to be administered to pigs for this purpose [1,2].

DES was at that time known as a strong non-steroidal oestrogenic chemical. It was extensively used both in the human and the veterinary medical practice. In human medicine, about 5 million pregnant women were exposed to DES therapy in the mistaken belief that it prevented miscarriage. Although initially no harmful effects appeared, later the exposure was linked to a rare form of vaginal cancer in the female offspring of mothers taking DES. Some sons of mothers who had been given DES were also reported to have epididymal cysts, microphallus, cryptorchidism, or testicular hypoplasia [20].

In the veterinary practice, DES was utilized first of all for the hormonal sterilisation of female pigs and in other fields of reproductive endocrinology. The result of the hormonal treatment of pigs was then believed to be a consequence of a negative feedback reaction. However, thorough investigations [10,11] revealed that the induced reaction was not a negative, but rather a positive feedback reaction (Figure 1). Later it became clear that this positive feedback reaction could be regarded as a manifestation of the protective effect of the reproductive endocrine system [10].

In the meantime it came to light that the medicament DES that had been used for hormonal castration of female pigs is a most potent endocrine disruptor [20]. The concepts of endocrine disruption and endocrine disruptors had been completely unknown earlier.

As regards the phenomenon of endocrine disruption, today we know that endocrine disruptor chemicals mostly act as mimetics to natural hormones [20]. Besides, some of them can antagonise the action or modify the synthesis, metabolism and transport of the endogenous hormones, producing a range of diseases both in humans and in animals alike [20].

Seeing the different mistakable elements and the uncertainty of interpretation, I decided to check up the arising problems and started the experiments described below.

## Materials and Methods

The relevant experiments were conducted from 1962 to 1974 and had been approved by the direction of the Veterinary Medical Station of Békéscsaba, Hungary. The experiments involved a total of 341 gilts. After the period of practical examinations the working up of the subject was continued to date. Hungarian white, meat-type or crossbred, 6-8 months old gilts were used in the experiments. The medicines used




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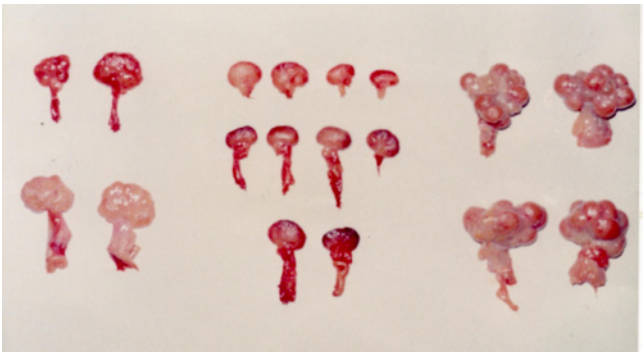

**Figure 1:** Images of the ovaries that can serve as a model of endocrine disruption.
**Left:** Ovaries of untreated gilts.
**Middle:** Follicular depression evoked by the treatment as a consequence of endocrine disruption, namely a negative feedback reaction.
**Right:** Luteal phase, namely a positive feedback reaction occurring as a consequence of the prevention of endocrine disruption.

were Syntestrin forte injection ad usum veterinarium (that contained 10mg DES per ml), and Choriogonin injection containing 1,500 international units (IU) of human chorionic gonadotropin (hCG) hormone in ampoules. Both products were manufactured by Gedeon Richter Chemical Works Co. Ltd., Budapest, Hungary. Each pig received 0.5mg/kg DES and 1,500 IU (or over 90kg body weight 3,000 IU) hCG parenterally. The type of the feedback reaction elicited was determined by inspection of the genital organs, first of all the ovaries. This became possible either simultaneously with castration or at the time of slaughtering the animals.

## Results

The ovarian signs of the positive and negative feedback reactions were demonstrative and spectacular (Figure 1). In the case of the positive feedback reaction the ovaries were large (30–45 mm in diameter) with 5-14 well-developed corpora lutea. In this particular case the intensive progesterone activity in consequence of a dominant corpus luteum phase resulted in a strong protective effect.

In contrast, in the case of the negative feedback reaction the ovaries were small (10-15 mm in diameter), did not contain any follicle or corpus luteum, and their smooth surface showed signs of strong follicular depression. In this case, the signs of the negative feedback reaction seemed to be those of endocrine disruption.

I did these experiments preferably in groups of 10-25 pigs in one pack, and the data can be found in the references [10,11].

## Discussion

Let us now follow the possible physiological events with attention and try to interpret them.

The disruptor finds the receptors in the ovaries and tries to bring about follicular depression. This works if there is no particular protection. However, if any suitable hormone (e.g. hCG or GnRH) is available, the reproductive endocrine system is able to defend itself through the protective effect of progesterone. The active corpora lutea intensively produce the necessary progesterone.

## Conclusion

Based on the results of my experiments I was led to the conclusion that the intensive corpus luteum activity can bring about a significant protective effect via the produced progesterone hormone in order to prevent endocrine disruption. These results can serve as a model for the phenomenon of endocrine disruption, at least in the case of ovarian function (Figure 1).

I wanted to get answers to the following questions:

Can the noxious results of endocrine disruption be prevented by the protective effect of progesterone? The answer is: Yes.

Can the ensuing results of endocrine disruption be transformed into useful vital processes by the aid of the effect of progesterone? The answer is: Yes, if there are still living follicles on the ovaries.

What happens if endocrine disruption coincides with the animal's relevant reproductive endocrine function(s)? The result can equally be synergy, antagonism, or indifference. Further experiments are necessary.

What about the extension of the protective effect of progesterone? Does it cover the embryos only and (some of) the sexual organs, or does it extend to other domains of the organism as well? Further experiments are required.

Again, here we can see the organism's own, natural shielding aimed at preventing certain disrupting factors. This seems to be a promising domain worthy of doing research work on.

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