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Case Study: A Human Pre-Natal Experiment in 1944—"Do No Harm"

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Abstract

Iris du Pré, a professional pianist, wanted a second child, did not conceive quickly and was injected in 1944 by a doctor in Oxford with pregnant mare serum gonadotropin (PMSG). The doctor joked "This child will be a racehorse winner!" In January 1945, Jacqueline du Pré, the remarkable, world-famous cellist was born. In the 1920's and 1930's, animal experimentation and clinical studies had shown that pituitary glycoproteins stimulated the ovary (follicle-stimulating hormone, FSH) and the corpus luteum (luteal-stimulating hormone, LH) which prepared the human womb for embedding a fertilized ovum and that pregnant mare's blood and urine contained the glycoprotein, PMSG whose origin was placental cells, but surprisingly in humans had the actions of both FSH and LH. However, the PMSG serum alone did not bring about pregnancy. The doctor did not know that without subsequent injection of another factor in correct sequence and timing, PMSG was pointless. In 1947, a placental glycoprotein, found in the 1920's in urine of pregnant women (human chorionic gonadotropin, hCG), when injected in mice subsequent to PMSG, achieved ovulation but not pregnancy. Human application of those findings was extremely risky due to impurities (up to 95%). The Federal Drug Administration (FDA), established in 1938, requested easily bye-passed marketing safety. Companies offered material "sufficiently" purified; professional bodies negated clinical use, tempting to a few. Evidence also suggests that, to sustain pregnancy the doctor also prescribed the new "eostrogen", diethyl stilbestrol (DES) of negative fame. In 1947, the Nuremberg Code of ethics demanded human experiments by qualified personnel and trials preceded by adequate animal studies. It is not the case here. From five, du Pré had a most exceptional musical memory, almost obsessive musicality and a very difficult school-time socially. Later history: adult masculine build, awkward gait, tendency to recurrent depressions from mid-adolescence, unbalanced thyroidal metabolism, symptoms of numbness in late teens, long breaks for rest from age 25, MS diagnosis at 28 when unable to play, death aged 42. Yet at sixteen and after, she astounded all with technique, passion and unique musical interpretation. Her husband, an out-

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standing musician: "She had a capacity to imagine sound such as I never met in any other musician". A close musician colleague: "… it was done before she was born"; perhaps much closer to the truth than realization, for her history it may suggest a fetal neurodevelopment abused in the womb.

Keywords

Human Infertility, Pregnant Mare Serum Gonadotropin, Fetal Neurodevelopment, Multiple Sclerosis, Jacqueline du Pré, "Do No Harm"

1. Introduction

By the 1930's, animal experimentation and clinical studies had ascertained that two glycoprotein pituitary factors, follicle stimulating hormone (FSH) and luteinising hormone (LH), stimulated development and maturation of the ovary, ovulation and the development of the corpus luteum which prepared the womb's surface to embed and sustain a fertilized ovum [1]. During the 1930's, it was found that pregnant mare's blood and urine contained a glycoprotein known now as equine chorionic gonadotropin, as its source was found later to be in certain placental cells [2]. However, though in equids its action was only LH-like, in other animals and in humans, it demonstrated both FSH and LH-like actions [3]. The extract from mare's blood used for animal and human fertility studies (pregnant mare's serum gonadotropin, PMSG), did not alone bring about pregnancy [4] [5]. In the 1920's, urine of a pregnant woman was found to contain another glycoprotein, also later found to be produced by placental tissue: human chorionic gonadotropin (hCG) [1] [2]. In 1947, sequential treatment of mice with chorionic gonadotropin closely after treatment with PMSG, achieved ovulation and coitus [6] but also, not pregnancy.

2. Safety First?

An Educational Bulletin of the Practice Committee of the American Society for Reproductive Medicine in 2008 stated: "The consistent driving force ... [behind the development of gonadotropin products for treatment of infertility] ... was that they must be safe and effective. Gonadotropin treatment for induction of ovulation in anovulatory women began in the 1960's ..." [2]. If the intention in 2008 was to assure potential patients that all had been well in the State of Denmark, already in the Sixties and that this would be true also for their own treatment, this was inaccurate, to say the least. Alleviating some consciences could be nearer the mark. Attempts at gonadotropin treatment for human infertility started in the Thirties even though this was very risky, frowned on by professional bodies and rarely hinted at in reports [5] [7] [8]. Indeed, "These early discoveries .... tempted many scientists to seek gonadotrophic extracts with sufficient purity .... [for] treatment of infertile patients' with insufficient gonadotropin [1]". "Tempted" reveals how "sufficient" was purity.

Pharmaceutical companies such as IG Farben provided so-called "purified" extracts from the early Thirties. In the Forties, gonadotropic extracts were called "purified" when containing 95% of protein impurities; in the Sixties, even with advanced electrophoretic and chromatographic techniques available, impurity was still 80%. Even now with recombinant technology, purity cannot be guaranteed, is stated to be at least 95%, so regarded as relatively safe. However, a very minor "foreigner" can precipitate a major immunity or other problem.

2.1. Regulation?

The Federal Drug Administration (FDA) was only established in 1938. Though it required that drugs be shown to be safe before marketing, it was restricted in its restriction, poorly policed, easily bye-passed, including by not a few who had taken the Oath: "Do no harm". Progress in the jungle was very slow. A League of Nations declaration in 1938 on experimenting on humans, was not always followed in respect of fertility problems. Levels of protection in general in medicine for human subjects, have often only risen in response to major abuses. Some German atrocities of World War II were intended "for science"and in response, the 1947 Nuremberg Code [9] of medical ethics demanded that experiments be scientifically necessary, conducted by qualified personnel and human trials be preceded by animal studies—a cry lost in the wind (as the thalidomide tragedy struck in 1961, leading to strengthening of FDA oversight).

Remarkably, the Bulletin above and many other reports avoided mention of some early clinical activity concerning human infertility that was questionable. Though a potential mother could agree to risky action without informed consent, on emergence of a major problem, pregnancy could be terminated; or if a minor allergy ensued, it could be treated. The Nuremberg Code stated that an experiment should be discontinued immediately if it is "likely to result in injury, disability, or death to the experimental subject". However, in the world of human infertility treatment, the final product was not heard, till born-and when eventually heard, it could be too late.

2.2. The Case

2.2.1. This Child Will Be a Racehorse Winner!

Maud Greep was the mother of Iris du Pré, her only child. Another offspring was born weak and died. A further pregnancy ended in miscarriage. After that, Maud avoided further birth and put all her ambition into Iris who became a talented pianist, playing in music clubs and on the radio. She also taught piano. Married to Derek, she bore a daughter, Hilary in late April 1942. Over fifty years later, a strange story emerged. Hilary wrote in 1997 [10] when her mother was already deceased, that the latter had been unable to conceive a second child so took medical advice. Perhaps she feared the difficulties experienced by her own mother, Maud. However, barely two years after the birth of Hilary, being very ambitious Iris seemed to want children quickly and return to her career. At that time, she lived in Oxford where her husband, Derek a wartime enlistment was seconded by the army to teach at a College of the University. Research was in the University air and perhaps Derek made a suitable contact. Hilary's report was that a doctor had prescribed pregnant mare's serum [10]. Hilary probably heard this from her mother when she herself was pregnant. The doctor is said to have joked "This child will be a racehorse winner!".

2.2.2. The Experiment

By then, injections of PMSG were iv. Even in 2004, a respected, highly experienced researcher still found it necessary to ask "... is it medically prudent and ethically admissible to use preparations derived from urine of untraceable donor source, contaminated with extraneous proteins?" [1]. Did the doctor in 1944 ask himself in relation to PMSG-and also of hCG, if given by him-whether the treatment was necessary? Was the health of his patient his first consideration? Was he concerned also with the fetal outcome of his action? In 1964 the FDA demanded special care, in informed consent of minors. The needs of human fetuses were not mentioned, as supposedly completely excluded from human experimentation. Most tellingly, was the doctor a qualified person under the Nuremberg Code [9] (or did that only apply to alleged war criminals)? If so, he surely would have known in 1944 that the injections were pointless if not followed by injection of hCG at the right time post-PMSG, and if he did also give hCG, that the danger from impurities would be doubled. Presumably he did not know, so was not qualified

That the PMSG injections were indeed given to Iris, is confirmed by a separate, independent report that the mother of a friend of Iris's was told by Iris that to get pregnant she was getting injections from a pregnant mare [11]. Iris did not become pregnant due to the doctor's injections; they were given in vain. The first mammalian pregnancy to produce offspring was actually in a mouse in 1957, by a protocol developed over years by Fowler and Edwards [12] (the latter notable for the first IVF birth). Hilary also incorrectly reported in 1997 that the serum was "a form of oestrogen" [10]. To prevent possible miscarriage-a reminder from her mother Maud's bad experiences, when Iris became at last pregnant again, she quite likely received further help from the "up-to-date" doctor: a daily "form of oestrogen", diethyl stilbestrol DES (of later disrepute [13]). By 1944 this was the very cheap "latest thing" for sustaining pregnancy; a substitute for very expensive oestrogen extracted from urine. Reporting over thirty years after she heard about the "oestrogen" help, Hilary seems to have mixed up the injections of mare's serum with the DES.

2.2.3. A Miracle of Music and a Potential Disaster

Iris's second child, Jacqueline Mary du Pré, was born in an apparently normal order of events, on 26th of January, 1945, but was extraordinary. A child prodigy from five years old, she became one of the best and most loved cellists of all time. Between 1961 and 1973 in London at only sixteen and then globally, in a meteoric career she astounded the public and her profession with a musicality, technique, passion and charisma that exhibited an absolute commitment to music and a unique, personal gift for interpretation [14] [15]. However, from

early in adolescence she experienced bouts of depression and self-doubt, that was relieved in 1967 by a marriage apparently made in a musical Heaven to the Jewish pianist/conductor, Daniel Barenboim. That and accompanying conversion to Judaism shocked her narrow-minded, pious and problematic provincial family. This disturbed her deeply. Four years generally of happiness, were followed by three years of serious depressions, declining health, and an abrupt end to her career when diagnosed with multiple sclerosis (MS) in 1973 at age 28. For years after, she taught cello from a chair, before bad years and a tortured death in 1987, aged 42.

2.2.4. Like Non Other

A very close friend in her peak musical years said, “Jacqueline du Pré was a creature like non other ... there is no frame of reference ... musically, cellistically, as a personality ... you can’t compare her to anyone” [16]. A colleague regularly playing with du Pré has stated about the ability and musicality which made her immediately ready at any moment, without hesitation to play any music asked of her, that she could not be categorized: “Already it was done; ... I think it was done before she was born” [17]. He may have been closer to the truth than he realized. From early childhood, an exceptional combination of characteristics, anatomic, behavioral, neurological, metabolic, emotional, intellectual and musical distinguished du Pré from all in her family. In adulthood, she was 1.80 meters tall, broad and well built. Her gait was awkward; Hilary thought it unfeminine. Of her square, strong face and attractive but decidedly masculine features, her first flat mate [18] said “If you think of beauty in conventional terms, Jackie should have been a boy”, but she also noted du Pré’s “very mature soul... [and] ... deeply loving, mature and compassionate intellect ...”.

From the age of just five when she heard a cello on the radio and declared she wanted 'to make that sound' [10], she concentrated an obsessive focus on her cello, was utterly immersed in music, and apart from other children. During puberty the instrument was her only real friend and its music her only real language. Though not a delayed speaker, she did not converse, was socially awkward and at school between the ages of 8 - 14, did not make one truly special friend. A classmate [19] cannot “remember her having any special close friend. She seemed not to need anybody. We never really knew her ... we never took her into our lives” [20]. Another said: “I don’t remember ever playing with her during break ... I suspect that she was extremely lonely, that she found it extremely hard to make friends ... schoolmates were simply not up to understanding her most important aspect.” Another girl [21] remarked: “... she wasn’t really there in spirit. Watching her play you ... [knew] ... where she really was. She came alive when she played.”

Between seven and thirteen, du Pré spent much time with the only girl who thought herself a close friend [22]. However, the latter remarked “We never shared our feelings” ... “We couldn’t communicate with her through music, and she couldn’t communicate with words ... a strange creature .... to this day I have no idea who she was-a remarkable and telling conclusion. Generally, in late adolescence du Pré communicated more successfully, but even in adulthood, she could veer suddenly from chatter to a “cut off” mode, or from a long silence into sometimes inappropriate laughter [11]. Though her limits in social know-how have been ascribed to missing ordinary schooling, the descriptions above by adults and children and her exceptional hearing, perfect pitch and remarkable musical memory, suggest a deeper source.

This view is augmented by comments made by Daniel Barenboim, her husband, a pianist/conductor who probably knew her personally better than anyone: “... you felt like a mere mortal faced with somebody who possessed some kind of ethereal dimension”. “[She had an] ... almost physical contact with music”. “[Even as a teenager] she played with incredible intensity ...”. Telling is Barenboim’s comment. “She had a capacity to imagine sound such as I never met in any other musician [23]”. Such comments, like others above, may indeed suggest a unique fetal neurodevelopment. This was unfortunately unbalanced and incorporated eventually devastating pathological elements.

2.3. The Maternal Fetal Immune Environment

2.3.1. Early Protocol and Immunity

The injections of PMSG were given by Iris’s doctor in an unknown, intravenous protocol about the time Iris conceived. The glycoproteins persist in the circulation for up to two to three months [1]. In 1944, knowledge of immunity was very limited, and we do not know if the doctor was aware of two important monographs that had already been independently published in 1942: “Antigonadotrophic substances” [24] and “The antigonadotrophic factor with consideration of the anti-hormone problem” [25]. Both claimed that gonadotrophins from animal

origin produced “anti-hormones”, which decreased ovarian responsiveness in humans. Indeed, the latter monograph mentioned that already in 1930 it was noted during chronic treatment with gonadotrophic hormone the ovary maintained its response for a limited period, at the end of which the response becomes increasingly weaker and finally disappears. They further stated: “Chronic treatment of animals with gonadotrophic hormones evokes ... a new blood substance called an anti-hormone ... capable of inactivating gonadotrophin [s] ... *in vivo* and *in vitro*”. Indeed, in 1956 a hog pituitary hormone precipitated in women an anti-hormone to itself [26]. Thus long before immunological phenomena were recognized, “anti-hormone” to animal gonadotrophins in women were known but the clinical consequences were uncertain. Another issue was worrying.

2.3.2. Genetic and Epigenetic Consequences of “Inert” Additives

The immunological potencies of the different molecular species of gonadotrophins have now been known for well over two decades [27], but how did du Pré’s body behave towards the 95% of other, so-called “inert” proteins injected together with the PMSG? Whether they precipitated negative factors or not, did they interfere with normal neurodevelopment? Could it really be doubted that Iris's fetus was exposed immediately to many severe and possibly harmful challenges? The placenta is now known to be a hormonal organ and at a very early stage for a short period, the placenta and not the mother supplies the fetus with serotonin, a neurotransmitter important in neurodevelopment [28]. What if that mechanism was disturbed ever so slightly by just one of the protein “imports” influencing a genetically controlled pathway, or epigenetically? In some young autists, for example, accelerated maturation of white matter [29], disrupted neural synchronization [30] or dissociations of white matter volume [31] or defects in neurogenesis or neural migration are found [32]. Could such genetic changes, or unspecified environmental damage due to autoimmunity, inflammation or immune dysfunction have challenged also the fetus of du Pré?

What too, if Iris’s fetus was indeed also exposed to DES? What of a possible synergism between DES and a mare’s protein? Small studies after exposure to DES, indicated increased risk of auto-immune diseases or diseases involving impaired immune function in animals and humans, including abnormal natural killer cell activity, T cell-mediated immunity and thymic development [33]. In the first study assessing directly prenatal DES exposure and risk of MS despite limited statistical power due to very rare exposure, there was modest support for a positive association [34].

2.3.3. Thyroxine and the Fetus

Some foreign effects imposed on du Pré’s fetal development may also have had a less dramatic effect than the eventual MS. Circulating thyroxine is balanced by hypothalamic-pituitary-thyroid feedback in the fetus and is important for correct fetal neurodevelopment and growth [35]. Du Pré suffered regular discomfort and inconvenience from wide swings between excess and lack of circulating thyroxine. From childhood she was known to suffer from sudden loss of energy, even on holiday [10], yet was also known at times to suddenly run “like a great big colt” [11]. Though she was comfortable swimming in very cold waters, she perspired exceptionally when playing the cello, even when her movements were minimal, so she had special garments made to absorb the perspiration [11]. However, she also felt an increasing need to warm hands before performances.

3. A Conundrum

The Nature of du Pre’s Decline

Between the age of fifteen and the major blow at twenty-eight, du Pré’s health and personal life ran a topsy-turvy course apart from the early years of marriage which were so euphoric some observers believed it could not last—it didn’t. Beneath the glitter and the glory, starting with what seemed like adolescent depression that would pass, a closer view pointed to deeper issues present from infancy. Did the constant, intense protection and care that Iris afforded her from infancy to the age of fifteen express what, as a mother she instinctively felt early, but learnt of late? Though du Pré had great difficulties in social interaction until adulthood, she found exceptional relief when married, welcomed and integrated emotionally into a very small band of close, like-minded brilliant musicians and their friends who became the only true “home” she had after infancy. However, this could not restrain the sinister development of MS—and perhaps effects of DES—underneath a canopy of repeated depressions and periods of apparent lack of the normal physical resilience in a young woman. It is perhaps surprising that since it was first made public in only two or three sentences, the unusual fetal history of a

truly outstanding musician destroyed early by ill health, has been given zero attention.

There can be no doubt about the abuse in her womb imposed on du Pré, certainly by PMSG, most probably by DES. What was the nature of the possible damage, we cannot now know. Nevertheless, a case can be made perhaps for effects at least mindful of a degree of autism. Each case of autism is unique, requiring individual, detailed examination. She was not a delayed speaker and the kind of overwhelming talent she had for music could be regarded as an expression of high functioning autism (HFA) as in some superior mathematicians and musicians [36]. From infancy, when she took a cello into her hands, it seemed to fulfill a special need beyond words - specific, repetitive movements within an aural bubble. Indeed, whenever du Pré arrived home, she first took to her cello for a while [11].

Though a wide variety of anatomic and functional differences have been found between ordinary and some autistic brains [29]-[32]—as could be reasonably considered as potential affects of pregnant mare's serum and of DES, this cannot now be shown. HFA cases can often seem just like other children, but not quite [34], and though a minority may find some resolution in adulthood [37], difficulties may persist. Perhaps du Pré was lucky in the remarkably supportive adult human musical environment around her. Most cases of autism seem gene-related [38]-[41]; some may have at least one paranoid parent [42]. Du Pré's father was so. In his Fifties he would warn his children "Don't tell anyone this. It's highly confidential", when inappropriate. When older, he would hold the arm of his son and whisper "They're coming to get me"; "the Army or the police" [10]. Whether du Pré was autistic or not and whatever the pathological results of fetal abuse, Barenboim regards du Pré as "not mortal" as were the others in their string quartet. He declared when she could not give of herself musically, she had nothing else to give [22]. Certainly, she was just music; just one string to her bow-a characteristic of HFA.

4. Conclusion

As problems presented by PMSG and DES reached the media and tragedy struck her daughter, did Iris wonder and suffer silently? In du Pré, absence of social skills, unique, savant musicality and memory and artistic passion and intensity started in early childhood, while discomfort, anxiety, insecurity, depressions, oversleeping, lethargy and lack of motivation troubled adolescence. Complex behavior, such as staring into the eyes of friends, awkward gait, heavy spending and other problematic traits, were emphasized later in this totally "different", profoundly feeling, highly intelligent artist built like a man, but with the heart and soul of a woman. Whether autistic or not, abused in the womb, she is a reminder even today of the oath: "Do no harm". As an adult her best times were when embraced by a small band of gifted musicians and an adoring public. They wrapped her in a concerto of love and made her life possible. Finally MS struck. That, was not a joke.

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