Egon R. Diczfalusy, the discovery of the fetoplacental unit and much more

Fetal endocrinology is today recognized as a special branch of reproductive endocrinology, a subspecialty that has existed since the days when Egon Diczfalusy, some 50 years ago, started investigating the complex hormonal exchanges that take place between the maternal and fetal organism via the placenta. The father of this discipline turned 90 years a few months ago, and the occasion was celebrated by the Karolinska Institute in Stockholm with an ad hoc Symposium jointly sponsored with the Foundation dedicated to his name and that of his late wife Ann. Therefore, the time seems right to write about his life accomplishments and his legacy.

Egon Diczfalusy was born in Miskolc, a small city in northeastern Hungary on 19 September 1920; his was a family of military men, and his father eventually became a General in the army of the newly independent Hungary, the country born after the dissolution of the Austro-Hungarian Empire. At age 16 years, he moved with his family to the southern city of Szeged where he graduated summa cum laude in Medicine from the Semmelweis University. Working as an intern in the Department of Pathology and Bacteriology, he was assigned a research project to duplicate a study carried out in Stockholm by the group led by Prof. Hans von Euler, a Nobel laureate. Von Euler had found that suspensions of Escherichia coli possessed transaminase activity. Intriguingly, young Diczfalusy could not confirm these findings, and this negative report became his first publication [1]. After the war, the presence or absence of transaminase activity in bacteria stimulated him to go to Stockholm where, for almost 2 years, he worked as Prof. Hans von Euler’s assistant.

In 1947, Prof. Axel Westman, head of the Department of Obstetrics and Gynecology at the Karolinska Hospital, offered him a full-time position in the Hormone Laboratory of his clinic. This event changed his scientific career and life, with the focus of his work shifting to reproduction, a field he remained firmly attached to until the present. In 1953, he completed his thesis, Chorionic Gonadotropin and Oestrogens in the Human Placenta [2], and from there on, the main interest of his scientific work remained the hormones involved in human reproduction.

Only a year later, Egon Diczfalusy became the head of the Hormone Laboratory, and over the following decade, under his leadership, the laboratory developed into one of the leading institutions of the world for the study of steroid hormone biogenesis and metabolism. His scientific achievements received international recognition in 1963 when he received a very large Ford Foundation Grant in Reproductive Endocrinology: one-half million dollars to study steroid biogenesis and metabolism in the human fetus, placenta and maternal organism. The following 20 years of his life were dedicated to the development of a new concept: the existence during pregnancy of a functional unit made up of an incomplete steroidogenetic organ (the placenta) interposed between a complete steroid metabolic system (the maternal organism) and a second incomplete system (the fetus). The latter had the unique characteristic of being able to compensate for the deficiencies of placental enzyme systems.

In the early 1970s, Diczfalusy met Alexander Kessler, a young American scientist who was head of a small World Health Organization (WHO) unit dedicated to human reproduction, and together they conceived the creation of an Expanded Program of Research, Development and Research Training in Human Reproduction, known as HRP [3]. The main focus of the Human Reproduction Program was to develop new methods of contraception and further research on existing methods. Over the following 25 years, as Senior Consultant, he became involved with every group of scientists working in the program (the so-called Task Forces), while at the same time heading the WHO Collaborating Centre in Research and Research Training in Human Reproduction established by the Program in Stockholm. Eventually, the Program grew to become a “Special Program”, cosponsored by four international entities, the United Nations Development Program, the United Nations Population Fund, WHO and the World Bank [4], but Diczfalusy remained the driving force behind most of the activities. When, at age 75 years, he retired as HRP Consultant, he concentrated his work in analyzing our “ageing world” and the dire reality of a West with “Too many grandparents for too few grandchildren”. He became convinced that the future must deconstruct the deterministic worldview of past centuries and replace it with a “science-driven anthropocentric worldview” [5] and continued to battle on behalf of all ageing women of the world, their plight, their needs and their aspirations [6].
Finally, at age 85 years, he launched a Foundation dedicated to his legacy with a simple idea: breaking the historical barriers existing between the countries of Eastern Europe and in particular those in the Balkan Peninsula. Having been born in Hungary, he had direct experience of the consequences of the dissolution of the Austro-Hungarian Empire, of problems created by the Second World War and by half a century of Communist rule. He reasoned that, at the academic level, but not only at that level, the survival of the Eastern European region may depend on close collaboration between all countries in that area. Therefore, bringing together nations neighboring Hungary would create a long-lasting legacy for his name, while at the same time help young scientists struggling with a sluggish economy, isolation and a lack of new entrepreneurs.

Some of the major accomplishments of his life have already been recounted: his actions in creating and leading for 25 years the WHO Special Program of Research, Development and Research Training in Human Reproduction were presented on the occasion of the 15th and 25th anniversaries of the Program [4,7]; his role in creating a Chemical Synthesis Program at WHO has also been recently summarized [8]. In 2000, when he turned 80 years old, a brief history of his life was given at a Symposium organized by Schering AG (today part of Bayer AG) in Berlin [9]. Finally, the discovery and functioning of the human fetoplacental unit have just been published [10].

These publications, however, concentrated on his scientific and technical accomplishments and did not fully show the extent of his interest in the fate of his fellow men and women. For this reason, here we wish to concentrate not only on his work in the field of contraception, but also on elaborating and commenting on his humanistic views.

As already mentioned, at WHO, Diczfalusy concentrated his efforts in guiding most aspects of the Program’s research and development activities, whereas back in his laboratory, he and his team continued their traditional work in steroid hormone research. At the same time, because of the WHO’s focus, they became involved in a series of projects on existing and new contraceptives. The Stockholm Group was the first to investigate in detail the pharmacodynamics of progestin-only pills, publishing, from 1979 onward, detailed information on the effects of a norethisterone (NET)-based mini pill. They carried out an assessment in 43 women of daily changes in estradiol (E2), FSH, LH and progesterone (P) during a pretreatment cycle and the second month of administration. During the latter period, they also measured daily levels of NET. The study revealed four different types of ovarian reaction to the NET mini pill: 16% exhibited no signs of follicular or luteal activity; 23% showed a marked cyclic follicular activity, but no luteal function; 21% had a normal follicular activity, but an insufficient luteal activity and a shortening of the luteal phase; and 40% exhibited normal E2 and P profiles, with a lengthening of the follicular and a shortening of the luteal phase. The plasma levels of NET closely reflected the regularity (or irregularity) of pill-taking, although there was no correlation between the levels of NET and the types of ovarian reaction induced or of the bleeding profile.

Interestingly, there was a significant excess of nulliparous women in the group with no follicular activity; they exhibited a prolonged follicular and shortened luteal phase. On the other hand, as already mentioned, subjects with ovulatory cycles showed a shorter follicular and longer luteal phase compared to all other women. They concluded that the relative length of follicular and luteal phases has a predictive value for the expected ovarian reaction to the NET mini pill.

The group led by Diczfalusy also investigated hormonal effects of the deliberate omission of a combined oral contraceptive pill containing 30 mcg ethinyl estradiol (EE)+150 mcg levonorgestrel (LNG) in four different groups of eight subjects each [14,15]. Pill-taking was omitted on days 9–10, 11–12, 14–15 and 17–18. Analysis was carried out in 31 subjects, and in all of them, P levels remained below 1.5 nmol/L. One subject (with a premature LH surge) showed a marked follicular and an inadequate luteal activity in two of three cycles; in all other subjects, there was a varying degree of follicular activity associated with the absence of any luteal function. Diczfalusy interpreted these results as suggesting that repeated prolongation of the pill-free period might result in a gradual increase in ovarian activity.

Thirty years ago, there was widespread concern that depot medroxyprogesterone acetate (DMPA), the 3-monthly injectable widely utilized in the developing world, may negatively affect future fertility. Then, in 1980, Pardthaisong et al. [16] showed conclusively that DMPA only caused a delay in the resumption of fertility, estimated at 5.5 months over the approximately 15-week duration of the effect since the last injection. To investigate this delay, Diczfalusy’s group measured the duration of the effect of a single dose of 150 mg DMPA on pituitary, ovarian and endometrial function in relation to peripheral levels of the compound. They found that three of the eight subjects investigated were still anovulatory at postinjection weeks 30–33. Plasma DMPA levels at 140 days postinjection varied between 0.90 and 2.24 nmol/L; levels then gradually declined and became undetectable between weeks 17–24 (four cases) or some time after week 33 (the other four cases) [17].

On the same theme, they carried out a comparison of two monthly injectable preparations: one containing DMPA (25 mg) plus estradiol cypionate (5 mg); the other, norethisterone enantate (NET-EN) (50 mg) plus estradiol valerate (5 mg). Pharmacodynamic data indicated that the first ovulatory rise in P occurred between 71 and 90 days after the last DMPA-based injection and 59 to 87 days after the last NET-EN-based injection. This proved that the preparation containing NET-EN had a clear duration of 1 month, whereas the action of the one containing DMPA was closer to 2 months [18].

In another pharmacokinetic and pharmacodynamic study, Diczfalusy’s group investigated the LNG-releasing
implantable contraceptive Norplant, with a duration of effect of at least 5 years. Their data showed that after an initial burst of approximately 7 nmol/L, the levels of LNG rapidly decreased during the first month. The decrease continued to a nadir (1.1 nmol/L) 10 months later, followed by a new increase to a broad peak of 1.5 nmol/L 2 years after insertion. Thereafter, levels decreased slowly at a rate of approximately 18 pmol/month [19].

The group also made important contributions to the development of steroid-releasing vaginal rings. In a first study, they looked at the pharmacokinetic and pharmacodynamic effects of a vaginal device releasing NET [20], but quickly switched to devices releasing LNG at a rate of approximately 20 mcg/day for 3 months [21]. They then studied the effects of adding, for 1 week, an oral dose of 50 mcg EE around day 70 [22], and in a third trial, they looked at plasma levels, estimating that, after a rapid rise to 1 nmol/L at 12 h, they reached a plateau of approximately 1.6 nmol/L at days 3–4, after which levels declined in a linear fashion to 60% of the initial level in 90 days. Of the endometrial biopsies obtained during exposure to LNG, only one exhibited signs of atrophy, 80% showed suppressed or arrested proliferation, and 10% had a normal cyclic appearance [23].

In his contraceptive research, Diczfalusy became involved in the development of new modalities of administering steroids. After finding that P released from a vaginal device during the late proliferative phase (days 7–11) significantly diminished the number of glandular mitoses, the height of the glandular epithelium, pseudostratification and the number of plasmolemmal vesicles [24], he tested the effects of medroxyprogesterone acetate (MPA) administered orally on cycle days 7 to 10. At high doses (5.0 or 10 mg), MPA resulted in a lengthening of the duration of the E2 peak, an increase in the area under the E2 peak, a decrease in the area under the curve and a reduction in the height of the LH peak. Furthermore, in 5 out 12 subjects, there was no ovulatory-like P pattern during the cycle in which MPA was administered [25]. Finally, he tested the oral administration of 300 mcg NET and 30 mcg LNG on cycle days 7–10. The NET treatment resulted in an increase in the area under the E2 peak, a reduction in the number of subjects with normal P profile and a decrease in the area under the P curve; it suppressed the LH peak and P levels in half the subjects and induced marked subnuclear vacuolation in the endometrium. The LNG treatment resulted in a decrease in the proportion of subjects with normal P profiles and in the area under the P curve, and it suppressed the LH peak and P levels in 50% of the women. Finally, LNG did not significantly increase the diameter of endometrial glands or induce subnuclear vacuolation [26].

This brief summary reveals that Diczfalusy was personally involved in contraceptive research and development, taking full advantage of the skills developed by his laboratory. It was the tyranny of age that prevented him from further contribution to the field of contraceptive development.

A chronicle of Diczfalusy’s life would not be complete without mentioning his outlook on the future of humanity. These views have been described in a book issued a few months ago in concomitance with his 90th birthday [27]. He believes that our future offers two faces: on the one hand, there is a series of daunting challenges facing men and women of the 21st century; on the other, there is the prospect of moving to a more truly human world in which it will be possible to improve the human condition through a judicious use of science. In other words, he and his coauthors believe that progress (i.e., science and technology), not to be confused with historical and political evolution, will help create a more humane world.

Diczfalusy believes that before progress can exercise its beneficial effects, an enormous challenge for the masses of the planet must be met: the incredible acceleration of progress that has taken place over the last 50 years. This positive phenomenon is making it increasingly difficult for the average person to “digest” new realities and adjust to change. Importantly, these advancements are occurring at the same time as new social networking and knowledge management platforms such as Facebook, Google, Wikipedia and YouTube have begun shaping the way we live, interact and learn. These platforms are horizontal and dynamic in structure, replacing traditional hierarchical management models as the most effective way of doing business, sharing knowledge and making an impact on social issues [28–30]. It is sad, but possibly inevitable, that many confronted with a reality that considers “the sky” as the limit take refuge in the stubborn refusal of any change. This inability is at the core of a phenomenon that, totally unexpectedly, has characterized and pervades the beginning of the third millennium: fundamentalism and its refusal of any rational approach.

Looking at Europe, Diczfalusy believes that there is one phenomenon that will be even more fateful and should concern each and every European: the inevitable (banning a miracle) decline of the “old world”. Indeed, it is today well established that, in Europe, fertility is everywhere below replacement level, causing a sharp ageing of population and a need for an imported workforce. He is convinced that problems created by these interrelated phenomena are not only daunting, they have not even been fully comprehended! An ageing Europe is today besieged by hundreds of millions of people dreaming to cross its borders that look more and more as defense walls against “herds of invaders”, the “illegal immigrants”.

Diczfalusy points out that the very low fertility in most European countries will have enormous consequences: when the proportion of people over 80 years is higher than that of those below 14 years, an alarm bell should ring loudly [31]. Much has been said about this phenomenon typical of the Old World. Chesnais [32] has pointed out that we have witnessed a true “gender revolution”: women’s increased autonomy, education, participation in the labor force and the instability of marriages/unions are, in his view, the main
reason for fertility decline. This is unconvincing since the only Western country with a fertility rate above replacement is the United States, a champion of the gender revolution. Obviously, there are other determinants, such as urbanization, social atomization and contraception. The latter, however, is nothing more than a powerful tool to achieve what couples have already decided and, for this reason, can hardly be the engine behind low fertility in Europe. More convincing are economic reasons: raising children in a modern urban context and caring for and educating them are costly, and unless strong infrastructures are created, it is hard for women to have multiple children.

At the same time, Diczfalusy is aware that modern contraception brought to Europe and to most of the Western world a true social revolution [33], and irrespective of the sometimes conflicting moral judgments that have been passed on these technological advances, they have had a profound social impact.

In conclusion, Diczfalusy believes that we are perhaps too close to the beginning of this reproductive revolution to see how the situation will stabilize or even begin to reverse itself in a not too distant future. For this reason, he does not believe that doomsday is the inevitable future of Europe; on the contrary, he is convinced that we cannot and must not underestimate the strong natural desire to have children and the fact that unchecked capitalism, far from representing the “ultimate social structure”, may end up in the wastebasket of history. He hopes that progress will free humans from fanaticism, obscurantism and senseless violence and is convinced that science can constitute the right ingredient to improve the human condition. Science alone, however, will not suffice since the history of progress has been equally that of scientific advancement as it has been that of new ideas and of new principles, the only engines that can guide it.

We hope to have shown in a few paragraphs that the nonagenarian Diczfalusy not only is still active, but is fully capable of contributing to the creation of new human values and, therefore, of a brighter future for our world.

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