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Laudatio: Egon Diczfalusy and the Identification of the Human Feto-Placental Unit

G. Benagiano

In September 2000 I was invited to Berlin where Schering AG had organised a conference to celebrate Professor Egon Diczfalusy's 80th birthday and – in the best German tradition – they asked me to give a Laudatio in his honour [1]. I remember that, at the time I told the audience that I had already volunteered to give his 100th birthday Laudatio again in Berlin. Although history moved on and Schering AG no longer exists, having been absorbed into Bayer AG, I seem to be half way to maintain my promise, having now been asked to recount Diczfalusy's life achievements on the occasion of his 90th birthday, on September 19, 2010. I accepted with pleasure as I feel that an uninterrupted association and close friendship with him during almost 50 years gives me an unique opportunity to provide a picture of the man, the scientist, the humanitarian, the visionary, the philosopher, with a degree of accuracy quenched only by the bias of affection.



Giuseppe Benagiano

At the same time, to be meaningful a Laudatio must be focused and, for this reason, after a brief account of his early personal life, I shall concentrate on a description of the work that gave Egon Diczfalusy international fame: the definition of the concept of the Human Feto-placental Unit. This will be followed by a few words on his many and important subsequent achievements.

Egon Diczfalusy was born in Miskolc, a small city in northeastern Hungary on September 19, 1920; his father was a member of the new Hungarian army, created after the dissolution of the Austro-Hungarian Empire and eventually became a General. When he was 16, his family moved to the southern city of Szeged where he graduated *summa cum laude*, in Medicine from the Semmelweis University. As a second year medical student in that University he worked as an intern in the Department of Pathology and Bacteriology where his research project consisted in duplicating a study carried out at the Stockholms Högskolan (the name with which the University of Stockholm was known in those days) by the group led by Professor Hans von Euler, a Nobel laureate. This group had published that suspensions of *E. coli* possessed transaminase activity. Intriguingly, young Diczfalusy could not confirm these findings, and this negative report became his first publication [2]. After the war, the issue of transaminase activity in bacteria was instrumental in stimulating him to go to Stockholm where, during almost two years, he worked as Professor's Hans von Euler's assistant.

In 1947, Prof. Axel Westman, head of the Department of Obstetrics and Gynaecology at the Karolinska Hospital in Stockholm offered him a full-time position in the Hormone Laboratory of his clinic. This event changed his scientific ca-

reer and life with the focus shifting to reproduction, a field he remained firmly attached to until the present days. In 1953, he completed his thesis on "Chorionic Gonadotropin and Oestrogens in the Human Placenta" [3] and, from there on, the main focus of his scientific work remained the hormones involved in human reproduction.

By 1948 Egon Diczfalusy had become the head of the Hormone Laboratory and, over the following decade, under his leadership the laboratory became one of the leading institutions in the world on steroid hormone biogenesis and metabolism, to the point that in 1963 he received one of the largest Ford Foundation Grants in Reproductive Endocrinology of those days: one half million dollars to study "Steroid biogenesis and metabolism in the human fetus, placenta and maternal organism".

I joined the "Stockholm Group" in 1964, right after the Grant was awarded and became one of the first Ford Foundation Fellows in Reproductive Endocrinology. This gave me the opportunity to be part of team that investigated and unravelled the intricacies of the Human Feto-placental Unit, defining the new concept. It is for this reason that I am able to provide a first-hand report of those incredible days.

Everything started from the recognition that the fetus and the placenta exert endocrine functions, a discovery that goes back to the beginning of the 20th century [4]. The classical concept postulated that, during gestation, a "temporary endocrine organ", the placenta, carried out most of the greatly increased steroid biosynthesis at mid-gestation. At the same time, it was Diczfalusy who, much later, recognised the close inter-relationships between the fetus and the placenta [5]. He was the first to understand that the situation was much more complicated and that certain steroids present in the urine of pregnant women represent mainly metabolites of placental origin, whereas others seem mainly of maternal production, with others yet resulting from a joint activity by the fetus and the placenta.

Starting from these premises, Diczfalusy and his group developed a new concept: the creation 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 unique characteristic of the latter is its ability to compensate for the deficiencies of placental enzyme systems.

In 1964, Professor Diczfalusy enunciated the new concept [6]: the placenta and the fetus both lack certain enzymes which are essential for steroidogenesis; however, the enzymes that the placenta lacks, are present in the fetus and, *vice versa*, those absent from the fetal organism are active in the placenta. Thus, the integration of the two compartments allows the elaboration of most, if not all, biologically active steroids. It must be

stressed that we still do not have full information on the situation at term, although – even in this case – Diczfalussy and other groups have collected important data indicating that the situation at term does not differ from the one at mid-pregnancy [7–10].

Diczfalussy's work dealt with the full range of metabolic pathways leading to biologically active steroid hormones, starting with de-novo synthesis. His group was able to demonstrate that – contrary to earlier results [11, 12] – when ^{14}C -labelled sodium acetate, is perfused into isolated placentas, little, if any, labelled cholesterol can be isolated from the placental tissue [13] and that all steroids isolated from the placenta and perfusates were devoid of any ^{14}C -label [14]. Finally, when complete feto-placental units were perfused with ^{14}C -labelled sodium acetate, no ^{14}C -labelled cholesterol was isolated from the placentas, although an abundant conversion to cholesterol was demonstrated in several fetal tissues [15].

In contradistinction to the placental situation, the group of Diczfalussy demonstrated that, following perfusion of ^{14}C -labelled sodium acetate into pre-viable human fetuses, considerable incorporation of acetate occurred, not only into cholesterol [15], but also into a variety of steroids [13, 16]. The liver and adrenals formed large amounts of cholesterol and cholesterol was isolated from all perfusates, indicating that the mid-gestation fetus utilises part of the newly synthesized cholesterol for its own needs, while it secretes some of it to the placenta.

The Stockholm group also extensively investigated the side chain cleavage leading from cholesterol to pregnenolone and discovered that this metabolic step can take place in several fetal tissues [16, 17] and is especially active in the placenta [18], although the subsequent step leading from pregnenolone to progesterone, is extremely limited in the fetal organism, occurring mostly, if not exclusively, in the placenta [18] from circulating cholesterol, mainly of maternal origin [19]. The placenta then secretes pregnenolone both to the mother and to the fetus, where it is extensively metabolised by various tissues [18, 20]. The placental contribution to fetal pregnenolone synthesis is however limited: the major part of fetal pregnenolone is formed by de novo synthesis and immediately sulphurylated [17, 21]. Worth of mention is the fact that the placenta does not sulphurylate pregnenolone, although it is capable of hydrolysing it. The quantitatively most important metabolic product of pregnenolone sulphate in the fetal organism is dehydroepiandrosterone sulphate (DEAS) formed by the adrenals [21].

A unique feature of the work of Diczfalussy and his group is the study of the fate of progesterone reaching the adrenals; they discovered that this typical pregnancy steroid undergoes a variety of hydroxylation reactions and, in this way, fetal adrenals can produce all the biologically important corticosteroids, including deoxy-corticosterone, corticosterone, cortisol, and aldosterone [18, 22, 23]. Since the placenta is not capable of carrying out these hydroxylation reactions [20], it follows that the placental contribution to corticosteroid synthesis is restricted to the conversion of the hydroxylated 3β -hydroxy- Δ^5 -steroids of fetal origin to the corresponding α - β -unsaturated 3-keto-steroids. Indeed, Diczfalussy's group has shown that the fetal adrenals can convert pregnenolone to 21-hydroxypregnenolone and that the perfused placenta can convert large quantities

of the latter to deoxycorticosterone [24]. Many of the corticosteroids are rapidly sulphurylated by the fetus at carbon atom 21; these sulphates however are not metabolised to any major extent by fetal tissues [25].

Another very important discovery made by the Stockholm group deals with the metabolic fate of DHEAS, the most important steroid secreted by fetal adrenals. They started with the observation that the fetus and the placenta produce a series of androgens including androstenedione and testosterone [16, 17, 26, 27] although by different metabolic pathways [28, 29]. In the fetal liver and gastro-intestinal tract, androstenedione and testosterone are freely interconverted, whereas in all other tissues more testosterone is converted to androstenedione than vice versa [30]. Fetal adrenals transform androstenedione and testosterone into 11β -hydroxylated forms and also convert testosterone to testosterone sulphate [30]. Androstenedione and testosterone are actively metabolised by fetal tissues and testosterone is rapidly sulphurylated [31]; this steroid is then transferred to the mother without hydrolysis [32].

The bulk of the large quantities of DHEAS circulating in the fetus reaches the placenta with the umbilical circulation and is rapidly converted to estrone and estradiol (but – strikingly – not to estriol) through a series of reactions involving first the hydrolysis of DHEAS. One pathway involves the direct conversion of DHEA to androstenedione, followed by aromatisation to estrone [18]; another involves the direct conversion of testosterone to estradiol [31]. Thus, DHEAS of fetal and maternal origin represents the most important precursor of placental estrone, and estradiol [33, 34]. Aromatisation can also take place, although in a limited fashion, in the fetal liver [35].

I have already mentioned that the placenta is unable to produce estriol, quantitatively the most important estrogen during the human pregnancy, accounting for more than 90 % of the total estrogen urinary excretion. Diczfalussy and his group have proven that, whereas the placenta possesses a very active aromatising system, it lacks the ability to carry out hydroxylation at carbon atom 16 of the steroid ring D, the critical reaction leading to estriol [36]. In further investigating this issue, the Stockholm group identified two separate pathways for the formation of estriol, named the “neutral” and the “phenolic” pathways. They differ because in the former, 16α -hydroxylation precedes aromatisation, whereas in the latter aromatisation is followed by 16α -hydroxylation. The “neutral” pathway can be considered a typical feto-placental activity: in it, DHEAS from fetal adrenals is hydroxylated in position 16α , mainly in the fetal liver; the 16α -DHEAS formed in this way is then converted to estriol by the placenta following hydrolysis and the formation of an intermediary product, 16α -DHEAS [18, 37].

The “phenolic” pathway, on the other hand, represents a materno-placental activity: in this case, estrone and estradiol of placental origin are hydroxylated in position 16α – mainly in the maternal liver [18, 37]. Interestingly, the fetal liver is also capable of synthesising estriol directly from estradiol [38].

The investigation of the complex mechanisms involved in estriol formation and its further metabolism to 15α -hydroxy-

estriol [39, 40], will always be linked to the work of Egon Diczfalussy: he – for the first time – pointed out that estriol synthesis involves a process of high substrate and organ specificity, as well as enzymatic mechanisms active in the fetal and maternal adrenals (formation of DHEAS), in the liver (16α -hydroxylation of DHEAS and estrone sulphate) and in the placenta (aromatisation of DHEAS and of 16α -DHEAS).

Whereas this intense work and the major results obtained would have been sufficient to fulfill most people's dreams, for Egon Diczfalussy this was only a phase in his life.

In the 1970s, a second major development occurred in his life: it was 1971 and Alexander Kessler, a young, bright and determined American scientist working in the World Health Organisation (WHO) as head of a small Unit, conceived the idea of a research programme in human reproduction and invited Diczfalussy to join as Senior Consultant of the newly established "WHO Expanded Programme of Research, Development and Research training in Human Reproduction". Over the next 25 years, he became involved with every Task Force Steering Committee, while at the same time heading the WHO Collaborating Centre in Research and Research Training in Human Reproduction established by the Programme in Stockholm. This took him to the four corners of the World where he participated in literally hundreds of Congresses, Conferences and Workshops.

Eventually the Programme grew to become a "Special Programme", co-sponsored by 4 international entities, UNDP (the United Nation Development Programme), UNFPA (the United Nations Population Fund), WHO and the World Bank [41] and Diczfalussy continued to be the intellect behind the various activities. When, in 1995, as Director of the co-sponsored Programme, I was told by the WHO's Personnel Division Director that Diczfalussy could no longer act as a Consultant because of his age, the "young-75 years old" visionary started a new career and devoted his energies to an Ageing World. He became convinced that the future must deconstruct the deterministic worldview of past centuries and replace it with a "science-driven anthropocentric worldview" [42].

He lectured extensively on a topic that attracted the attention of new generations, which he summarised with the words: "To many grand parents for too few grand children". He also continued to battle on behalf of all older women of the world, their plight, their needs, their aspirations [43].

Finally, at the age of 85, he met what seems to be the last challenge of his life: the creation of a Foundation dedicated to his legacy and that of his late wife: his original idea was simple, while at the same time revolutionary: 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 breaking down of the Austro-Hungarian Empire, of the problems created by the 2nd World war and half a century of communist rule. To him, bringing closer the countries neighbouring Hungary would create a long-lasting legacy for his name, through an achievement that many have considered impossible, at least in the short term.

Egon Diczfalussy believes that – at the Academic level, but not only at that level – the very survival of the Eastern European region may depend on close collaboration between all countries in that area of the world.

In conclusion, what lesson can young scientists draw from learning the achievements of such an outstanding scientist and humanitarian?

A first important point is that made a few years ago by Paul G. McDonough [44], who – after summarizing his view of Joseph W. Goldzieher, one of the founding fathers of hormonal contraception – invited readers to go to the web (MedLine, PubMed, Scopus etc.) "to retrieve the most important years of Reproductive Endocrinology". He concluded that from this search "you will be dismayed to realize how precious and perishable fundamental scientific knowledge can be, but you will be rewarded to learn that studies of the past can provide important scientific information for the future". A second major point can be made by quoting a great writer of the past century who said: "*The past is never dead; it is not even past*" [45].

My personal conclusion is that we have a duty to remain active and productive at all stages of our life: the focus of our attention can and, perhaps, even should change. What must remain, as Egon Diczfalussy taught us, is the strength to meet the challenge, to continue to fight for humanity and especially for the under-privileged among humans.

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