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How genetics came to the unborn: 1960–2000

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ABSTRACT

Prenatal diagnosis (PND) is frequently identified with genetic testing. The termination of pregnancy for foetal malformation was called 'genetic abortion', in spite of the fact that in many cases the malformation does not result from changes in the genetic material of the cell. This study argues that the 'geneticization' of PND reflected the transformation of the meaning of the term 'genetics' in the 1960s and 70s. Such transformation was linked with the definition of Down syndrome as a genetic condition, and to the key role of search for this condition in the transformation of PND into a routine approach. The identification of PND with the polysemic term 'genetics' was also favoured by hopes that cytogenetic studies will lead to cures or prevention of common birth defects, the association of genetic counsellors with prenatal diagnosis, and the raising prestige of clinical genetics. In spite of the impressive achievements of the latter specialty, more than fifty years after the first prenatal diagnoses, the main 'cure' of a severe foetal malformation remains the same as it was in the 1960s: the termination of a pregnancy. The identification of PND with genetics deflects attention from the gap between scientists' capacity to elucidate the causes of numerous birth defects and their ability (as for now) to prevent or treat these defects, and favours the maintenance of a powerful regimen of hope.

1. Congenital malformations before 1960s: heredity vs. environment

In the late 1960s, physicians acquired the capacity to see 'what is about to be born'.[1] At the same time, the liberalization of abortion in the majority of Western countries made possible the legalization of the termination of pregnancy for foetal conditions that produce severe disability (Löwy, in press).[2] Less than 10% of such conditions are 'classical' genetic diseases, that is conditions known to be transmitted in families. Nevertheless, prenatal diagnosis (PND) of foetal malformations became strongly associated with genetic testing (Burginion, Briscoe, & Nemzer, 1999; Hashilony-Dolav, 2007; Kerenromp, Idema, van Spijker, Christianens, & Bergsma, 1992; Rothenberg & Thomson, 1994). Today the term 'prenatal genetic diagnosis' has two distinct meanings: a pre-1960 one, a search for a pathological condition present in a given family, and a second, post-1960, one, a search for chromosomal anomalies, mostly a chance event.[3] Taken together, hereditary diseases and chromosomal defects are responsible for less than a half of termination of pregnancy for foetal anomalies.[4] Nevertheless, from the 1970s on, PND became increasingly identified with 'genetic testing'. The shift in meaning of the term PND, this text argues, was to an important extent the consequence of the generalization of prenatal testing, above all for a non-hereditary condition, Down syndrome.[5]

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[1] The Mishnaic adage 'Who is the wise man? He who sees what is about to be born', which originally praised foresight, is employed in Israel to promote prenatal diagnosis (Ivry, 2009, pp. 195).

[2] For controversies on meaning of 'severe disability', see Parens & Asch (2000).

[3] On shifting meaning of 'genetic testing' see e.g. Paul (1999) and Hogan (2012).

[4] This statement is based on European and French data on causes of termination of pregnancy for foetal indications. EUROCAT Reports, 2002–2008; Rapports of the French Agnece de Biomedicine, 2008–2010; Dommergues, Mandelbrot, Mahieu-Caputo, Boudjema, & Durand-Zaleski (2010).

[5] Such a shift was not general. For example in oncology 'genetic' frequently continues to be synonymous with 'hereditary' and 'genetic testing' (e.g., for BRCA mutations) is a search for familial predisposition to malignancy.

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From the early modern periods on, professional and lay understanding of pregnancy and birth were linked with a strong interest in the transmission of specific traits, including pathological. Until the 1960s the only way to prevent a hereditary disease was to refrain from marrying a person from a 'tainted' family, and for people from such families to refuse procreation, an approach that culminated with eugenics in the twentieth century (López-Beltrán, 2006, 2007). Efforts to prevent inborn defects followed a very different path: the one of prenatal care. The Scottish obstetrician, John William Ballantyne, was the first to propose, in the early twentieth century to treat pregnant women in order to improve the future child's health. Ballantyne became interested in neonatal and foetal malformations ('monstrous births'). He arrived at the conclusion that the appropriate medical care of expectant mothers reduced the frequency of malformations in newborns (Al Gailani, 2009; Ballantyne, 1892, 1902). While doctors might regard Ballantyne as pioneer of surveillance of pregnant women, the French obstetrician, Adolfe Pinard (1844–1934), can be seen as the pioneer of a social approach to the management of pregnancy. Pinard focused on sickly rather than malformed children and was mainly interested in the prevention of premature births. Women from lower socio-economic strata, he argued, had a much higher rate of such births, and thus higher rates of newborn mortality and morbidity. To prevent premature births, Pinard advocated medical care, but above all, adequate nutrition, rest, and the cessation of strenuous work in later stages of pregnancy. Accordingly, he promoted social measures such as paid maternity leave (Cova, 1997).

In the interwar era, some experts argued that one should distinguish between the promotion of general newborns' health and the prevention of 'true' congenital malformations, that is, ones that are not accidents of birth or post-natal period. The first goal was to be achieved by helping mothers to stay healthy during the pregnancy, and avoid premature childbirth. The second was to be achieved only through eugenic measures, because severe inborn malformations nearly always stem from hereditary defects in the germ plasm. The two exceptions to this rule were infectious diseases that affected the foetus, such as syphilis, and a traumatic childbirth (Adair, 1934). The Philadelphia obstetrician Douglas Murphy argued in his 1940 textbook that congenital malformations "arise solely from influences which affect the germ cells prior to fertilization. No evidence is available to indicate that they result from factors which operate for the first time after fertilization has taken place." (Murphy, 1940, pp. 83). In a 1947 edition of his book Murphy took into account two recent developments: the uncovering of teratogenic effects of an infection with rubella virus, and of radiation (Murphy, 1947, pp. 87–100).[6] Nevertheless he remained persuaded that, "the incidence of developmental abnormalities resulting from environmental factors acting after the fertilization has taken place is extremely small in proportion to those which result from genetic causes." (Murphy, 1947, pp. 113). In 1947, the term 'genetic causes' usually referred to conditions that ran in families, an observation illustrated by Murphy's claim that families which have one malformed child, have a 25 times higher probability to have another child with a birth defect than the general population (Murphy, 1947, pp. 81–83).[7]

2. 1960s: chromosome anomalies and inborn defects

The year 1959 has been presented as a turning point for the domain of clinical genetics (Harper, 2006). That year researchers had found out that several congenital malformations: Down syndrome, Klinefelter syndrome and Turner syndrome, were aneuploidies—they were caused by the presence of an abnormal number of chromosomes (Christie & Zallen, 2002; Harper, 2006). Geneticists were aware of the fact that conditions such as haemophilia could occasionally arise from de novo mutations (i.e. congenital malformations that do not run in families) but may nevertheless reflect changes in the hereditary material of the cell (Morrison, 1952, pp. 21–23; Penrose, 1946). Thus, some experts proposed in the 1930s that Down syndrome was the result of the nondisjunction of chromosomes (Codell Carter, 2002). The latter proposal was, however, seen as but one hypothesis among many. The 1959 demonstration of the role of chromosomes in several congenital malformations was seen as a major paradigm shift, and an important boost for the development of medical genetics. As the Canadian geneticist Clarke Fraser put it: "genes were interesting hypotheses but here was a cause of genetic disease that physicians could actually *see*" (Fraser, 2008, pp. 2188. Italics in the text).

Before the advent of cytogenetics, the only way to visualize changes in genetic material was an indirect one: the drawing of a pedigree. With the rise of cytogenetic methods, researchers could directly observe changes in the genetic material of the cell, but also dissociate such changes from studies of hereditary transmission of specific traits. Prior to studies of aneuploidies, physicians were not particularly interested in the role of genes in mongolism, because—with a handful of exceptions—this condition did not run in families. Fraser's statement points to an important transformation of the meaning of the term 'genetic disease'. Moreover, while earlier debates on links between hereditary material of the cell and inborn diseases remained restricted to an esoteric circle of specialists, the new view of 'genetic diseases' was popularized rapidly and radically transformed the public discourse about genetics.[8]

In the early 1960s, geneticists who observed chromosomal anomalies such as aneuploidies, translocations, deletions, ring chromosomes and mosaic patterns, hoped that they will be able to correlate each anomaly with specific phenotypic manifestations (Gaudillière, 2001; Jacobs et al., 1960; Penrose, Ellis, & Delhanty, 1960; Therman, Patau, Smith, & Demars, 1961). Studies made by Klaus Patau and his collaborators at the University of Wisconsin illustrate this stage of aneuploidy studies. The Wisconsin groups focused on chromosomal anomalies, especially trisomy 13 and 18 and translocations (Smith, Patau, Therman, & Inhorn, 1960; Smith, Patau, Therman, Inhorn, & deMars, 1963). The main participants in that group were the geneticists Klaus Patau and his wife, Eeva Therman the paediatrician David Smith and Canadian geneticist Irene Uchida. Researchers associated with the Wisconsin group focused at first on attempts to unravel the clinical manifestations of chromosomal anomalies, mainly through studies of unusual cases.[9] Uchida reported that they had in their clinics a E trisomic (a child with trisomy 18) in a mild form (this aneuploidy is frequently lethal), a 'mongol' with 48 chromosomes (usually people with Down syndrome have 47 chromosomes), and an interesting family that showed some, but not all the 'stigmata of the E syndrome', a

[6] Murphy sustained that women accidentally irradiated or infected with rubella virus early in pregnancy should be entitled to a legal abortion (Murphy, 1947, pp. 106).

[7] Murphy, *Congenital Malformations*, 2nd edition, pp. 81–83. In his textbook of foetal and neonatal pathology Edgar Morrison estimated that that in absence of consanguinity between the parents, the figures given by Murphy were probably too high (Morrison, 1952, pp. 14).

[8] E.g. the French popular science journals *La Nature* and *Science et Vie* published in 1959 articles about 'pathological heredity' that explained this notion (De Grouchy, 1959; Lejeune, 1959).

[9] Irene Uchida to Klaus Patau, July 5, 1960. Patau's papers, University of Wisconsin, Madison, Wisconsin. Irene Uchida worked at the Children Hospital of Winnipeg (subsequently, Patau's papers).