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AMBIGUOUS CELLS: THE EMERGENCE OF THE STEM CELL CONCEPT IN THE NINETEENTH AND TWENTIETH CENTURIES

by

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This paper elucidates the origins of scientific work on stem cells. From the late nineteenth century onwards, the notion of stem cells became customary in scientific communities of Imperial Germany. Adopting the term *Stammzelle* from Ernst Haeckel, Theodor Boveri was influential in introducing the concept in embryological studies and early genetics around 1900, describing a capacity of stem cells for self-renewal as well as differentiation. At the same time, blood stem cells were conceptualized by histologists such as Ernst Neumann and Artur Pappenheim in studies of physiological haematopoiesis and various forms of leukaemia. Furthermore, building on Julius Cohnheim's theory that tumours arise from 'embryonic remnants' in the adult body, pathologists aimed at identifying the cells of origin, particularly in the embryo-like teratomas. Embryonic stem cells thus assumed an ambiguous status, partly representing common heritage and normal development, and partly being seen as potential causes of cancer if they had been left behind or displaced during ontogeny. In the 1950s and 1960s experimental research on teratocarcinomas by Leroy Stevens and Barry Pierce in the USA brought together the strands of embryological and pathological work. Alongside the work of Ernest McCulloch and James Till at the Ontario Cancer Institute from the early 1960s on stem cells in haematopoiesis, this led into the beginnings of modern stem cell research.

Keywords: stem cells; embryology; haematopoiesis; tumours; teratoma

INTRODUCTION

In an article in 2009, Canadian historian and philosopher of medicine Lawrence Burns has argued that much of the current public discourse on embryonic stem cells follows the metaphor of the 'superhero'.[1] Because of their pluripotency, stem cells are expected to be capable of virtually anything in terms of providing future regenerative therapies. For sufferers of conditions such as spinal cord injuries or severe Parkinson's disease they may be the last source of hope. However, summoning the 'superhero' also involves a difficult moral choice: the destruction of early human embryos (in their blastocyst stage) in harvesting embryonic stem cells from the inner cell mass. In view of the pervasiveness of metaphors in

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the present debates on stem cells, a phenomenon that has similarly been emphasized by the linguist Andreas Musolff,[2] it seems worthwhile to enquire into the meanings and connotations of those cells when they were first conceptualized—more than a century ago.

This paper discusses the specific scientific contexts in which the notion of 'stem cells' was established in the late nineteenth century. Moreover, it shows how, at the start of the twentieth century, embryonic cells became a concern for pathologists who attempted to explain the genesis of tumours. It concludes by indicating how this early work on embryonic cells and tumours led to modern stem cell research after 1950. In this way it complements recent scholarship on this topic that has focused on developments since World War II, especially the study of blood-forming (haematopoietic) stem cells.[3] I argue that in the early twentieth century embryonic stem cells assumed an ambiguous status by carrying positive connotations of common heritage and normal development as well as negative meanings as potential sources of cancer.

Ernst Haeckel and the *Stammzelle*

The origins of the term 'stem cell' can be traced back to the late nineteenth century.[4] Ernst Haeckel (1834–1919), the controversial Darwinist and professor of zoology at Jena,[5] referred in his published lectures on *Natürliche Schöpfungsgeschichte* (1868) to unicellular organisms or protozoa, which he believed to be the phylogenetic ancestors of multicellular organisms, as *Stammzellen* (stem cells). The genealogical and evolutionary concept of the *Stammbaum* (family tree or phylogenetic tree) and of the biological *Stamm* (phylum) formed the linguistic context of his coinage of this new term. According to Haeckel, the stem cells themselves had originated from the most primitive forms of life, the so-called *Moneren*, which he thought of as tiny lumps of mucus or protein. The 'fact' that the stem cells formed the evolutionary basis of all plants and animals was in his view evident from the analogy of individual embryological development from a single egg cell.[6] Obviously, this assertion derived from Haeckel's famous 'biogenetic law' that ontogeny is a rapid and shortened recapitulation of phylogeny.[7] In 1877 he applied the notion of stem cells to ontogeny against this background and used the name *Stammzelle* or *Cytula* to describe the fertilized egg cell as the cell of origin of all other cells of an animal or human organism. Addressing a general educated audience in another series of lectures, on *Anthropogenie*, he explained:

> The name 'stem cell' seems to me the most simple and appropriate one, because all other cells stem from it and because it is in its most literal sense the stem father as well as the stem mother of all the countless generations of cells of which the multicellular organism is later composed.[8]

The new term was necessary, according to Haeckel, to make clear that the fertilized egg cell was quite different—morphologically, chemically and physiologically—from the original egg cell. In fact, in 1875 his student Oscar Hertwig (1849–1922) had demonstrated in sea urchins that fertilization could be understood as the fusion of the nucleus of an egg cell with that of a spermatozoon.[9] The stem cell, Haeckel stressed, 'is partly of fatherly and partly of motherly origin; and we will now no longer find it astonishing if the child who develops from this stem cell inherits individual characteristics from both parents'.[10] Thus, for Haeckel, the stem cell represented the whole future child.

Haeckel's neologism was rooted in the metaphorical language that was then common in talking about cells and the body. Particularly through the influence of Rudolf Virchow (1821–1902), who since the 1850s had compared the body's cells with citizens cooperatively forming a state (*Zellenstaat*, 'cell state'), it had become customary to speak metaphorically of cells as human individuals.[11] As Virchow had argued in his influential *Cellularpathologie*:

> The character and the unity of life cannot be found in one particular single point of higher organization, such as the human brain, but only in particular, constantly recurring arrangements, which every single element owns. From this it follows that the composition of a larger body, the so-called individual, always results in a kind of social arrangement, [and] represents *an organism of a social kind*, in which a mass of single existences is dependent on each other, but in such a manner that each element (cell or, as *Brücke* says very well, *elementary organism*) has a particular activity for itself, and that each, although it may receive the stimulus for its activity from other parts, still is itself the origin of its actual work.[12]

Haeckel, who had studied medicine with Virchow, similarly described the human body as a social arrangement of cells, but turned Virchow's liberal, relatively egalitarian conception of a cell state into a more hierarchical and centralized version.[13] Significantly, not only were such metaphors employed when addressing lay audiences, but they were also used in scientific texts. Metaphors had a heuristic value for scientists in shaping new research questions.[14] Haeckel's notion of stem cells soon found its way into research papers of other zoologists and anatomists.

Stem cells in embryology around 1900

In the early 1890s the term 'stem cell' was adopted in the context of embryological studies in the wake of August Weismann's (1834–1914) theory of the continuity of the 'germ plasm'.[15] Segregated into primordial germ cells during the earliest phases of embryonic development, this 'germ plasm' (*Keimplasma*), which was identified with the organized substance of the cell's nucleus, was thought to carry hereditary characteristics through the egg and sperm cells from one generation to the next.[16] Valentin Haecker (1864–1927), then an assistant to Weismann at the Zoological Institute of the University of Freiburg (Breisgau), published a paper in 1892 on the embryonic development of the crustacean *Cyclops*, in which he referred to the 'stem cell' (*Stammzelle*) as the common precursor cell of the primordial germ cells and of the primordial somatic (mesoderm) cells.[17] In a similar sense 'stem cells' were introduced later in the same year by Theodor Boveri (1862–1915). At this time Boveri worked at the Zoological Institute of the University of Munich under Richard Hertwig (1850–1937), who like his brother Oscar had been a student of Haeckel's. In a lecture to the Munich Society for Morphology and Physiology on the embryo of the roundworm of the horse (*Ascaris megalocephala*), then a common model organism for cytological research, Boveri described as *Stammzellen* those cells that derived from the fertilized egg cell and led to the primordial germ cell (*Urgeschlechtszelle*), and from which the various primordial somatic cells (*Ursomazellen*) branched off. In other words, in each of the earliest cell generations, from the two-cell stage of the embryo onwards, one 'stem cell' divided into two daughter cells, of which only one maintained the character of a stem cell whereas the other divided into the precursors of somatic cells. The various primordial somatic cells

subsequently formed the basis of the different layers—ectoderm, endoderm and mesoderm—of the embryo. After five divisions, in the 32-cell stage of the *Ascaris* embryo, the stem cell (now called the primordial germ cell) began to differentiate into germ cells, leading ultimately to the formation of eggs or of spermatozoa. Boveri explicitly mentioned that he had adopted the term 'stem cell' from Ernst Haeckel.[18]

However, neither Theodor Boveri nor Valentin Haecker turned stem cells as such into central objects of investigation. Of interest to them was, rather, the distribution of 'chromatin', namely the stainable nuclear substance suspected to carry hereditary characteristics, to the germ cells on the one hand and to somatic cells on the other. In line with Weismann's theory of a continuity of the 'germ plasm', the stem cells were thought to maintain and pass on the full chromatin of the fertilized egg cell, whereas it was believed to be only partly distributed to the somatic cells ('chromatin diminution'), thus leading to cell differentiation. In this early work Haecker and Boveri were already describing the doubling and distribution of 'chromatin loops' or 'chromosomes' during cell divisions. Boveri, who was appointed to the chair of zoology and comparative anatomy at Würzburg University in 1893, became a founder of the chromosome theory of heredity in the early 1900s.[19] Haecker, who was made director of the Zoological Institute at the Technical University of Stuttgart in 1900, and subsequently at the University of Halle from 1909, likewise developed his main research interests in the field of genetics. He established the approach of 'phenogenetics', which worked 'backwards' from the outer traits of an organism to their suspected causes in the germ cells.[20] In 1914 he propagated the notion of 'pluripotency' as the potential for several different developmental options, which he ascribed generally to the 'germ plasm' of an organism (not specifically to its stem cells). The germ plasm was now thought to be a complex 'biomolecule', in which even small changes in a few 'atom groups' might produce new qualities.[21]

Boveri's description of the cell lineage in the *Ascaris* embryo, which he had illustrated with drawings and diagrams (figure 1) that reappeared with small modifications in several of his publications,[22] found its way into textbook and handbook accounts of early embryonic development. For example, the American biologist Edmund Beecher Wilson (1856–1939), a lifelong friend of Boveri's since their first collaboration at Richard Hertwig's Zoological Institute in Munich in the early 1890s, included versions of Boveri's cell lineage diagrams and drawings in his influential handbook *The cell in development and heredity*.[23] Robert William Hegner (1880–1942), then assistant professor of zoology at the University of Michigan and later an international research leader in protozoology and parasitology at Johns Hopkins University, did the same in his textbook *The germ-cell cycle in animals*.[24] Similarly, the early development of *Ascaris megalocephala* as well as that of stem cells featured in a biological contribution by the Berlin anatomist Richard Weissenberg (1882–1974) to the *Handbuch der Sexualwissenschaften* of the sexologist Albert Moll (1862–1939).[25] Weissenberg was a former assistant to Oscar Hertwig, who had been appointed director of the Anatomical–Biological Institute of Berlin University in 1888.[26] In Weissenberg's account, the term 'stem cells' (*Stammzellen*) referred specifically to early precursor cells of egg cells and sperm cells, the *Oogonien* and *Spermiogonien*.[27] In this way the concept of stem cells gradually became established in the fields of embryology and cytology, although with some variations in its precise meaning. However, the essential characteristic of a stem cell, as described by Boveri, was clear: a capacity for self-renewal as well as for differentiation into specific types of somatic cells or germ cells.

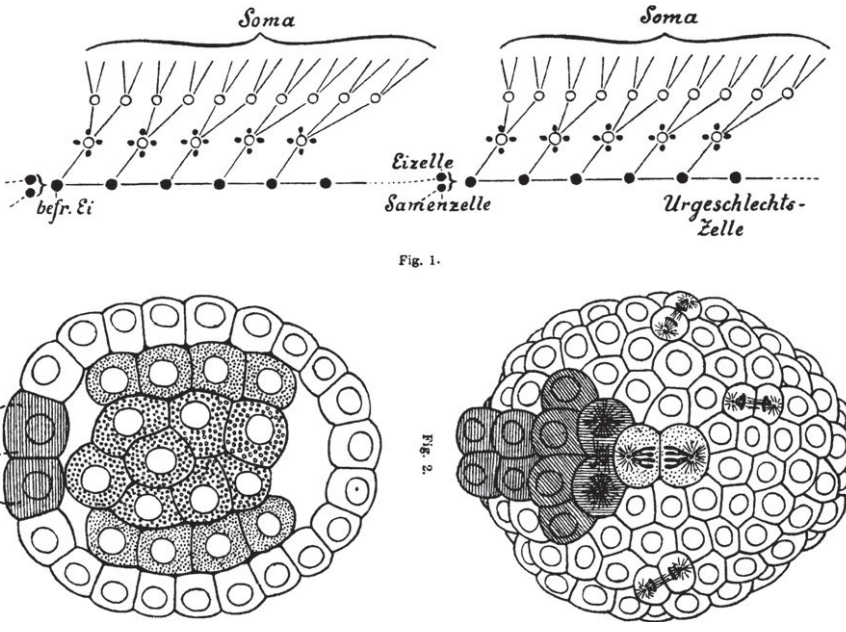

Figure 1. Theodor Boveri's representations of the early embryonic development of the intestinal worm *Ascaris megalocephala*, showing self-renewal as well as differentiation of stem cells.[96] The blackened circles along the horizontal line in Fig. 1 represent the 'stem cells' (*Stammzellen*) with full chromatin content, starting with the fertilized egg cell and leading after five divisions to the 'primordial germ cell' (*Urgeschlechtszelle*). The empty circles with surrounding black dots symbolize the 'primordial somatic cells' (*Ursomazellen*), in which 'chromatin diminution' occurs as the initial step towards cell differentiation. The empty circles represent early somatic cells with reduced chromatin. Figs 2 and 3 illustrate, respectively, a ventral view and an optical section of the *Ascaris* embryo at a stage of about 120 cells; two primordial germ cells that have just divided are shown in the centre of Fig. 2. (Bayerische Staatsbibliothek München, Signatur: Bavar. 2469 dz-7/8.)

Stem cells in haematological research before World War I

The notion of stem cells also resonated with researchers outside the specific field of embryology. For example, in 1896 Artur Pappenheim (1870–1916), working at Virchow's Pathological Institute in Berlin on the formation of red blood cells, called the common precursor cell of the red and white blood cell lineages the 'stem cell' (*Stammzelle*).[28] Assuming that he was justified in approaching a matter of clinical relevance (such as for the diagnosis and prognosis of anaemia) through comparative and embryological studies on phylogenetically lower animals, he examined the blood of amphibians (for example frogs and salamanders) at different developmental stages and ages. Amphibians were at that time commonly used for haematological studies because of the relatively large size of their blood cells. Moreover, Pappenheim believed that his findings on blood formation during the ontogeny of different species of amphibians illustrated Haeckel's biogenetic law.[29] Although he cited neither Valentin Haecker nor Theodor Boveri, Pappenheim was aware that 'stem cells', or 'mother cells' (*Mutterzellen*) as he also called them, with different developmental options had been described more widely in embryology. He mentioned the differentiation of stem cells into egg cells and follicle cells; into spermatoblasts and spermatogonia; into the sensory cells and supporting cells of sense

organs; into ganglion cells and neuroglia cells; and into the different cell types of connective tissues.[30] Thus, his conception of the stem cell was that of an embryonic cell that had the potential to differentiate into diverse cell lines and in this way to form the basis of different types of blood cells, body tissues and germ cells.

By the early twentieth century the stem cell concept seems to have been fairly well established in haematological research.[31] Pappenheim continued to apply the notion of stem cells in his later clinical–pathological work on different forms of leukaemia, arguing that myelocytes and lymphocytes originated from the same 'lymphomyeloblast multipotent stem cell'.[32] To illustrate his hypotheses about the genealogical relationships of different types of blood cells he drew increasingly complex 'stem trees' (*Stammbäume*) (figure 2). Wera Dantschakoff (born in 1879), who then worked at the Institute for Histology and Embryology of the University of Moscow on blood formation in the chicken embryo, concluded that the 'lymphocyte' was the 'common, indifferent stem cell' for erythrocytes as well as granulated leucocytes.[33] And the St Petersburg histologist Alexander Maximow (1874–1928), speaking in 1909 to the Berlin Haematological Society, suggested that the 'lymphocyte' was 'the common stem cell' of all types of blood cells, both during embryonic development and in the adult life of mammals. Significantly, the term 'stem cell' (*Stammzelle*) featured in the title of Maximow's paper.[34] All three authors were committed to the 'monophyletic' or 'unitarian' view that the various types of blood cells ultimately derived from a common, haematopoietic stem cell.

A powerful supporter of this view was the Königsberg professor of pathology, Ernst Neumann (1834–1918), who had demonstrated in 1868 that bone marrow was a site of blood formation in humans and other mammals.[35] On the basis of his later studies in frogs, he suggested that 'lymphocytes' in the bone marrow were the earliest, common precursor cells of the erythrocytes, of the polymorphonuclear leucocytes (granulocytes) and of the lymphocytes of the circulating blood. This 'unitarian' view contrasted with the 'dualist doctrine' of Paul Ehrlich (1854–1915), who assumed that the lymphocytes and leucocytes (granulocytes) originated from morphologically different precursor cells in different organs: the lymphocytes developed in lymph nodes and the spleen, and the leucocytes in the bone marrow.[36] In 1912 Neumann speculated that the haematological controversy between 'unitarians' and 'dualists' might one day be decided if it became possible to grow isolated blood cells in pure cultures, as Robert Koch (1843–1910) had done with bacteria.[37]

Beginnings of tissue culture

By this time, embryonic cells that gave rise to nervous tissue, the so-called neuroblasts, had for the first time been studied in isolation, outside the embryo.[38] During the years 1907–09 the American anatomist and biologist Ross Granville Harrison (1870–1959) investigated the growth of nerve fibres from these cells. The context for his investigation was contemporary controversy about the processes involved in the formation of nervous connections during embryonic development. In experiments on frog embryos, started at Johns Hopkins University and continued after his move to Yale in 1907, Harrison explanted small pieces of prospective nervous tissue and placed them in drops of frog lymph on coverslips. After the lymph had clotted, the slips were inverted over hollow slides (thus encasing the drops and tissues), and the preparations were sealed with paraffin (the so-called 'hanging-drop technique', which was then common in bacteriology for studying the growth of

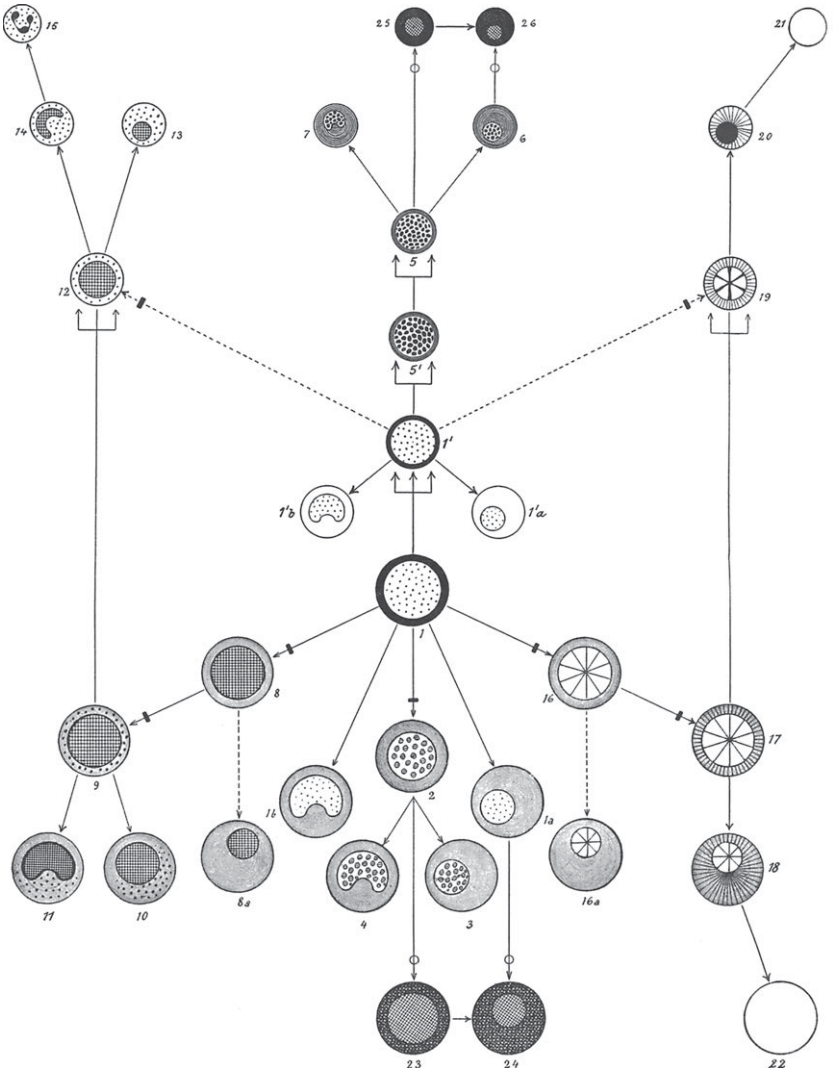

Figure 2. A haematopoietic stem tree by Artur Pappenheim.[97] The multipotent stem cell (no. 1) in the middle of the scheme is emphasized by the bold circle. It is the origin of the 'myeloleukoplastic branch' (to the left), the 'erythroplastic branch' (to the right), 'the lymphoplastic branch' (in the middle, upwards), and the 'splenoplastic branch' (in the middle, downwards). (Staatsbibliothek zu Berlin, Signatur: 4″ Kv 1955.)

microorganisms). The embryonic tissue stayed alive for a week or more under these conditions if strict asepsis had been observed during the procedure, and Harrison was able to observe under the microscope how the neuroblasts grew nerve fibres into their environment. In control experiments with tissues from various other parts of the embryo he described how other embryonic cells differentiated in a characteristic manner under the same conditions, for example into epidermis cells or muscle fibres. In epidermis cells, cilia were formed that moved; and muscle fibres contracted if they had a connection with nervous tissue.[39]

The differentiation of the embryonic cell, specifically that of the neuroblast into a nerve cell with an axon, was in Harrison's view due to 'forces immanent in the neuroblast itself' or 'self-differentiation', although he conceded that secondary factors in the environment of the cell might influence the path of the growing nerve fibre.[40] His experiments marked the beginning of the method of tissue culture, which was developed by other researchers, especially the Franco-American experimental surgeon Alexis Carrel (1873–1944) at the Rockefeller Institute for Medical Research, over the subsequent decades.[41] From the beginning, Harrison himself was well aware of the great potential of his method, speaking of its 'many possibilities in the study of the growth and differentiation of tissues'.[42] Ernst Neumann pointed to the first successes of Carrel in tissue culturing as a reason for his hope that blood cell cultures might in future be produced as well.[43]

Early connotations of stem cells

Collectively, those research developments concerning various aspects of stem cells in embryology, haematology and histology carried positive connotations of development, differentiation and reproduction, which entered the public discourse on the 'cell state' as notions of common heritage, equality, and division of labour. Oscar Hertwig, reflecting on the state as an organism in the early years of the Weimar Republic, made such associations very explicit, treating descent from a common 'mother cell' as a scientific argument for the principle of human equality:

> The doctrine of the equality of human beings, correctly understood, rests neither on an empty delusion of out-of-touch founders of a religion nor on a misleading, passionate philosophy of *Rousseau*, who wanted to realize the gospel of Christianity also in the institutions of the earthly world. It can also be explained, as I have attempted, scientifically. For, in full recognition of the countless inequalities that exist between human beings, they are still equal in the core of their nature; they are equal in exactly the same way as cells in a cell state, which—although they are in their higher development, as in the body of a vertebrate animal, differentiated into sometimes very different forms of tissue—are still equal among themselves as cells of one and the same organism and as descendents of a common mother cell. Inequality and equality are therefore in both cases only apparent contradictions; they are quite well compatible, like many contradictions that philosophy introduces to us, if thought about more deeply, because they can be dissolved.[44]

Moreover, a popular edition, in 1926, of Haeckel's *Natürliche Schöpfungsgeschichte* explained that the 'stem cell' or fertilized egg cell was a 'totally new being' due to the mixture of the 'nuclear masses' of the sperm and egg cell and that this fertilization process, not birth, marked the true beginning of 'the living existence of the [human] individual'.[45] At about the same time, popular science writer and medical doctor Fritz Kahn (1888–1968) disseminated knowledge about human ontogeny and cell differentiation in his work *Das Leben des Menschen* by arranging the various kinds of cells in a *Stammbaum* (family tree), starting with the egg cell.[46] The 'cell state' of the human body was for him a 'republic' that was led by a 'hereditary aristocracy of intelligence' (*erbliche Geistesaristokratie*), the brain cells.[47] He also explained the formation of primordial germ cells and body cells, using the example of Boveri's *Ascaris* studies. Echoing Weismann's theory of the

continuity of the germ plasm, Kahn compared the germ cells with 'state property' or 'national assets' that had to be passed on from one generation to the next.[48] However, by this time the notion of pluripotent stem cells and germ cells had also acquired a 'darker' and dangerous side: they could be the sources of tumours and cancer.

Embryonic cells and tumour formation before World War I

Considerable and long-lasting influence derived from the theory of the Breslau professor of pathology, Julius Cohnheim (1839–94), a former student of Virchow's, which stated that tumours arose from residual, displaced embryonic cells or rudiments (*Anlagen*) in the extra-uterine body. Provided that they received a sufficient supply of blood, these cells could start to grow, because of their 'embryonic nature', in an uncontrolled manner to form tumours and cancers. Tumours were thus, in Cohnheim's definition, 'atypical neoplasms of tissue based on an embryonic rudiment' and were thus related to embryonic malformations. Both tumours and malformations resulted from some 'mistake' during embryonic development.[49] The malignancy of a tumour depended in his view on the lack of 'physiological resistances' in the body.[50]

First fully formulated in 1877 as part of his lectures on general pathology, Cohnheim's theory (as it came to be known) was widely discussed in late nineteenth-century and early twentieth-century medicine, being seen as an alternative to then current 'parasitic' (bacteriological), mechanical, and chemical theories on the causes of cancer.[51] To test Cohnheim's theory, numerous animal experiments were performed that involved the implantation or injection of embryonic tissues with the aim of producing tumours artificially. Many of these experiments were only partly 'successful': the implanted embryonic cells initially multiplied and differentiated, but growth stopped after some weeks or months, and the new tissue was resorbed.[52] However, if embryonic tissues were injected into the abdominal cavity of rats, there was more frequent development of 'real', lasting tumours. Max Askanazy (1865–1940), professor of general pathology in Geneva and formerly assistant in Neumann's Pathological Institute in Königsberg, was able to produce teratoma-like tumours ('teratoids') in this way.[53]

In fact, the analogy between embryonic development and tumour growth was regarded as particularly obvious in the case of teratomas, because these tumours typically included a mixture of undifferentiated and differentiated tissues (such as skin, hair, bone, cartilage, teeth, gut, muscle, glands and nervous tissue). According to Askanazy, the development of teratomas from 'embryonic germs', was the most 'beautiful' illustration of Cohnheim's theory.[54] In 1907 Askanazy gave an overview lecture on teratomas at the conference of the German Pathological Society, in which he emphasized the 'organism-like' (*organismoide*) structure of these tumours and their presumed origin from displaced embryonic cells that were almost equivalent to eggs (*eiwertige Keime*). He also referred to these 'egg-equivalent' cells as 'stem cells' (*Stammzellen*) and assumed that they were residual embryonic cells that had been segregated during an early embryonic phase, up to the blastocyst stage, and been delayed or arrested in their development.[55]

This was the so-called 'blastomere theory' (*Blastomerentheorie*) of teratoma formation, which had been proposed around the turn of the century by Felix Marchand (1846–1928), professor of pathology in Marburg, and the Greifswald anatomist Robert Bonnet (1851–1921).[56] Another hypothesis, first suggested by Marchand, was that teratomas might

develop from fertilized 'polar bodies'; that is, the rudimentary or 'abortive' eggs left over from oogenesis.[57] Both hypotheses rested on the observation that most teratomas were composed of a mixture of tissue types that derived from all three germ layers (ectoderm, endoderm and mesoderm), which meant that these tumours resembled embryos. In the 1890s, the Leipzig surgeon Max Wilms (1867–1918) had demonstrated this composition for teratomas of the testes and ovaries (their most frequent location) and had therefore suggested referring to them as 'embryomas'. Wilms initially assumed that an embryoma developed from a germ cell in the ovary or testis, but later agreed with the blastomere theory of Marchand and Bonnet.[58] Moreover, Cohnheim's theory that tumours arose from displaced, residual embryonic cells and that their development mirrored embryonic development received critical support by the Bonn professor of pathology, Hugo Ribbert (1855–1920), who taught a modified version of it. According to Ribbert, a displacement of embryonic cells might occur not only during embryonic development but also in post-foetal, extra-uterine life. The crucial factor for triggering the cells' uninhibited growth was a lack of 'tissue tension' in their new environment. Had those cells stayed in their normal place, within their physiological tissue connections, their growth tendency would have been kept in check by this 'tension'.[59]

Significantly, Theodor Boveri, too, became interested in the problem of the causes of tumour formation, although he could only comment (as he admitted) from the perspective of a zoologist who had familiarized himself with the relevant medical literature. However, he felt entitled to comment on the basis of his research into the biology of cells.[60] In a monograph on the problem, published in 1914—one year before his premature death—he suggested that malignant tumours arose from a primordial cell (*Urzelle*) with an 'incorrectly combined stock of chromosomes'. Such a cell might arise from an atypical cell division (multipolar mitosis) and have a tendency for growth that it passed on to subsequent cell generations together with its abnormal chromosome combination.[61] In his view, a connection between malignant tumours and residual embryonic cells existed in only a minority of cases. In most cases, the immature, indifferent character of tumour cells was instead a secondary phenomenon in the development of cancers.[62] Although Boveri's chromosomal theory of tumour causation might have provided to some extent a new alternative to the theory of 'embryonic remnants', it seems to have found little resonance in its own time.[63] Various reasons have been suggested for the contemporary lack of attention to Boveri's final work: a chilly response from the medical community, delays in exploring his claims as a result of 'inadequacies' of tumour chromosome preparations, and the disruption of communications between German and English-speaking scientists during World War I.[64]

During the late nineteenth and early twentieth centuries, then, embryonic cells, and stem cells of the germline, had assumed an ambiguous status. On the one hand they gave rise to normal development and reproduction, but on the other they could become the source of malignant tumours if they strayed from the right path, as it were. The language used by scientists to describe the processes of tumour formation was hardly less metaphorical than that which had been used in depicting the physiology and normal structural organization of the body. The very notion of embryonic 'rudiments' in Cohnheim's theory was metaphorical in so far as his German term for it, *Anlagen*, implied an assemblage of cells as well as a general disposition for future development.[65] Cohnheim also used the then common comparison of tumours with parasites that take for themselves 'materials' that would otherwise have been used for physiological purposes of the body.[66] In a similar

sense, Boveri wrote that the cell of a malignant tumour had lost certain characteristics, so that it fell back from an 'altruistic state' (serving the body as a whole) to an 'egoistic state', manifested in 'unlimited reproduction'. According to Boveri, the uncontrolled multiplication of tumour cells might also result from a lack of 'inhibitory mechanisms' (*Hemmungsvorrichtungen*) that were normally present in cells.[67] Ribbert's idea that cells that had escaped the control of their physiological tissue environment would become dangerous through their unchecked growth was mirrored in the statement by the Berlin pathologist Otto Lubarsch (1860–1933) that disease originated from the 'uprising of the small people, the proletariat' in the cell state.[68] In Lubarsch's mind, cells were likened to proletarians who might become dangerous to the state if they were not integrated into society.

Teratoma research before and after World War II

Cohnheim's theory of embryonic remnants and the blastomere theory of Marchand and Bonnet did not remain unchallenged. In the late 1920s, Gilbert William de Poulton Nicholson (1878–1949), professor of morbid anatomy at Guy's Hospital, London, argued, on the basis of histological evidence, against the view that teratomas were homologous to embryos or even 'rudimentary embryos'. Lacking the characteristics of 'independent existence' that embryos owned, such as membranes, segmentation and their own vascular system, teratomas were for Nicholson malformations of the somatic tissues of the host in reaction to stimuli from their environment.[69] He placed the origin of teratomas at a later developmental stage, in which, as he polemically put it, 'nebulous and impossible polar bodies, blastomeres and similar pathological *monstra* cease to trouble'.[70] For him, teratomas and tumours more generally were pathological manifestations of physiological growth processes.[71] Nicholson therefore remained sceptical regarding a presumed cell of origin:

> I believe that [cell] differentiations are reactions to stimuli which, although unknown, are not unknowable, and that they will be analysed and classified one day. I am prepared to accept the absence of the essential steps of ontogeny as the cause of the failure of a toti-potent cell to produce a soma and organism, when the cell and its toti-potence will have been established in teratoma formation.[72]

Moreover, a key element of the embryonic theory of tumour formation, the *displacement* of embryonic cells, became doubtful in the late 1940s. Using the collection of human embryos at the Carnegie Embryological Laboratory, Emil Witschi (1890–1971), professor of zoology at the State University of Iowa, studied in serial histological sections the migration of primordial germ cells from the endoderm of the yolk sac to the primitive gonads. Although there were obvious variations in the cells' paths, his observations did not produce any evidence of actually displaced cells. They rather indicated that cells that failed to migrate regressed and were resorbed.[73] Furthermore, Witschi, who under the supervision of Richard Hertwig had received his PhD in 1913 on sexual differentiation in frogs and who had briefly worked with R. G. Harrison in 1926, denied that there was any uncontested evidence for the development of germ cells into any other cell type than either egg cells or sperm cells. Although they were *genetically* totipotent (that is, they carried the hereditary material for all parts of the new organism), they had not been seen

to transform into somatic cells during ontogeny. For Witschi, they were therefore as specialized as neurons or muscle cells.[74]

Despite such findings and expert criticisms, the theory that teratomas and other tumours might arise from residual embryonic, pluripotent cells, particularly those of the germ line, continued to have currency in the period after World War II. Since the nineteenth century, a large number of cases of human teratoma, mostly in the ovaries and testicles but also in various other locations, had been described.[75] In 1953 the pathologists Frank J. Dixon (1920–2008) of the University of Pittsburgh and Robert A. Moore of Washington University in St Louis reported on their histological re-examination of about 1000 cases of testicular tumours recorded in the files of the Armed Forces Institute of Pathology in Washington DC.[76] The vast majority (96.5%) of these tumours were classed by them as germinal tumours (that is, seminomas, embryonal carcinomas, teratomas, choriocarcinomas, or combinations of these types). Dixon and Moore postulated that these tumours originated from germ cells because their tissues displayed 'a multipotentiality that approaches that of the germ cell itself'—an argument that was remarkably similar to Askanazy's hypothesis of 'egg-equivalent' stem cells formulated almost half a century earlier.[77] The fact that teratoid tumours had generally been found most frequently in the gonads (in men as well as women) further supported Dixon and Moore's view; in addition, regarding the relatively uncommon cases of such tumours occurring in other sites, the idea of germ cells that had been somehow 'misplaced' during early embryonic development still was for them 'an attractive hypothesis'. They had to concede, however, that the precise type of cell that gave rise to germinal (teratoid) tumours, whether 'undifferentiated germ cell, embryonic germ cell, spermatogonia, or spermatocyte', remained an open question.[78]

Embryonal carcinoma cells and the beginnings of modern stem cell research

This was the state of knowledge about the cellular origins of teratomas when, in 1953, Leroy Stevens, then a postdoctoral researcher at the Jackson Laboratory in Bar Harbor, Maine, made a chance finding in a particular strain of mice—a finding that set in motion an extensive series of experiments that ultimately led to the isolation of embryonic stem cell lines. The Jackson Laboratory had been founded in 1929 by the Harvard-trained geneticist and former president of the University of Michigan, Clarence Cook Little (1888–1971), as a facility for the breeding of standardized, genetically defined strains of mice, particularly for the purpose of cancer research.[79] Stevens, who had earned his PhD in developmental biology and had become Little's assistant in 1952, was given the task of systematically studying potential mutagenic and carcinogenic factors, including the influence of tobacco and cigarette paper, in particular strains of mice.[80] Routinely examining a large number of mice, he encountered within a period of eight months three cases of teratoma in the testes of inbred 'strain 129' mice, a finding that attracted attention in the laboratory because this type of tumour had only very rarely been observed previously in mice.[81]

By September 1954 Stevens and Little were able to report that 30 out of 3557 male strain 129 mice examined—that is, nearly 1%—had a spontaneous testicular teratoma. One of these tumours could be maintained through serial transplantation; that is, the injection of tumour material under the skin or into the abdominal cavity of other

mice, over 16 generations. Significantly, this transplantable tumour was composed of 'undifferentiated, rapidly dividing embryonic-type cells', and Stevens and Little therefore agreed with Dixon and Moore's view that testicular teratomas probably arose from totipotent, undifferentiated cells of the germ line. Moreover, these findings indicated for Stevens and Little not only a particular genetic disposition for this type of tumour in this specific strain of laboratory mice but provided, as they pointed out, an 'important tool' for studying the biology of teratomas extensively and in depth.[82] Stevens grasped this opportunity 'with great excitement' and made teratomas the focus of his research over the following decades.[83]

In his subsequent research Stevens demonstrated that teratoma cells produced embryo-like ('embryoid') bodies when transplanted into the abdomen of mice[84] and that, conversely, certain embryonic tissues and fertilized egg cells gave rise to teratomas and teratocarcinomas if implanted into the testes of mice.[85] The notions of pluripotent embryonic stem cells and of embryonal carcinoma cells became increasingly exchangeable.[86] Lewis Kleinsmith and Barry Pierce of the Pathology Department of the University of Michigan found in the early 1960s that embryonal carcinoma cells transplanted into mice gave rise to differentiated somatic tissues as well as embryonal carcinoma, and interpreted this result as supporting the stem cell theory of cancer.[87] Remarkably, they pointed out that Askanazy, in 1907, had been the first to propose that the somatic tissues of teratomas might derive from undifferentiated stem cells.[88] Working with teratocarcinoma cells from one of Stevens's mouse cell lines, Beatrice Mintz and Karl Illmensee at the Institute for Cancer Research in Philadelphia reported in 1975 that these tumour cells supported normal development if injected into early mouse embryos at the blastocyst stage. The malignancy of those cells thus seemed to be reversible.[89] Six years later, Martin Evans and Matthew H. Kaufman at the University of Cambridge and Gail Martin at the University of California in San Francisco isolated and cultured mouse embryonic stem cells, which resembled teratocarcinoma cells and were pluripotent.[90] Retrospectively, this constituted a decisive step in the history of modern embryonic stem cell research, because these cells could now be cultured directly from blastocysts without taking the detour of producing teratocarcinoma cell lines.[91] In 1998 the groups of John Gearhart at Johns Hopkins University and of James Thomson at the University of Wisconsin each reported that they had been successful in isolating and culturing human embryonic stem cells.[92] The sources of these cell lines were aborted embryos (Gearhart) and supernumerary *in vitro* fertilization embryos (Thomson), respectively.

Another important contribution to modern stem cell research was developed in the early 1960s by Ernest McCulloch (1926–2011) and James Till of the Ontario Cancer Institute in Toronto when studying the effects of radiation on haematopoiesis in the bone marrow. In irradiated mice, which had subsequently been injected with bone marrow cells, nodules were found in the spleens on post-mortem examination. As Till and McCulloch showed, the number of these nodules was proportional to the dose of marrow cells that the mice had received, each nodule representing a cell colony that derived from one haematopoietic stem cell or 'colony-forming unit' (CFU), as the two researchers cautiously called it.[93] The 'spleen colony assay' was the first *quantitative* assay for blood stem cells and still retains its relevance for our understanding of haematopoiesis. It helped in the eventual vindication of the 'monophyletic' or 'unitarian' view of Pappenheim and Neumann that all types of blood cells originate from one multipotent stem cell in the bone marrow.

Conclusion

The concept of stem cells was first used in the writings of zoologists and medical scientists in Imperial Germany. Adopting the term *Stammzellen* from Ernst Haeckel, Theodor Boveri was particularly important in making these cells known as carriers of the so-called 'germ plasm' and as the starting points in embryological development of differentiated body cells as well as germ cells. Boveri's concept of a stem cell included both a capacity for self-renewal and a capacity for differentiation; these are the basic defining characteristics of stem cells that are still accepted today. The notion of stem cells was also readily applied at the start of the twentieth century in haematological work by histologists such as Artur Pappenheim and Ernst Neumann who, contrary to Paul Ehrlich's 'dualist' view, assumed the existence of a multipotent stem cell in the bone marrow that was able to differentiate into any type of blood cell. In the haematological context the focus of discussion of stem cells gradually began to move from the genealogical perspective of Haeckel and Boveri to the cells' developmental possibilities or pluripotency. Although the exact meaning of 'stem cells' fluctuated between different authors, and names such as 'mother cells' or 'primordial germ cells' were sometimes used synonymously, they carried broader, positive connotations of common heritage, renewal, physiological development and differentiation.

In the same period, however, embryonic cells began to be suspected as causes of cancer in the extra-uterine body. This hypothesis, originating with Julius Cohnheim, turned out to be very fruitful for tumour research, in particular experimental and pathological–anatomical work on teratomas. The multiple types of tissues found in teratomas led Max Askanazy and others to the hypothesis of pluripotent 'germs' or 'stem cells' as their points of origin. Embryonic cells were also seen as potentially dangerous, if they had lost their integration in a physiological tissue environment. The 1950s research of Leroy Stevens into teratomas and teratocarcinomas, which is commonly regarded as a foundation of modern work on embryonic stem cells, should be seen against this historical ambiguity of positive and negative sides of the 'stem cell'. Transplanted embryonal carcinoma cells, as Stevens, Barry Pierce and others showed in animal experiments, could produce various differentiated tissues as well as cancer. Moreover, as Alison Kraft has recently argued, in the history of leukaemia research in the second half of the twentieth century stem cells also assumed an ambiguous status, being seen as a 'biological force for good' in the context of bone marrow transplantation as well as having a 'dark side' through the concept of the cancer stem cell.[94] Indeed, as novel stem cell therapies, for example for neurological conditions such as Parkinson's disease, have been tested in the last few years, concern about the risk of tumour formation has become a feature of both clinical and ethical debate.[95] In this situation it may well be appropriate to remember the historical understandings of stem cells as delineated in this article.

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