2011

Graphical and computationally intensive techniques for presenting and disseminating information about the genetics of disease: Possibilities, limitations, and additions

Leeming, William

2011

Graphical and Computationally Intensive Techniques for Presenting and Disseminating Information About the Genetics of Disease: Possibilities, Limitations, and Additions

William Leeming
OCAD University
bleeming@faculty.ocadu.ca

Leeming, William. "Graphical and Computationally Intensive Techniques for Presenting and Disseminating Information About the Genetics of Disease: Possibilities, Limitations, and Additions." *Science Communication* 33.4 (2011): 415–447. Web.

The final form of this article is available here: http://scx.sagepub.com/content/33/4/415.short.

Leeming, W. (2011). Graphical and Computationally Intensive Techniques for Presenting and Disseminating Information About the Genetics of Disease: Possibilities, Limitations, and Additions. Science Communication, 1075547011401631.

Pre-Publication Draft

Graphical and Computationally Intensive Techniques for Presenting and Disseminating Information about the Genetics of Disease – Possibilities, Limitations and Additions

Abstract: It is now a commonplace to think that genetic factors are involved in disease causality. Yet, exactly how genetic factors contribute to the onset of disease is not fully understood and the aetiology of the genetics of disease is incomplete as a theory. All the same, information and images pertaining to genetics and disease remain arguably serviceable when they produce agreeable diagnostic, prognostic and, ultimately, therapeutic results in patient care. This paper begins with a historical survey of graphical techniques involved in representing the genetics of hereditary disease. Representations began to appear early in the twentieth century soon after the re-discovery of Mendel's laws of inheritance. Family pedigrees were drawn to signify episodes of hereditary disease in families. The disposition for hereditary disease among family members was subsequently 'linked' to chromosomal operations. The article then goes on to show how the scope of genetic information gathering and representation broadened steadily through the twentieth century to accommodate, first, laboratory technologies for identifying chromosomal anomalies and genetic metabolic disease and, second, molecular biological techniques and large-scale automated genomic sequencing. This leads, in a final step, to considerations of the emergent digital environment of online databases associated with computational genetics and genomics and their capacity to generate working models of what causes disease.

Keywords: disease causality, genetics, chromosome mapping, genetic testing, genomics.

Introduction

The history of ideas concerning genetics, disease and medicine in North America and the UK has mainly been studied in relation to eugenics in the first half of the twentieth century and to advancements in molecular biology in the final third. With regard to the former, the history of eugenics has been well traversed by historians.[1] In the latter case, by contrast, historians of molecular biology have produced excellent studies of the discovery of DNA and the considerable effort to map disease-causing genes.[2] But what have been left out of the picture are the ways increasing medical interest in human genetics after the Second World War led to support for new ideas about the genetics of disease.

To fully appreciate changes in medico-scientific conceptions about the genetics of disease, we must first look at changing ideas about the relationship between heredity and heritable disease. In doing so, we must remind ourselves that ideas about heredity predate whole vistas of medical science including epidemiology, immunology, endocrinology, and laboratory diagnostics. Historians of medicine studying the topic of heredity and disease have posited an early or pre-modern period in which stories were collected about so-called 'monstrous births' in the naturalist tradition of sixteenth-century Europe (Daston and Park, 2001: 149; López-Beltrán, 2006). Case studies of *morbid haereditarii* (heritable disease) recounted a range of physical/developmental forms as well as

biographical aspects of illness episodes or narratives in time.[3] That being said, the early chroniclers of cases of heritable illness limited their attention to individual cases of disease and not family histories *per se*. Staffan Müller-Wille and Hans - Jörg Rheinberger (2007: 3) note, for example, that until the mid-eighteenth century, the 'generation of living beings' was viewed, to varying degrees, in terms of unique and isolated events. Heredity was not separated from

> … the contingencies of conception, pregnancy, embryonic development, parturtition, and lactation. Similarity between progenitors and their descendants arose simply because of the similarity in the constellation of causes involved in each at of generation. (*ibid.*)

All the same, as particular 'clues' and 'symptoms' took on special roles and significance (e.g., missing or supernumerary limbs, birth marks, diminished stature) case studies took on emblematic status (Bruner, 1991). The notion of the 'familial taint' lent typicality to the case at hand.[4] The physician became 'a chronicler of bodily events and systematic narrator of particular phenomena in a particular context' (Epstein, 1995: 25). Case studies in turn supported natural history and the seeking out of nosological categories for medical classifications of heritable disease.

Laure Cartron (2007: 160-1) has indicated that physicians and physiologists in eighteenth-century France were the first to link the word heredity (*hérédité*) with ideas of hereditary disposition to disease, predisposing diathesis (i.e., an acquired susceptibility of the body to disease), and constitutional weakness (i.e., inherent weakness in the physical make-up of a person). This follows earlier work by Erwin Ackerknecht (1982) who showed that the notion of diathesis gained popularity in medical circles at the end of the eighteenth century and 'constitution studies' went on to flourish in the United States,

France, and Germany by the 1920s. At the same time, Ackerknecht (1982: 325) points out that interest in these topics was waning and being 'outdistanced by bacteriology, endocrinology, serology, vitaminology, the neurology of the vegetative system, or genetics' by the 1940s. Indeed, Antonio Ciocco, in his 1936 article on the 'modern study of constitution,' complained about the apparent growing disregard of the 'genetic school of constitutionalists' for the field constitutional somatology.

Some psychologists and physical anthropologists interested in constitutional somatotyping would subsequently take up studies of the human constitution. [5] Genetics, in contrast, came to occupy an increasingly central position in the study of heredity as a result of a scientific line of inquiry that confined investigations to a few specific problems associated with the transmission of physical characteristics between generations. More particularly, genetic research on aspects of factoral transmission, sexual reproduction, and the production of physical variation in organisms served to limit the scope of inquiry after 1930. This departed significantly from earlier research to establish links between heredity, embryonic development and evolution (Richmond, 2007: 169-70; Amundson 2005). What is more, associated interest in connections between genetics and medicine resulted in a movement in support of the creation of examining and teaching positions for geneticists in North American medical schools after 1940 (Leeming, 2010). The intellectual and specialist aspects of the movement were emergent phenomena, created, split, and reattached to different groups of actors, and reconfigured numerous times over the course of four decades. In each instance, new kinds of working relationships appeared. Sets of diverse actors in local university-hospital settings coalesced into a new

collectivity; and, as a collectivity, actors defined and redefined occupational roles and work rules.

I have written elsewhere about the growth of human genetics and the formation of a new specialty area in Anglo-North American medicine (i.e., medical genetics) (Leeming, 2004; 2005; 2010). This article examines in greater detail the development of tools that were developed by the proponents and supporters of medical genetics to represent and disseminate information about the genetics of disease. Specifically, I go back and trace the underlying continuity of aims and objectives connecting graphical techniques developed to visualise the genetics of disease in the early twentieth century to contemporary computationally intensive techniques developed for storing and accessing genetic data. The first section of the article looks at ostensive representations of the genetics of familial disease associated with early Mendelian genetics. Chromosomal theories on 'linkage' and chromosome mapping are pursued in the second section, while techniques to store and disseminate data are introduced in sections three and four. The discussion in sections three and four includes examination of new approaches to presenting types of diagnostic test results after 1960. These occur with the advent of new laboratory technologies for studying chromosomal anomalies and genetic metabolic disease and, subsequently, with the add-on of molecular biological methods of analysis and large-scale automated genomic sequencing. This all leads, in a final step, to considerations of the emergent digital environment of online databases associated with computational genetics and genomics and their capacity to generate working models of what causes disease.

Ostensive representations of genetics and familial disease

Gooding (2004: 3) defines 'ostension' as 'the act of linking a token to the object it names or denotes.' He (2004*b*: 4) asks: 'What do you do when you want to describe a phenomenon that has never been seen before or features which have never been noticed or deemed as relevant to the depiction of a phenomenon or process?' How do you, for example, describe the genetics of Huntington's disease, a disease known to 'run in families'?

In 1872, the Ohio physician George Huntington (1850-1916) published a now famous description of what people experience who live with the neurological disease that has since borne his name.[6] However, Alf L. Ørbeck (1959) noted that at least five earlier descriptions of inherited forms of chorea pre-existed Huntington's account, including a particularly interesting description of inherited St. Vitus's Dance [7] provided by the Norwegian physician Johan Christian Lund (1830-1906) in his State Medical Report of 1860 for Saetersdalen. Lund's report is of interest for its effective use of a family pedigree. The pedigree tells us the names, marital status, and dates of death of members of two families in the Parishes of Valle and Byglands over four generations. (See figure 1.) It also identifies the relative severity of the 'attack' of the disease over time. To do this, the pedigree plots choreic episodes on a timeline of familial illness in a manner that recalls what the Russian literary critic and semiotician Mikhail Bakhtin (1895-1975) called 'chronotopicity.'

Drawing on Alexis Alexeevich Ukhtomsky's (1875-1942)[8] notion of the 'chronotope' (literally 'time space'), Baktin defined chronotopicity as 'the intrinsic connectedness of temporal and spatial relationships' (Bakhtin, 1981: 84; cf. Holquist, 1983). The principle of chronotopicity holds that those things 'that are static in space cannot be statically described, but must rather be incorporated into the temporal sequence of represented events and into the story's own representational field' (1981: 251). Moreover, words, diagrams and other 'mediating markers of spatial categories' are carried over into temporal relationship (*Ibid.*). Lund's family pedigree illustrates chronotopicity in so far as it is a means of shaping meaning in a long and complex chain of social (i.e., familial) and biological (i.e., disease) interactions over time and in space. This is accomplished by reducing the 'tree' form commonly used in European genealogical diagrams to simple timelines on which family members affected with choreic episodes of varying severity are mapped. This is innovative in so far as it demarcates and contextualizes the spatial and temporal limits of instantiations of inherited illness. Furthermore, it graphically calls to attention the point that *some thing* is being passed from one generation to the next. This is a detail that increasingly preoccupied researchers in the life sciences nineteenth and early twentieth centuries (Bowler, 1989; Wallace, 1992; Sapp, 2003). Indeed, this is a detail that continues to haunt researchers today with respect to *how some thing* contributes to the onset of inherited disease (Pearson, 2007; Moss, 2003).

Lund's family pedigree is notably different from the pedigrees produced by contemporary anthropologists who tended to use different kinds of data in order to

illustrate a mixture of biological and social factors characteristic of families. Moreover, biological and social factors feature prominently in the pedigrees used by the eugenics societies and associations of the late nineteenth and early twentieth centuries (Kevles, 1985; Mazumdar, 1992). So, for example, the persistence of 'pauperism' in a family might include indicators for drunkenness, theft, laziness, tuberculosis, and 'mental deficiency' in a composite illustration (Mazumdar, 1992: 82-5). The salient point, for the purposes of the present study, is that the use of family pedigrees in medico-scientific circles would increasingly concentrate on marking episodes of disease and other biological events in time and space in order to identify individuals who have passed on disease to the next generation.

Pauline H. Mazumdar has indicated that there was steadily increasing demand among geneticists after the 1920s 'for research rather than demonstration, for statistical treatment, for controls, and above all, for investigation of the effects of environment' regarding the use of family pedigrees (1992: 5).[9] In large part, this had to do with shifts and changes in the professional ideologies of the individuals analysing the pedigrees.[10] This is not to suggest that the *sociality* of the instantiations of certain traits (e.g., alcoholism, 'feeble-mindedness,' homosexuality) vanished from the scope of pedigree analysis. Rather, analysts would underscore the rising importance of the *medico-scientific* contributions of human genetics to the study of heredity and advancement of preventive medicine. Indeed, the expansion and growth of heredity counselling services provided by geneticists coincided with early publications promoting 'medical genetics' as a new field of study (Hogben 1931, 214-16; cf. Macklin 1931, 614; 1933, 1335). [11]

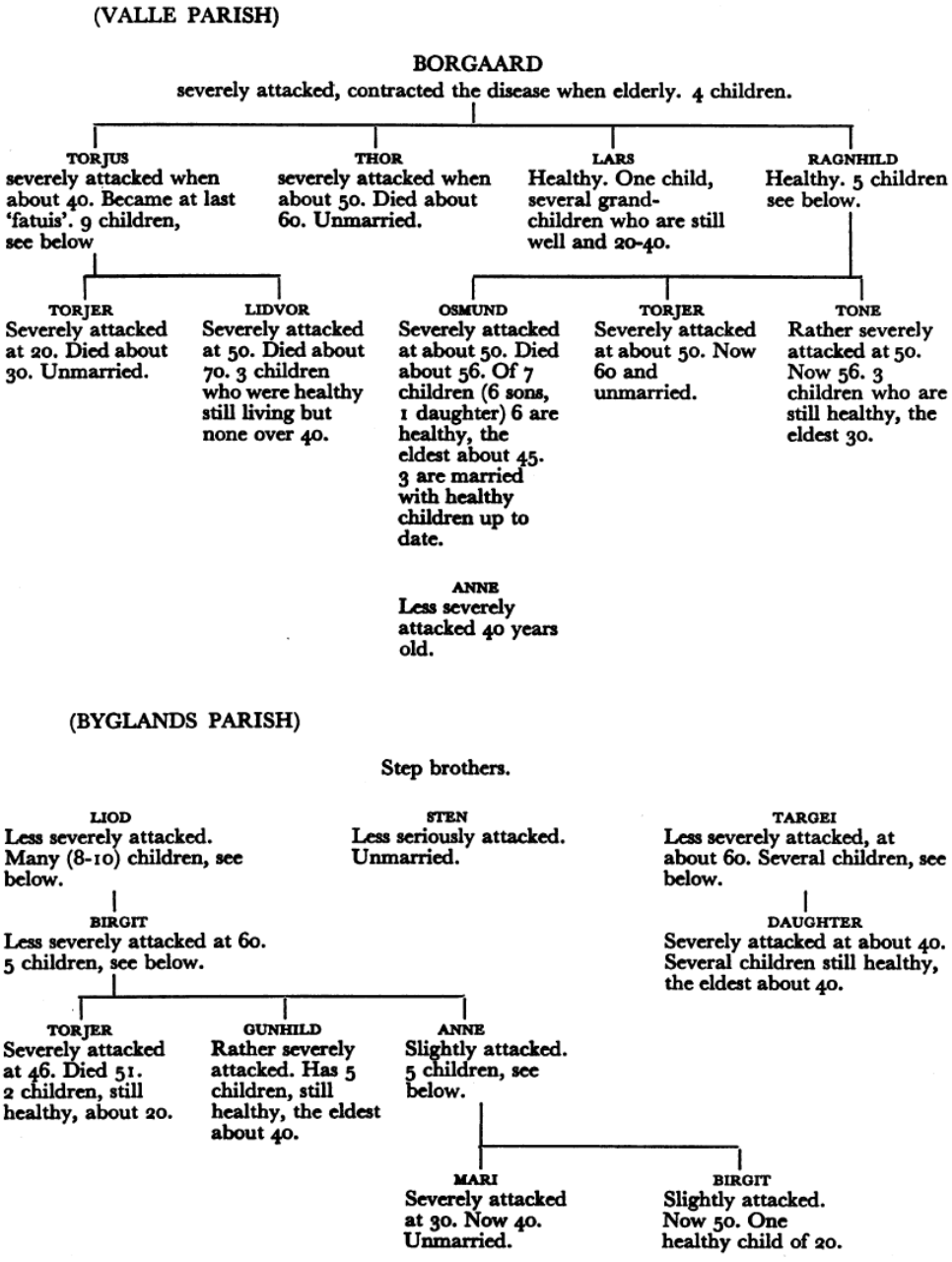

Figure 1. Lund's pedigree showing occurrence of inherited St. Vitus's Dance in two Norwegian families over four generations. (Pedigree reproduced from Ørbeck [1959] courtesy the Wellcome Trust. Reproduced with permission.)

With specific regard to changes in the clinical use of family pedigrees, the 'tree' form was reduced to a simple linear drawing on which family members affected with particular heritable traits (i.e., physical characteristics, disease, disorder) were identified by shaded squares (males), circles (females) and diamonds (sex unknown) set alongside unaffected members (blank squares, circles and diamonds) and labelled according to status (i.e., kinship, sibship, birthdates, marital, living/dead). The completed pedigree was accompanied by a legend identifying the traits under investigation. (I have provided an interpretation of Lund's pedigree of 1860 in figure 2 using standardised human pedigree nomenclature as outlined in Bennett *et al.*, [1995].)

The expression of the trait was the propositus (i.e., the member who brings the family to the attention of the investigator). This represented the starting point in plotting the relationship of biological entities on the tree, and was used as a basis of comparison of trait expression in affected relatives. On rare occasions, more than one family member would be considered propositi. For example, in a mid- twentieth century study of Huntington's chorea in six families collected over a period of two years at the University of Minnesota Department of Neuropsychiatry and the University of Minnesota Hospitals, individual members were collectively represented as propositi in one kinship network in which five brothers and sisters were identified as choreic (Oliver and Schiele, 1945). The decision was made after the names of the siblings of the propositi were compared by analysts and the married names of some of the choreic individuals were connected as incidences of Huntington's chorea.

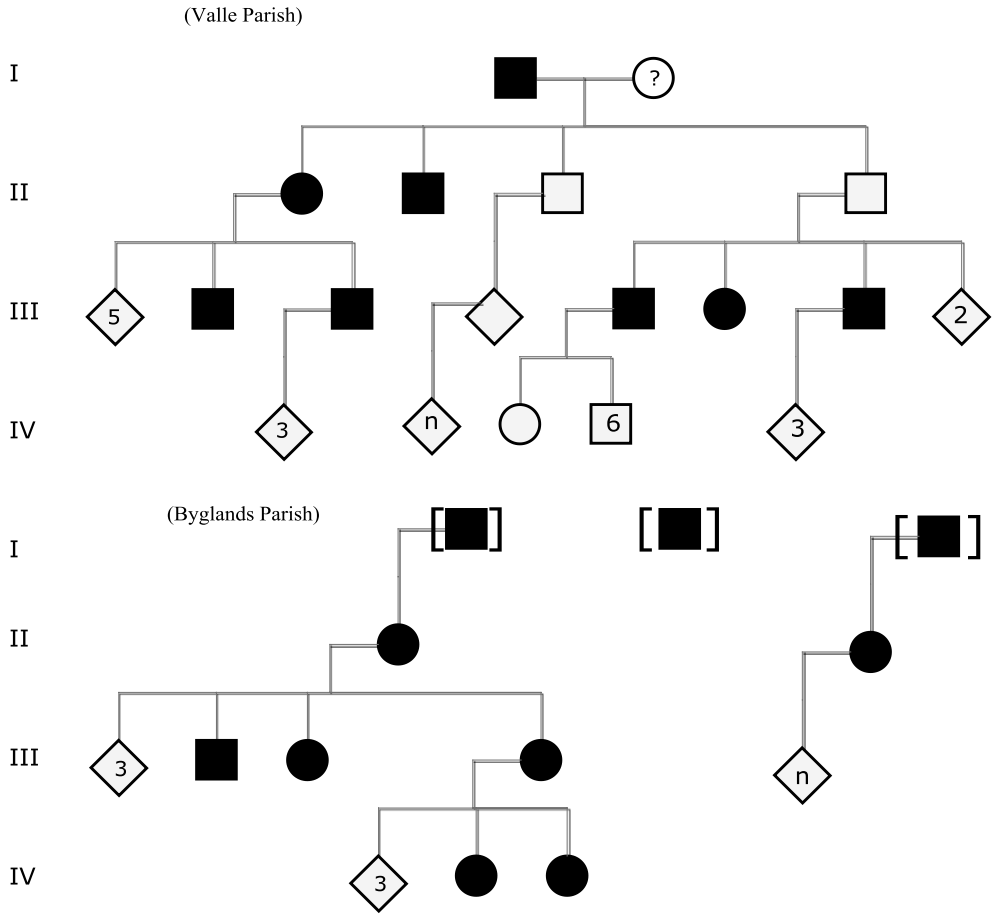

Figure 2. Lund's pedigree showing occurrence of inherited St. Vitus's Dance in two Norwegian families over four generations using standardised human pedigree nomenclature as outlined in Bennett *et al.*, (1995).

Health service providers continue today to use standardised human pedigree nomenclature to record episodes of illness recurring in families. But, again, whilst a pedigree is useful tool for plotting the chronotopicity of inherited disease, it neither demonstrates nor explains the mechanics of heredity. In what follows, I look at the translatory movement from using family pedigrees in ostensive systems to represent the genetics of hereditary disease to increasingly more sophisticated graphical techniques

associated with, first, chromosomal theories on 'linkage' and chromosome mapping, and, second, diagnostic testing.

From 'biological relatedness' to 'related to chromosomes and genes'

The geneticists who were the early proponents of heredity counselling and medical genetics were especially enthusiastic about chromosomal theories on 'linkage' and techniques associated with 'chromosome mapping.' Chromosomal theories on 'linkage' said that the inheritance of particular physical traits was associated with chromosomal activity. 'Linkage' was here derived from the idea that the nearer two affective genes lie on a chromosome, the greater their chance of being inherited together during reproduction, while the farther away they are from each other, the more chance of their being separated by the process of 'crossing over.' So, for example, Thomas Hunt Morgan (1866-1945) and his students at Columbia University demonstrated through breeding experiments with *Drosophila melanogaster* (i.e., vinegar fly) that genes affecting eye color and wing length are inherited. Equally, many geneticists in the 1930s believed that because the genetics of serological difference in humans was universally expressed (i.e., all humans belonged to one or another blood-group), the blood group categories might provide a specific set of chromosomal markers to which the genes for other traits (e.g., inherited conditions) could be 'linked.'[12] Thus it was hypothesised that if linkages could be found between the gene for, say, amaurotic idiocy and the blood group AB, researchers could suppose that, on the one hand, the "amaurotic idiocy gene" lay on the same chromosome as the AB gene, and, on the other, the relative distance between the two genetic factors.[13] A resulting keenness for 'linkage studies' led geneticists working in

the early heredity counselling clinics to collect vast amounts of information on known heritable traits including complexion, eye colour, hair colour, hair appearance (e.g., straight, curly, wavy), direction of hair whorl (cowlick), handedness (i.e., right, left, ambidextrous), ear lobes (i.e., attached, free), taster/non-taster trait (i.e., PTC test), blood group, sight defects, and hearing defects.

The roots of the chromosomal theory of heredity lay in cytology and microscopic observation of the structure of cells. A watershed event in the formation of chromosome theory was the proposal by the American cytologist and palaeontologist Clarence E. McClung (1870-1946) that what had been described in the 1890s as an association of sex-determination with a chromosomal element represented an 'accessory chromosome' (McClung, 1902). Over the next five years, McClung's proposal gathered the support of zoologist and cell biologist Edmund Beecher Wilson (1856-1939) at Columbia University (Kingsland, 2007). One of Wilson's students, Walter S. Sutton (1877-1916), following the work of the German cytologist Theodor Heinrich Boveri (1862-1915), went on to develop what would become definitive arguments concerning the association and orderly behaviour of paternal and maternal chromosomes as constituting the physical basis of the Mendel's laws of inheritance (Crow and Crow, 2002). The chromosome theory, as expounded by Boveri and Sutton, went on to provide a conceptual framework for others who sought to localise hereditary events in the nucleus of the cell.

The research of Thomas Hunt Morgan (1866-1945) and his students at Columbia University would go on to crystallize and support theories that the fundamental carriers of heredity are the chromosomes, which, following Wilhelm Johannsen (1857-1957), [14]

contained ‘genes’ which by analogy, following Carl Correns (1864-1933), could be visualised as entities arranged like ‘beads-on-a-string.’ [15] Morgan’s initial article on the subject, ‘Sex Limited Inheritance in Drosophila,’ was published in *Science* in July 1910, initiating a first step in the chromosomal theory of heredity. He followed this in 1911 by postulating that two paired chromosomes could ‘crossover’ between each other, and that the strength of ‘linkage’ between genes depended on the distance between them on the chromosome. Morgan’s student, Alfred Henry Sturtevant (1891-1970), subsequently pursued an idea that variations in the strength of linkage could be used as a means of ‘mapping’ genes on chromosomes by determining relative spatial distances. Sturtevant drew the first ‘chromosome map’ in 1913, mapping six sex-linked genes of *Drosophila* into a linear order, suggesting that the linear structure of the linkage group was analogous to what could be seen on the chromosome.

Sturtevant’s map consisted of six letters representing X-linked genes situated on a straight line with measurements to show calculated distances from ‘B.’ (See figure 3.) ‘B’ represented a gene for black body color of *Drosophila*. ‘C’ represented a gene that allowed color to appear in the eyes. Flies with the ‘P’ gene had vermilion eyes instead of the typically red. Flies with two copies of the recessive ‘O’ gene had eyes that appeared have a different shading of colour, eosin. The ‘R’ and ‘M’ represented genes affecting the wings. Sturtevant placed ‘C’ and ‘O’ at the same point because the data indicated they were always inherited together. Sturtevant then ordered the remainder of the genes according to available calculations of the day noting,

> [o]f course there is no knowing whether or not these distances as drawn represent the actual relative spatial distances apart of the factors. Thus the distance CP may

> in reality be shorter than the distance BC, but what we do know is that a break is far more likely to come between C and P than between B and C. Hence, either CP is a long space, or else it is for some reason a weak one. The point I wish to make here is that we have no means of knowing that the chromosomes are of uniform strength, and if there are strong or weak places, then that will prevent our diagram from representing actual relative distances — but, I think, will not detract from its value as a diagram. (1913: 6)

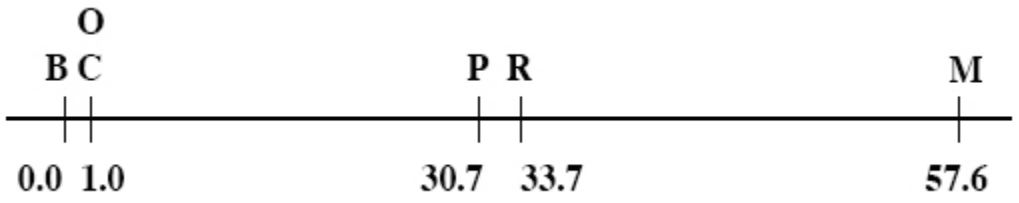

Figure 3. Sturtevant's first chromosome map. (Diagram reproduced from Sturtevant [1913] courtesy the Electronic Scholarly Publishing Project. Reproduced with permission.)

To be clear, it is important to understand that Sturtevant's chromosome map was constructed from a purely hypothetical and abstract analysis linking mathematical observations to possible spatial terms. That being said, he managed to lay the groundwork for ongoing graphic experiments in visualisation by analogy in which heredity appeared as a background assumption for a formal system of chromosomal operations. As Barbara Maria Stafford (1999: 23-4) has observed, analogy is 'a demonstrative or evidentiary practice – putting the visible into relationship with the invisible and manifesting the effect of that momentary unison.' Analogies 'materialise, display, and disseminate an enigma that escapes words' (1999: 24).

A series of chromosome maps were constructed in the first half of the twentieth century that shared in common a structure of part-and-whole relations with a topological

component (i.e., gene mereotopology) that accentuated relations of contact and connectedness; to the visualisation of limit, continuity, surface, point, node, and so on. Harvard University's William E. Castle (1867-1962) was the first to produce a three-dimensional model prototype (Castle, 1919) in counterpoint to the linear chromosome model published in Morgan and Bridge's *Sex-linked inheritance in Drosophila* (1916: 22). By contrast, University of Texas's Theophilus Shickel Painter (1889-1969) drew the mass of chromosomes as a composite in a manner reminiscent of the microscopists of the nineteenth century (Painter, 1923). At the same time, unlike the drawings of the microscopists, Painter's composite was an aggregate in which each chromosome could be differentiated and identified in terms of shape and size. This perspective proved to be highly useful in genetics instruction to demonstrate chromosomal events in three dimenstions using clay models (e.g., Winchester, 1965: 89, 143, 171, 175).

A series of dramatic confirmations of the natural correlation between chromosomal processes and phenotypic effects occurred in 1929 with experiments at the University of Texas and Columbia using X-ray-induced structural changes of the chromosomes (Muller and Painter, 1929; Dobzhansky, 1929). Major chromosomal aberrations that could be observed microscopically in mitotic and meiotic metaphase plates permitted the localisation of the genes not only in organisms with relatively large chromosomes but even in the small chromosomes of *Drosophila.* The following year the Bulgarian geneticist Dontcho Kostoff (1897-1949) drew attention to the 'discoid structure of the spireme' in *Drosophila* (Falk, 2003: 106). The discoid structure (i.e., bands) of the chromosomes, Kostoff said, indicated the existence of chemical differences in the

varying structural capacity to absorb haematoxylin. These features were, in turn, represented in new graphic methods by Theophilus Painter. Painter, while studying the comparatively enormous structures in the larval salivary glands of *Drosophila*, noted the visible banding patterns were constant enough from larva to larva to allow him to make detailed pictures of the entire chromosome set (Wallace, 1992: 70-71). Painter (1933, 1934) subsequently developed what became known as the 'salivary gland method' for the study of chromosomes. In the following years increasingly naturalistic cytological maps of the salivary gland chromosomes were produced, mainly by another one of Morgan's students, Calvin Bridges (1889-1938).

The method Painter (1934) employed for the preparation of slides was to dissect out the salivary glands of old larvae about ready to pupate, place these on a slide, add aceto-carmine, cover with a cover glass and stain for a few minutes. The specimens were then crushed by pressing on the cover glass with a needle, the excess of stain removed with filter paper, and the slide sealed with Vaseline. The specimen was then studied with a microscope under blue-green light. Drawings were made using a camera lucida at table level. Calvin Bridges remarked that in order to achieve the 'finest detail' in drawings, the following requirements were necessary:

> One is relatively light transparent staining of the chromosomes, with avoidance of heavy 'contrasty' staining, which may give the heavy lines very dark but the lighter lines not at all. Much iron and heating tend to spoil the finer details. The crispness of detail seen in larvae fully grown in pair cultures at a low temperature is lost in larvae from old cultures, from mass cultures and in larvae which have begun pupation. …
>
> Another requisite is selection of chromosomes or portions which are straight (i. e., not kinked or coiled) and are stretched somewhat. The lax chromosomes are from 70 to 110 times as long as normal gonial chromosomes,

> but the somewhat stretched chromosomes which are most favourable for observation are 150-160 times normal length. The maps presented herewith are drawn only from such partially stretched chromosomes, averaging 150 times normal. … The gross structure of salivary chromosomes is somewhat like that of an accordion, and unless these chromosomes are stretched the doubleness of most bands is not visible and many fine or dotted lines are obscured by their appressed neighbors. (1935: 61)

Further to this, Bridges designed a system of chromosome map nomenclature for cataloguing salivary bands (1935: 61-62). He divided the five main chromosome limbs (1=X, 2L, 2R, 3L and 3R) each into twenty sections, 100 in all. Sections were numbered 1 to 20 for X, 21 to 40 for 2L, 41 to 60 for 2R, 61 to 80 for 3L and 81 to 100 for 3R. Chromosome 4 had sections 101 and 102. Hence the number of a section was itself a key to the chromosome limb and to the relative position along that limb.

It is noteworthy that Bridges's maps are still widely referred to and his cataloguing system is still in use by those who prepare chromosome maps today. This has to do with the ways the visualisation system adapted to changes in theory about cytological structures (e.g., inversions, translocations, deletions, repeats) and processes. Briefly, the representational system offered the cognitive advantage of reducing data-sets to simple visual images. The system experienced improvements and incorporated: advanced techniques in staining specimens from mid-1930s, camera lucida drawing techniques in the 1930s and 1940s, micrographs after 1950, light microscopic photomaps after the mid-1970s, electron micrograph maps after late 1970s, whole mount electron micrograph maps after mid-1980s, and early computational database and ontological techniques for the exchange and integration of data after late-1990s. In each of these cases, the representational system enhanced and reconstituted ways of explaining facets

of chromosomal theory in terms of previously unknown, unobservable physiological structures. This, in turn, generated a representational system of greater complexity and information content, upholding a common dynamical structure for visual representations.

Genetics and computationally intensive methods for storing and accessing information

The number of diseases and disorders being ostensibly identified as 'genetic' climbed steadily through the second half of the twentieth century. When Sheldon C. Reed (1910-2003) took over the directorship of the Dight Institute for Human Genetics at the University of Minnesota, he was able to catalogue quite succinctly each of the two hundred and sixteen genetic counselling cases that had been conducted at the Dight between 1947 and 1949 (Reed 1949, 13-14). In his 1951 Dight Institute Report, however, Reed noted that the categories had grown 'so long that it is too unwieldy for publication' (1951: 9). In view of this, he provided only the frequency for each of the twenty most common requests for counselling services. This can be contrasted, a decade and a half later, with the one thousand, four hundred and eighty-six entries that Victor McKusick (1921-2008), a geneticist at Johns Hopkins, published in his 1966 catalogue of known genes and genetic diseases, *Mendelian Inheritance in Man.*

McKusick wrote, in 1960, a lengthy article on the X-chromosome, then the only human chromosome to which specific hereditary traits had been attributed. He discussed recent discoveries on the topic and listed the sixty known X-linked traits (McKusick, 1960). He provided a designation for each trait, a natural history of the trait, available aetiological information on the genetics of the trait, along with bibliographic references.

McKusick later decided to develop a comprehensive, regularly updated catalogue of Mendelian phenotypes, both recessive and dominant, using the format employed in his work on the X-chromosome. In 1966, the first edition of *Mendelian Inheritance in Man* mostly cited genes mapped through family linkage studies. Starting in the late 1960s, entries were also created for individual genes for which no associated Mendelian phenotype was known. Somatic cell hybridization (a technique for isolating individual human chromosomes from cultures of fused mouse and human cells) had made it possible to locate genes on human chromosomes without using family linkage maps. Similarly, later advances in molecular technologies facilitated expansion of the catalogue. *Mendelian Inheritance in Man* was made available on the internet in 1987 as *Online Mendelian Inheritance in Man,* a continually updated database linked with National Center for Biotechnology Information and the National Library of Medicine (McKusick, 1992; 2007). The 12th and final print edition was published in 1998 at which time publication became unfeasible given the number of text entries. At the time of McKusick's death in July of 2008, *Online Mendelian Inheritance in Man* had 18,847 entries.

How, then, should we understand the relationship between the expansion in genetic knowledge and the expanding interface between genetic technologies and medicine? First of all, it is important to understand that the genetic technologies used in medical diagnostics did not progress in the sense of one technology overtaking or replacing another. The taking of family histories and the ostensive representations of the genetics of disease designed for the production of pedigrees continue to be used in both

the genetic counselling of families and clinical research in human genetics – including the databasing of various human populations. The scope of genetic information gathering, on the other hand, steadily broadened to include, first, a range of new laboratory technologies for identifying chromosomal anomalies and genetic metabolic disease and, subsequently, molecular biological techniques. This included the development of large-scale automated genomic sequencing and new approaches to mapping and determining the fine structure of the human genome for purposes of comparing and interpreting genomic data (genetic loci) with the phenotypes of disease.

It became a commonplace in the 1960s and 1970s to think of genetic test results as evidence of genetic factors as being causally relevant in explaining the hereditary transmission and/or onset of disease. Moreover, the patient who tested positive was typically viewed as either having or being at risk for the disease under investigation. Nonetheless, even as test results suggested that genes are causally operative in determining phenotypic effects, geneticists could not fully account for how genes function in tandem with other factors (e.g., the environment) in the onset of disease. To this day, the genetic basis for disease causality is not fully understood and is incomplete as a theory (Pearson, 2007; Moss, 2003). This means that understanding entities is limited, the entities possessing only a finite number of properties with which the system is concerned (i.e., the causal explanation of the expression of disease).

The early examination of the chromosomes of *Drosophila melanogaster* individually through the microscope has already been described in the previous section of this article. Since the 1940s, the preparation of examination specimens benefited from

such innovations as the use of colchicines for the arrest of mitosis, hypotonic treatment to spread and tease the individual chromosomes apart, Painter's 'squash' technique to present chromosomes on a two-dimensional plane, and camera lucinda and photomicrography techniques to record and document observations. Having said that, the human chromosome set was much larger than that of *Drosophila melanogaster*.

The story of hold-ups and delays in the progress of cytological research on human chromosomes is well-known in the history of genetics (e.g., Harper, 2008: 139-147; Kevles, 1985: 238-248). Briefly, early attempts to count chromosomes in the normal human cell were inconsistent and made more difficult by the fact that cytologists used tissues taken from corpses, often those of executed criminals (Kevles, 1985: 238-239). It is now known that mammalian chromosomes tend to clump together with the death of the organism, confounding efforts to count them. It was accepted, until 1956, that the diploid chromosome number in humans was forty-eight. This changed with the work coming out of the Institute of Genetics in Lund, Sweden and published in the Institute's Journal, *Hereditas* (e.g. Tjio and Levan, 1956). Peter Harper (2008: 147-149) has proposed that it was Jo-Hin Tjio's (1916-2001) masterly technical skills in the preparation and photography of chromosomes that were the critical factor in arriving at a consensus among scientists that there were a total of forty-six human chromosomes. The use of cultured foetal lung fibroblasts from aborted embryos had produced a quality of preparation never seen before. Finally, researchers at the Harwell Medical Research Unit in England published work based on the use of testicular material that lent support to Tijo and Levan's findings in Sweden (Ford and Hamerton, 1956). These were followed

relatively quickly with renewed efforts to find correlations between chromosomal anomalies and heritable human disease.

Advances in karyotype analysis permitted some types of defects, including missing or extra copies of a chromosome or gross breaks and translocations, to be detected by microscopic examination. It was researchers in France who, amongst several research groups in Europe, finally revealed a consistent trisomy of one of the smallest chromosomes in persons with Down syndrome (Lejeune *et al.*, 1959). By the late 1950s, the syndromes of Turner, and Klinefelter were correctly karyotyped and women with triple-X identified. A standard system of nomenclature for human mitotic chromosomes in medicine followed in 1960 (Anonymous, 1960). This classificatory system, in turn, facilitated greater cooperation among laboratory scientists in France, Sweden, Japan, North America, and the UK, as well as enhancing the diagnostic potential of cytogenetics in laboratory medicine. New ways of thinking about the genetics of disease consequently emerged. After 1960, a regular division of labour emerged in cytogenetic analysis. Individuals with backgrounds in cytology and genetics were recruited to perform a service function in cytogenetic laboratories, and a new occupational category appeared: 'cytogeneticist.'

Biochemical testing emerged as a parallel development to chromosome analysis in laboratory medicine. It provided new ways of identifying genetic diseases by revealing abnormal metabolites in body fluids. The basic division of labour involved in biochemical testing in the 1960s followed a pattern similar to that of chromosome analysis. Individuals with backgrounds in chemistry were recruited to perform a service

function in ‘biochemical laboratories,’ and a new occupational category appeared: ‘biochemical geneticists.’ Physicians would look for tell-tale signs and symptoms (e.g., failure to thrive, developmental delay, dysmorphic features) that might be indicative of a metabolic disorder. A genetic counsellor would be consulted regarding the family history and, if a laboratory evaluation was in order, blood or urine was obtained and shipped to the laboratory where it would undergo testing. A laboratory report would be returned to the consulting physician.

It is important here to stress the novelty of human cytogenetics and biochemical analysis in the 1960s and the 1970s. Chromosomal and biochemical analyses provided the first clinical tools to diagnose the genetical element of certain rare heritable diseases. Furthermore, one can take note of a reductionist manoeuvre to unify and subsume (i.e., *reduce*), on the one hand, all that had been observed in early Mendelian accounts of biological relatedness and episodes of familial illness and, on the other, all that was being theorised about cells, chromosomes, genes, proteins, and enzymes in order to explain processes and structures talked about in complex higher-order theories concerning the aetiology of genetic diseases. The conceptualisation of ‘genetic disease’ as a unique entity, like the common tendency in medicine to segment ailments of the body according to organ sites, opened up new vistas of clinical research and practice. This, in turn, justified the study of human genetics as a matter of serious concern for clinicians in the second half of the twentieth century. By the time diagnostic applications of recombinant DNA techniques and ‘DNA testing’ arrived in the 1990s, a solid infrastructure was in place for incorporating ‘molecular genetics’ into laboratory medicine (Weatherall, 1985;

Elles, 1996). Molecular genetic methods of analyses can be viewed in this context as a kind of add-on in the clinical toolkit of medical genetics.

Early textbooks and atlases that were produced to introduce human genetics into medical specialty areas such as pathology, obstetrics and gynaecology, and paediatrics were explicit about the need for clinicians to attribute a genetic basis for understanding congenital anomalies as well as heritable disease. A layering of information was achieved by composite representations based on groups of somatic features observable to the trained eye (e.g., 'very small stature, not skeletal dysplasia,' 'senile-like appearance') or by field of clinical interest (e.g., 'chromosomal abnormalities,' 'muscular disorders with associated defects,' 'neuroloecial disorders other than mental deficiency with associated defects'). A composite included graphic elements like illustrations of chromosomes placed alongside photographs of patients, sometimes with family pedigrees, graphics of chemical compounds, radiographs, and /or autoradiographs. Text annotations explained the visual elements in relation to 'common' and 'occasional' characteristics and traits seen in clinical settings. Characteristic and occasional characteristics and traits would, in turn, follow certain high points and milestones of a 'natural history' observable over time in the trajectory of patients' illness. As American paediatrician David W. Smith (1926-1981) observed:

> The occurrence of these 'occasional abnormalities' is of interest and has been loosely ascribed to 'developmental noise.' In other words an adverse influence that usually causes a particular pattern of malformation may occasionally cause other anomalies as well. Possibly it is differences of genetic background, environment, or both that allow some individuals to express these 'occasional' anomalies. The important feature is that they are not random for a particular syndrome. For example, clinicians who have seen a large number of children with

> Down's syndrome are not surprised to see 'another' Down's syndrome baby with duodenal atresia, web neck, or tetralogy of Fallot. (1970: 19)

Text explanations of genetic aetiology, correspondingly, served to anchor the process of assessment by offering a root cause supported by chromosomal or biochemical tests. Furthermore, they distinguished genetics-based anomalies from teratogenic effect (i.e., defects caused by major environmental substances), deformations caused by mechanical constraint (e.g., uterine size, leiomyomas), and defects in the foetus itself (e.g., neurological, connective tissue).

The craft of interpreting symptoms here rested in the final analysis with the scientist/clinician's role as explicator. As in other areas of clinical practice, the diagnosis of patients was at once part of a diagnostic system with its own classifications and nomenclature, a part of a trajectory of patient care, and a part of medicine *in toto*. Connections can be seen to occur among layers of information in two distinct contexts: At the outset, in order to select relevant features of complex phenomena or data to be tested, and later when interpreting a link between a complex construct and evidence for it. Different patterns of inference occur according to the discipline, subdiscipline, or field of study that is involved and different forms of representation make it is possible for multiple domains of knowledge to access a wider body of taxonomic knowledge. At the same time, the extent of the ability of the user to move between different forms of representation (i.e., text, photographs, diagrams) is dependent on the level of his/her experience in the many knowledge domains. Correspondingly, the cataloguing and classification systems of genetic information towards the end of the twentieth century grew increasingly reliant on an array of specifically designed laboratory and analysis

technologies that strove to find complementarity among ways to store and access increasingly complex collections of data (cf. Leonelli, 2009; Kell and Oliver, 2003).

Anticipating and assessing accelerating advances in computationally intensive systems to store, disseminate and access information

Libraries of hybrid mammalian cell cultures were assembled in the 1970s to hold chromosomes or fragments of chromosomes (Gilbert, 1992: 69; Bishop and Waldholz, 1991:75). Correspondingly, bacterial cDNA libraries were being developed to store and reproduce snippets of DNA which provided genetic material for research and experimentation. Initially, the materials and instruments required to undertake this type of work could all be readily made locally in research laboratories. With no expensive instrumentation, set-up costs for libraries were low. This changed with ambitions to perform more detailed forms of analysis that could characterise a gene's structure through ascertaining the sequence of DNA bases of which it was composed (i.e., DNA sequencing). Molecular genetic techniques lent themselves well to codification in this context and the complete sequencing of viral genomes became possible by the early 1980s (Hopkins 2004; chapter 7). The manual techniques, however, were slow and laborious. The use of radioactive materials made them unpopular as did the incidence of human error common in reading autoradiographs. The automation of DNA sequencing came about as a solution to these problems (Cook-Deegan, 1994: 64). The launch of a machine in 1983 that could synthesize oligonucleotides was the first of a series of innovations in this area which led to a host of other research programs focused on the

sequencing of whole genomes. The terms ‘computational genetics’ and ‘genomics’ followed in the 1990s, indicative of the amplification and intensification of speed with which large amounts of information could be analysed. This involved an increasingly polycentric organisational network of research relationships with multiple bases of interest extending more and more into new domains of biological study.

The National Center for Biotechnology Information (NCBI) Genome Database represents one of the earliest examples of such a network, consisting of multiple repositories, databases, and bio-ontologies,[16] as well as scientists acting as ‘curators’ in charge of developing them.[17] It has provided digital tools for viewing a variety of model organism genomes (including humans), complete chromosome sets, sequence maps with contigs (i.e., a series of overlapping clones or a genetic sequence defining an uninterrupted section of a chromosome), and integrated genetic and physical maps.

The NCBI itself is part of the United States National Library of Medicine, a branch of the National Institutes of Health, founded in Bethesda, Maryland in 1988. As noted in the previous section of this article, the NCBI supports the Online Mendelian Inheritance in Man, initiated by Victor McKusick. It also supports and distributes a variety of other databases for the medical and scientific communities including the Molecular Modeling Database of 3D protein structures, the Unique Human Gene Sequence Collection, and the Cancer Genome Anatomy Project, in collaboration with the National Cancer Institute. NCBI assumed responsibility for the GenBank DNA sequence database in October 1992. NCBI staff here build and curate the database from sequences submitted by individual laboratories and by data exchange with the international

nucleotide sequence databases in North America, the European Molecular Biology Laboratory and the DNA Database of Japan.

Of particular interest, for the purposes of the present study, is 'Entrez,' NCBI's search and retrieval system which provides users with integrated access to sequence, mapping, taxonomy, and structural data. Entrez, on the one hand, provides graphical 'views' of sequences and chromosome maps. On the other, it retrieves related references of interest to the user with journal literature made available through PubMed, a Web search interface that provides access to over eleven million journal citations in MEDLINE. In practice, users are invited to interactively 'root' down through layers of digital information in a manner reminiscent of the graphic design strategy used in textbooks and atlases in the final quarter of the twentieth century. But there are significant differences.

Entrez users select organisms to 'view' from a 'home' window listing of integrated views of chromosome maps for forty organisms including vertebrates, invertebrates, protozoa, plants, and fungi. Selecting 'homo sapiens' will bring up a window with the human genome represented by a schematised graphic of the set of chromosomes including mitochondrion. Selecting one of the chromosomes brings up yet another screen that displays human genomic sequence data as well as cytogenetic, genetic, physical, and radiation hybrid maps. As in the case of the earlier forms of graphic visualisation, Entrez's refined and extended repertoire of search categories offers users different levels and types of information. In this regard, I am inclined to side with

Eugene Thacker (2004) in his use of remediation theory to explore the connections between old and new techniques and methodologies.

The authors of remediation theory, Jay David Bolter and Richard Gruisin (1999), proposed that historically situated art and communications media are likely to 'remediate' prior media effects (i.e., reconfigure and reconstitute prior media effects). Remediation also involves a complex dynamic between two technological processes with accompanying cognitive effects: 'immediacy' and 'hypermediacy' (1999: 21-44). A sense of immediacy is obtained to the extent that users of media lose awareness of the media, bringing forth a kind of direct experience where the media is no longer noticed by the user. Hypermediacy, on the other hand, involves overcoding, heterogeneity, and saturation of the user's senses by different media, intensifying the experience of process or performance. 'If the logic of immediacy leads one either to erase or render automatic the act of representation,' state Bolter and Gruisin (1999: 33-34), 'the logic of hypermediacy acknowledges multiple acts of representation and makes them visible.'

Following Bolter and Gruisin, we would ideally want to see the orderly unfolding of evidence in medical diagnosis benefit from a host of investigative media and 'erase all traces of mediation' in order to enhance and make immediate (i.e., instantly readable) the contents of a clinical investigation. But following Thacker, it is probably more accurate to say that the techniques associated with history of representing and disseminating information about the genetics of disease get caught between the poles of immediacy and hypermediacy (2004: 10). As shown in the previous section of this article, the layering of information featured in early text and atlas presentations of cases of genetic disease

aimed to achieve a certain fidelity to nature through the simultaneous use of multiple graphic media (i.e., photographs of patients, family pedigrees, pictures of chemical compounds, radiographs, autoradiographs). The idea here was to align genetic diseases alongside the taxa of other ailments of the body based on groups of somatic features observable to the trained eye and/or by fields of clinical specialisation including organ sites. Moreover, the presentation of materials aimed to simultaneously bring to light the background knowledge that geneticists bring to research practices as well as setting down directions and orientation for action in clinical settings (e.g., diagnostic testing). This has not changed over time. However, the digital tools now produced by software designers and engineers for accessing information are not merely descriptive. They are openly performative, encouraging interaction among users and those individuals involved in cataloguing and presenting data (i.e., curators) (Leonelli, 2010). It is important to understand that the composite presentations of photographs of patients, family pedigrees, pictures of chemical compounds, radiographs, and autoradiographs produced in the twentieth century were intended to arrange in single units a resource that could be *taken away* by a multiplicity of disciplines, subdisciplines, and fields of study. Once 'taken away,' the information could be adapted to suit disciplinary purposes (i.e., disciplinary purposes of molecular biologists, radiologists, pathologists, paediatricians, etc). The curators of bio-ontologies associated with the production of online databases, by contrast, represent themselves as cutting across epistemic divides and promoting interdisciplinarity across the spectrum of disciplines, subdisciplines, and fields of study – even transdisciplinarity (Guarino, 1995; Clancey, 1993; cf. Guizzardi and Halpin, 2008; Soffer

and Hadar, 2007; Purao and Storey, 2005). The change in thinking advanced here says that because the expansion of genetic knowledge has been so rapid and genetic knowledge itself is becoming so complex, it is necessary for disciplines, subdisciplines, and fields of study to *come together* to stake new knowledge claims. Furthermore, as research endeavours to draw on new domains of biological knowledge, it is important that the various users be well-integrated and not highly differentiated from one another. Without sufficient integration there will not be the quality of horizontal communication with frequent interaction across diverse fields that will be prerequisite for major discoveries in the future – genomic, post-genomic, or otherwise.[18] *Apropos,* Sabina Leonelli (2010: 106) has observed:

> The 21st century has brought immense technological advances in the production of genomic data. Sequencing is now an automated activity taking no more than a few hours; collecting data on gene expression can also be done automatically, resulting in billions of data-points per day. This level of automation means that data collecting has never been as disjointed from activities of theory-building. Contrary to data resulting from experiments associated to the testing or the production of hypotheses, automatically produced data bear no obvious connection to specific hypotheses about the phenomena that they are documenting, other than to the theoretical assumptions used to build the instruments through which data were produced. More than any other source of evidence, automatically produced data require great interpretive efforts to determine what they can be evidence *for*. The scientific focus is thus shifting from efforts to produce data, characteristic of late 20th century biology, to efforts to exploit these data as evidence towards new claims.

Summary and Discussion

In this article, I have highlighted the 1930s and 1940s as being a period of proleptic anticipation regarding the future of genetics and medicine.[19] I have also taken into account that the genetics of disease remains today incomplete as a theory of disease

causality. All the same, information and images pertaining to genetics and disease remain arguably serviceable when they produce agreeable diagnostic, prognostic and, ultimately, therapeutic results in patient care.

Initially, an elite of geneticists exhibited specialised expertise in a manner that recalls what the political scientist Victor Thompson (1964: 25-7) called 'personal specialisation.' This is particularly evident in my discussion of the work of Thomas H. Morgan and his students at Columbia University regarding the chromosomal theory of heredity. Specialist status arose from the *person*, and not the *task*. Using Thompson's nomenclature, there was high personal specialization in the science of genetics prior to the Second World War. However, in the translatory movement from science to medical applications, the ideological direction of clinical practices conformed to a pattern widely adopted among contemporary medical specialties. As a result, formal job classifications (i.e., heredity counsellor, medical geneticist, cytogeneticist, biochemical geneticist, molecular geneticist) became viable as occupations in medicine by the 1970s and 1980s. 'Task specialisation' followed with counselling and laboratory services becoming standardised. This aspect has been examined in great detail in my earlier work (Leeming, 2004; 2005; 2007; 2010).

In this article, I have concentrated on the development of tools to visualise and disseminate images and information concerning the genetics of disease. At the start, pedigrees demarcated and contextualized the spatial and temporal limits of instantiations of inherited disease (i.e., chronotopicity) and chromosome maps represented part-whole relations in the genetics of disease with a topological component (i.e., gene

mereotopology). Chromosomes, contained 'genes' which, by analogy, could be visualised as entities arranged like 'beads-on-a-string.' Drawing on the chromosomal theory of heredity of the 1920s, early maps based on purely hypothetical and abstract analyses laid the groundwork for ongoing graphic experiments in the 1930s and 1940s. New discoveries in the fields of cytology and genetics were accompanied by a level of illustrative realism and progressively more detailed diagrams of chromosome sets in the second half of the twentieth century.

There was also a noteworthy expansion in the interface between genetic technologies and medical diagnostics after 1960. The genetics used in medical diagnostics did not progress in the sense of one technology overtaking or replacing another. The taking of family histories for the production of pedigrees continued (and continue) to be used in both the counselling of families and clinical research in human genetics. Nonetheless, the scope of genetic information gathering and image production steadily broadened to include, first, a range of new laboratory technologies for identifying chromosomal anomalies and genetic metabolic disease and, subsequently, molecular biological techniques. This included the introduction of large-scale automated genomic sequencing and new approaches to mapping and determining the fine structure of the human genome for purposes of comparing and interpreting genomic data (genetic loci) with the phenotypes of disease. Genetic diagnoses here provided for both manipulating matter (e.g., blood, urine, cheek cells) *and* manipulating symbols garnered from the evolving nomenclature of chromosome maps, genomic sequence maps with contigs, and integrated genetic and physical maps (i.e., remediation). It also became a commonplace

to think of genetic test results as evidence of genetic factors as being causally relevant in understanding the transmission and/or onset of disease.

The number of diseases and disorders being ostensibly identified as 'genetic' climbed steadily during the second half of the twentieth century. Correspondingly, the dissemination and knowledge transfer systems associated with, on the one hand, cataloguing, and, on the other, education became increasingly unwieldy. Layerings of information incorporated illustrations of chromosomes placed alongside photographs of patients, sometimes with family pedigrees, graphics of chemical compounds, radiographs, and /or autoradiographs. Text annotations explained the visual elements in relation to the milestones of 'natural history' and 'genetic aetiology.' The craft of interpreting symptoms here rested in the final analysis with the scientist/clinician's role as explicator. This, in turn, helped to shape and inform what I have described elsewhere as the bifurcated ideological construct of 'medical genetics,' a new medical specialism (Leeming, 2007: 155-6; 2010: 55). This construct stipulates, on the one hand, that the mandate of medical genetics is to add a new set of medical procedures to the clinical repertoire of *all* health disciplines. On the other hand, it specifies that when and where service providers are unable to deliver the new procedures, a class of specialists (i.e., medical geneticists) are available for consultation.

As a final point, I will propose for future consideration that contemporary online databases associated with computational genetics and genomics may significantly contribute to the first aspect of the bifurcated ideological construct of medical genetics. Present day digital tools being produced by software designers and engineers for

information sharing purposes are described in this article as being openly performative and intended to attenuate traditional distinctions between disciplines, subdisciplines, and fields of study (cf. Daston and Galison, 2008: 382-415; Thacker, 2004). In spite of this, I agree with Timothy Lenoir (1997: 74) that research programs utilising such tools 'cannot remain expansive and powerful without eventually serving as resources for disciplinary programs.' To be sure, current medical interest in the digital environment of computational genetics and genomics comes from its capacity to generate working models of what causes disease.

Acknowledgements

The project upon which this article is based is funded by the Social Sciences and Humanities Research Council of Canada (SSHRC award no. 410-2008-0162). I want to thank the editor and two anonymous reviewers of *Science Communication* for their critical comments and feedback on the manuscript. I also want to thank participants in the 'From Biodigital Lives to Bio-IT Worlds' sessions at the 2010 EASST conference in Trento, Italy for their questions and comments concerning a paper in which I focused on aspects of this article.

References

Ackerknecht, E. H. (1982) 'Diathesis: The Word and the Concept in Medical History', *Bulletin of the History of Medicine* 56: 317-25.

Amundson, Ron (2005) *Changing Role of the Embryo in Evolutionary Thought: Roots of Evo-Devo* (Cambridge: Cambridge University Press).

Anonymous (1960) ‘A Proposed Standard System of Nomenclature of Human Mitotic Chromosomes’, *Lancet* 1: 1063-65.

Bakhtin, Mikhail M. (1981) ‘Forms of Time and of the Chronotope in the Novel’, in M. Holquist (ed.), *The Dialogic Imagination. Four Essays by M. M. Bakhtin* (Austin: University of Texas Press): 84-258.

Bennett, Robin L., *et al.* (1995) ‘Recommendations for Standardized Human Pedigree Nomenclature’, *American Journal of Human Genetics* 56: 745-52.

Bishop, J. E., & M. Waldholz (1991) *Genome* (New York: Simon & Schuster).

Bolter, Jay David, and Richard Grusin (1999) *Remediation. Understanding New Media.* (Cambridge MA: MIT Press).

Bowler, Peter J. (1989) *Evolution: The History of an Idea* (Berkeley, CA: University of California Press).

Bridges, Calvin B. (1935) ‘Salivary Chromosome Maps with a Key to the Banding of the Chromosomes of Drosophila Melanogaster’, *Journal of Heredity* 26: 60-4.

Bridges, Calvin B. (1938) ‘A Revised Map of the Salivary Gland X-Chromosome of Drosophila Melanogaster’, *Journal of Heredity* 29: 11-13.

Bruner, J. (1991) ‘The Narrative Construction of Reality’, *Critical Inquiry* 18: 1-20.

Cartron, L. (2007) ‘Degeneration and “Alienism” in Early Nineteenth-Century France’ in S. Müller-Wille and H.- J. Rheinberger (eds.), *Heredity Produced: At the Crossroads of Biology, Politics, and Culture, 1500-1870* (Cambridge, MA: MIT Press): pp. 155-74.

Cantor, C. R. (1990) ‘Orchestrating the Human Genome Project’, *Science* 248: 49-51.

Castle, William E. (1919) ‘Is the Arrangement of the Genes in the Chromosome Linear?’, *Proceedings of the National Academy of Sciences* 5 (2): 25-32.

Ciocco, A. (1936) ‘The Historical Background of the Modern Study of Constitution’, *Bulletin of the Institute of the History of Medicine* 4: 23-38.

Clancey, William J. (1993) ‘The Knowledge Level Reinterpreted: Modeling Socio-Technical Systems’, *International Journal of Intelligent Systems* 8: 33-49.

Comas, J. (1960) *Manual of Physical Anthropology* (Springfield, ILL: Charles C. Thomas).

Cook-Degan, R. (1994) *Gene Wars: Science, Politics, and the Human Genome Project* (New York: Norton).

Crow, Ernest W. & James F. Crow (2002) '100 Years Ago: Walter Sutton and the Chromosome Theory of Heredity', *Genetics* 160: 1-4.

Daston, Lorraine, & Peter Galison (2008) *Objectivity* (New York: Zone).

Daston, Lorraine, & Katharine Park (2001) *Wonders and the Order of Nature* (New York: Zone).

Dobzhansky, Theodosius (1929) 'Genetical and Cytological Proof of Translocations involving the Third and the Fourth Chromosomes of Drosophila Melanogaster', *Biologisches Zentralblatt* 49: 408–19.

Elles, R. (1996) 'An Overview of Clinical Molecular Genetics' in R. Elles (ed), *Methods in Molecular Medicine: Molecular Diagnosis of Genetic Diseases* (Totowa, NJ: Humana Press): 1-15.

Epstein, J. (1995) *Altered Conditions: Diseases, Medicine and Storytelling* (New York: Routledge).

Falk, Raphael (2003) 'Linkage: From Particulate to Interactive Genetics', *Journal of the History of Biology* 36 (1): 87-117.

Farrall, Lindsay (1985) *The Origins and Growth of the English Eugenics Movement 1865-1925.* New York: Garland Press.

Ford, C. E., & J. L. Hamerton (1956) 'The chromosomes of man', *Nature* 178: 1020-23.

Fujimura, Joan (2005) 'Postgenomic Futures: Translations Across the Machine-Nature Border in Systems Biology', *New Genetics and Society* 24: 195-225.

Gilbert, W. (1992) 'A Vision of the Grail', in D. Kevles & L. Hood (eds), *The Code of Codes* (London: Harvard University Press): 83-97.

Gooding, David C. (2004) 'Visualization, Inference and Explanation in the Sciences' in G. Malcolm (ed), *Multidiciplinary Approaches to Visual Representations and Interpretations* (Amsterdam: Elsevier): 1-26.

Guarino, Nicola (1992) 'Concepts, Attributes and Arbitrary Relations: Some Linguistic and Ontological Criteria for Structuring Knowledge Bases', *Data & Knowledge Engineering* 8: 249-61.

Guarino, Nicola (1995) Formal Ontology, Conceptual Analysis and Knowledge Representation', *International Journal of Human Computer Studies* 43 (5/6): 625-40.

Guizzardi, G., & T. Halpin (2008) 'Ontological Foundations for Conceptual Modelling', *Applied Ontology* 3: 1-12.

Harper, Peter S. (2008) *A Short History of Medical Genetics* (Oxford: Oxford University Press).

Hogben, Lancelot (1931) *Genetic Principles in Medicine and Social Science* (London: Williams and Norgate).

Holtzman, N. A. (1989) *Proceed with Caution: Predicting Genetic Risks in the Recombinant DNA Era* (Baltimore: John Hopkins University Press).

Holquist, Michael (1983) 'Answering as Authoring: Mikhail Bakhtin's Trans-Linguistics' *Critical Inquiry* 10 (2): 307-319.

Hopkins, Michael M. (2004) *Technique-Led Technological Change and The 'Hidden Research System': Genetic Testing in the NHS* (DPhil Thesis, University of Sussex).

Kell, Douglas B., & Stephen G. Oliver (2003) 'Here is the Evidence, Now what is the Hypothesis? The Complementary Roles of Inductive and Hypothesis-Driven Science in the Post-Genomic Era', *BioEssays* 26 (1): 99-105.

Kevles, D. J. (1985) *In the Name of Eugenics: Genetics and Uses of Human Heredity* (Berkeley: University of California Press).

Kevles, D. J., & Hood L. (Eds) (1992) *The Code of Codes* (Cambridge, MA: Harvard University Press).

Kingsland, Sharon E. (2007) 'Maintaining Continuity through a Scientific Revolution: A Rereading of E. B. Wilson and T. H. Morgan on Sex Determination and Mendelism' *Isis* 98 (3): 468–88.

Lee, T. F. (1991) *The Human Genome Project: Cracking the Genetic Code of Life*. New York: Plenum Press.

Leeming, William (2004) 'The Early History of Medical Genetics in Canada', *Social History of Medicine* 17: 481-500.

Leeming, William (2005) 'Ideas about Heredity, Genetics, and 'Medical Genetics' in Britain, 1900-1982', *Studies in History and Philosophy of Biological and Biomedical Sciences* 36: 538-58.

Leeming, William (2007) ‘On the Relevance of the ‘Genetics-Based Approach’ to Medicine for Sociological Perspectives on Medical Specialization”, *Canadian Review of Sociology and Anthropology*, 44 (2): 151-73.

Leeming, William (2010) ‘Tracing the Shifting Sands of “Medical Genetics”: What’s in a Name?’ Tracing the Shifting Sands of ‘Medical Genetics’: What’s in a Name? *Studies in History and Philosophy of Biological and Biomedical Sciences* 41: 50-60.

Lejeune, J., M. Gauthier & R. Turpin (1959) ‘Études des Chromosomes Somatiques de Neuf Enfants Mongoliens’, *Comptes Rendus de l’Académie des Sciences* 248: 1721-2.

Leonelli, Sabina (2009) ‘Centralising Labels to Distribute Data: The Regulatory Role of Genomic Cosortia’, in P. Atkinson, P. Glasner & M. Lock (eds), *Handbook for Genetics and Society: Mapping the Genomic Era* (London: Routledge): 469-85.

Leonelli, Sabina (2010) ‘Documenting the Emergence of Bio-Ontologies: Or, Why Researching Bioinformatics Requires HPSSB’, *History and Philosophy of the Life Sciences* 32: 105-126.

Lenoir, Timothy (1997) *Instituting Science: The Cultural Production of Scientific Disciplines* (Stanford: Stanford University Press).

López-Beltrán, C. (2006) ‘Storytelling, Statistics and Hereditary Thought: The Narrative Support of Early Statistics’, *Studies in History and Philosophy of Biological and Biomedical Sciences* 37: 41-58.

McClung, C. E. (1902) ‘The Accessory Chromosome-Sex Determinant?’ *Biological Bulletin* 3: 76-7.

MacKenzie, D. (1976) ‘Eugenics in Britain’, *Social Studies of Science* 6: 499-532.

McKusick, Victor (1960) ‘On the X Chromosome of Man’ *Quarterly Review of Biology* 37 (2): 69-175.

McKusick, Victor A. (1966) *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes*, 1st ed. (Baltimore: The Johns Hopkins University Press).

McKusick, Victor A. (1991) ‘Current Trends in Mapping Human Genes’, *Federation of American Societies for Experimental Biology Journal* 5: 12.

McLaren, Angus. (1990) *Our Own Master Race: Eugenics in Canada 1885-1945* (Toronto: McClelland and Stewart).

Macklin, Madge T. (1931) ‘A Conference on Heredity as Applied to Man’, *Science* 73: 613-14.

Macklin, Madge T. (1933) ‘The Teaching of Inheritance of Disease to Medical Students. A Proposed Course in Medical Genetics’, *Annals of Internal Medicine* 6: 1335-43.

Macklin M. T. (1935). ‘The Role of Heredity in Disease’, *Medicine, 14*, pp. 1-75.

Mazumdar, Pauline M. H. (1992) *Eugenics, Human Genetics and Human Failings* (London: Routledge).

Montagu, M. F. A. (1947) *An Introduction to Physical Anthropology* (Springfield, Ill: Charles C. Thomas).

Morgan, Thomas, & Calvin B. Bridges (1916) *Sex-Linked Inheritance in Drosophila.* (Washington: Carnegie Institution of Washington).

Moss, Lenny (2003) *What Genes Can’t Do* (Cambridge, MA: MIT Press).

Müller-Wille, Staffan, & Hans - Jörg Rheinberger (2007) ‘Heredity – The Formation of an Epistemic Space’ in S. Müller-Wille and H.- J. Rheinberger (eds.), *Heredity Produced: At the Crossroads of Biology, Politics, and Culture, 1500-1870* (Cambridge, MA: MIT Press): pp. 3-34.

Muller, H.J., & Painter, T.S. (1929) ‘The Cytological Expression of Changes in Gene Alignment Produced by X-Rays in Drosophila’ *American Naturalist* 63: 193-200.

Novas, C., & Rose, N. (2000) ‘Genetic Risk and the Birth of the Somatic Individual’, *Economy and Society* 29: 485-513

Oliver, Clarence P., & Schiele, B. C. (1945) ‘A Family History of Huntington’s Chorea Made Possible by the Recording of Surnames’, *Dight Institute of the University of Minnesota Bulletin* 3: 13-20.

Ørbeck, Alf L. (1959) ‘An Early Description of Huntington’s Chorea’, *Medical History* 3 (2): 165-68.

Painter, Theophilus S. (1923) ‘Studies in Mammalian Spermatogenesis II: The Spermatogenesis of Man’, *Journal of Experimental Zoology* 37: 291-335.

Painter, Theophilus S. (1933) ‘A New Method for the Study of Chromosome Rearrangements and the Plotting of Chromosome Maps’, *Science* 78: 585-586.

Painter, Theophilus S. (1934) 'The Morphology of the Third Chromosome in the Salivary Gland of D. Melanogaster and a New Cytological Map of the Element', *Genetics* 20: 301-26.

Paul, Diane B. (1998) *The Politics of Heredity: Essays on Eugenics, Biomedicine, and the Nature-Nuture Debate.* New York: State University of New York Press.

Pearson, Christopher H. (2007) 'Is Heritability Explanatorily Useful?', *Studies in History and Philosophy of Biological and Biomedical Sciences* 38: 538-58.

Petersen, Andrew (2006) 'The Genetic Conception of Health: Is It as Radical as Claimed?', *Health* 10: 481-500.

Purao, S., & V. C. Storey (2005) 'A Multi-Layered Ontology for Comparing Relationship Semantics in Conceptual Models of Databases', *Applied Ontology* 1(1): 117–39.

Reed, Sheldon C. (1951) 'Counseling in Human Genetics, Part II', *Dight Institute of the University of Minnesota Bulletin* 7: 6-17.

Richmond, M. L. (2007) 'The Cell as the Basis for Heredity, Development and Evolution: Richard Goldschmidt's Program of Physiological Genetics' in M. D. Laubichler and J. Maienschein (eds), *From Embryology to Evo-Devo: A History of Developmental Evolution* (Cambridge, MA: MIT Press): 169-211.

Robbins, D., & R. Johnston (1976) 'The Role of Cognitive and Occupational Differentiation in Scientific Controversies', *Social Studies of Science* 6: 349-68.

Rose, N., & C. Novas (2005) 'Biological Citizenship', in A. Ong & S. J. Collier (eds.), *Global Assemblages: Technology, Politics, and Ethics as Anthropological Problems* (Malden: Blackwell): 439-63.

Rossiter, B. J. F., & C. T. Caskey (1991) 'Molecular Studies of Genetic Disease', *Federation of American Societies for Experimental Biology Journal* 5: 21.

Sapp, Jan (2003) *Genesis : The Evolution of Biology* (New York : Oxford University Press).

Schneider, William H. (1983) 'Chance and Social Setting in the Application of the Discovery of Blood Groups', *Bulletin of the History of Medicine* 57: 545-62.

Sheldon, W. H., S. S. Stevens, & W. B. Tucker (1940) *The Varieties of Human Physique: An Introduction to Constitutional Psychology* (New York: Harper & Brothers).

Smith, David W. (1970) *Recognizable Patterns of Human Malformation: Genetic, Embryologic, and Clinical Aspects* (Philadelphia: W. B. Saunders).

Soffer, P., & I. Hadar (2007) 'Applying Ontology-Based Rules to Conceptual Modeling: A Reflection on Modeling Decision Making', *European Journal of Information Systems* 16: 599–611.

Soloway, R. A. (1998) 'From Mainline to Reform Eugenics – Leonard Darwin and C P Blacker', in R. A. Peel (ed.), *Essays in the History of Eugenics: Proceedings of a Conference Organised by the Galton Institute, London, 1997* (London: Galton Institute): 52-80.

Stafford, Barbara Maria (1999) *Visual Analogy. Consciousness as the Art of Connecting.* (Cambridge, MA: MIT Press).

Strathern, Marilyn (1992). *After Nature: English Kinship in the Late Twentieth Century.* (Cambridge: Cambridge University Press).

Sturtevant, Alfred H. (1913) 'The Linear Arrangement of Six Sexlinked Factors in Drosophila, as Shown by their Mode of Association', *Journal of Experimental Zoology* 14: 43-59.

Sulston, J. E., & G. Ferry (2002) *The Common Thread* (London: Bantam Press).

Sutton, W. S. (1903) 'The Chromosomes in Heredity', *Biological Bulletin* 4: 231- 51.

Thacker, Eugene (2004) *Biomedia* (Minneapolis: University of Minnesota Press).

Thompson, Victor A. (1964) *Modern Organization* (New York: Knopf).

Tjio, Joe-Hin, & Albert Levan (1956) 'The Chromosome Number of Man', *Hereditas* 42: 1-6.

Tucker, W. B., & W. A. Lessa (1940*a*) 'Man: A Constitutional Investigation', *Quarterly Review of Biology* 15: 265-89.

Tucker, W. B., & W. A. Lessa (1940*b*). 'Man: A Constitutional Investigation (Concluded)', *Quarterly Review of Biology* 15: 411-55.

Walker, F. O. (2007) 'Huntington's Disease', *Lancet* 369 (9557): 218-228.

Wallace, Bruce (1992) *The Search for the Gene* (Ithaca: State University of New York).

Waller, J. C. (2001) 'Ideas of Heredity, Reproduction and Eugenics in Britain, 1800-1875', *Studies in History and Philosophy of Biological and Biomedical Sciences,* 32: 457-89.

Watson, James D. (1990) 'The Human Genome Project: Past, Present, and Future', *Science*, 248: 44-8.

Weatherall, David J. (1985) *The New Genetics and Clinical Practice* (Oxford: University Press).

Webster, A. (2005) 'Social Science and a Post-Genomic Future: Alternative Readings of Genomic Agency', *New Genetics and Society* 24: 228-37.

Wilson, Philip K. (2007) 'Erasmus Darwin and the "Noble" Disease (Gout): Conceptualizing Heredity and Disease in Enlightenment England' in S. Müller-Wille and H.- J. Rheinberger (eds.), *Heredity Produced: At the Crossroads of Biology, Politics, and Culture, 1500-1870* (Cambridge, MA: MIT Press): pp. 133-54.

Winchester, A. M. (1965) *Heredity: An Introduction to Genetics* (New York: Barnes and Noble).

Wynne, Brian (2005) 'Reflexing Complexity: Post-Genomic Knowledge and Reductionist Returns in Public Science', *Theory, Culture & Society* 22 (5): 67-84.

Zapperi, Roberto (1995) 'Ein Haarmensch auf einem Gemälde von Agostino Carraci', in Michael Hagner (ed.), *Der falsche Körper: Beiträge zu einer Geschichte der Monstrositäten* (Göttingen: Wallstein): 45-55.

Notes

[1] See, in particular, Waller (2001), Paul (1998), Mazumdar (1992), Soloway (1990), Kevles (1985), Farrall (1985), MacKenzie (1976).

[2] See, for example, Cook-Degan (1993), Kevles and Hood (1992), Lee (1991), Holtzman (1989).

[3] Daston and Park (2001: 190-214) offer a wonderful collection of 'monstrous birth' case studies. More specifically, see the famous case of Petrus Gonsalvus, born with an

extreme hirsuite condition in Teneriffe in 1556 and raised at the court of Henry II of France (Zapperi, 1995).

[4] Philip K. Wilson's (2007) study of the work by Charles Darwin's grandfather on gout is a particularly good example of this.

[5] A comprehensive survey of biological interest in the human constitution is available in Tucker and Lessa (1940*a*, 1940*b*). As regards constitutional psychology, see Sheldon, Steven and Tucker (1940). Further to this, the human constitution was subsequently taken up and advanced by physical anthropologists interested in the anthropometrical aspect of constitutional somatotyping. See, for example, Montagu (1947), chap. 8; Comas (1960), chaps. 4, 5.

[6] It is a commonplace that physicians today looking for symptoms of Huntington's disease *in families affected by Huntington's disease* look for jerky, random, and uncontrollable movements (i.e., chorea) in patients (Walker 2007). The onset of Huntington's disease is expected to begin in adulthood with minor motor abnormalities typically preceding more obvious motor dysfunction by about three years. Rigidity, writhing motions or abnormal posturing appears as neurological degeneration progresses. Physical instability, abnormal facial expressions, and difficulties chewing, swallowing, or speaking are expected to appear later on. The symptoms of Huntington's disease thus accumulate over time according to a predictable trajectory of illness.

[7] Also called Sydenham's chorea for British physician Thomas Sydenham (1624–1689), symptoms of St. Vitus's dance include rapid, uncoordinated jerking movements affecting primarily the face, feet and hands. Today Sydenham's chorea is categorised as a

childhood disease and distinguished from Huntington's disease in adults. However, Lund recounted choreic episodes usually beginning between the ages of fifty and sixty years. Ørbeck is therefore justified in his characterisation of Lund's account as an early description of Huntington's chorea (i.e., Huntington's disease).

[8] A neuro-physiologist and a member of the Academy of Sciences of the USSR in the 1930s.

[9] Mazumdar's book concentrates on the rise of the Eugenics Society in Britain in 1907 and its decline in the 1930s. The study of pedigrees as scientific and medical genealogical diagrams is confined to this period.

[10] Following the example of Robbins and Johnston (1976: 353), I use the phrase 'professional ideology' in a restricted sense. It refers only to 'those systems of closely related beliefs, ideas and attitudes' that exist among the groupings of scientists and service providers studied in this article. It is not here used in its broader sense, i.e., as a *Weltanschauung*. I am interested only in how the individuals involved made sense of applied human genetics and sought to further their collective professional aims.

[11] Geneticists such as Herluf H. Strandskov (University of Chicago) and Laurence H. Snyder (University of Ohio) made reputations for themselves providing heredity-related family counselling. The Heredity Clinic of the University of Michigan opened its doors in 1940. The Charles Fremont Dight Institute of the University of Minnesota was established the following year. Likewise, heredity counselling was offered at Winston-Salem, North Carolina, in the Out-Patient Department of the North Carolina Baptist Hospital (the teaching hospital of the Bowman Gray School of Medicine). Other heredity

counselling clinics were set up through the 1940s at the Laboratory of Human Genetics, University of Utah; University of Texas; and the Hospital for Sick Children in Toronto. Heredity counselling in this period consisted mainly of providing answers to questions asked by lay-persons and clinicians about heredity and the effects of heredity in families. (See Leeming, 2004; 2010.)

[12] The ABO blood group had first been described by Karl Landsteiner in 1901. (See Schneider, 1983.) In 1919, the Polish husband and wife team of Ludwik and Hanna Hirszfeld made a case for serological blood groups resulting from two independent genetic loci. Felix Bernstein, using population data, subsequently argued for a model predicated on the existence of a single blood group gene with three alleles (an alternative form of a gene that is located at a specific position on a specific chromosome), corresponding to A, B, and O. Finally, Landsteiner proposed a new blood type system, which he called MN.

[13] Researchers pursuing linkage studies using blood groups ultimately failed to discover genetic linkages. In the last years of the 1980s, linkage mapping became associated with new techniques for examining the chromosomal DNA sequence itself. (See Hopkins, 2004: chap. 7.) The Southern blot technique pioneered in the 1970s, for example, chemically divided DNA into fragments (i.e., restriction-fragment length polymorphisms) and then established linkage through binding fragments to strands of DNA whose sequence was known. This, and other physical mapping methods that helped to localise genes and their markers on maps laid the groundwork for mapping the genome at the turn of the millenium.

[14] Thomas Morgan adopted the term 'gene' from the Danish botanist and plant physiologist Wilhelm Johannsen who lectured at Columbia University in 1909.

[15] Alfred Sturtevant, in his recollections of the period, mentioned the German botanist Carl Erich Correns who, in 1902, produced 'beads-on-a string pictures of chromosomes' to illustrate his work. Discussed in Wallace (1992: 58).

[16] Simply put, an 'ontology' in the world of bioinformatics is a software artefact designed with a specific set of uses and computational environments in mind (Guarino, 1992). In the context of molecular biology and genomic research, the goal is often to take a haphazard list of biological ideas, terms and images and turn them into a workable classification system.

[17] See < http://www.ncbi.nlm.nih.gov/ >.

[18] As regards the idea of "post-genomics," see Petersen (2006), Fujimura (2005),Webster (2005), Wynne (2005), Rose and Novas (2005), Sulston and Ferry (2002).

[19] Prolepsis refers to any use of a rhetorical device by which future events are presumed to have already occurred.