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Human cytogenetics at Johns Hopkins Hospital, 1959–1962

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Abstract

An account is given of the introduction of human cytogenetics to the Division of Medical Genetics at Johns Hopkins Hospital, and the first 3 years' work of the chromosome diagnostic laboratory that was established at the time. Research on human sex chromosome disorders, including novel discoveries in the Turner and Klinefelter syndromes, is described together with original observations on chromosome behavior at mitosis. It is written in celebration of the centenary of the birth of Victor McKusick, the acknowledged father of Medical Genetics, who established the Division and had the foresight to ensure that it included the investigation of human chromosomes.

KEYWORDS
human chromosomes, Turner, Klinefelter syndromes, X-inactivation

There were few clinical geneticists around the world when Victor A. McKusick was invited in 1957 to form a Division of Medical Genetics in the former Division of Chronic Diseases at Johns Hopkins Hospital. The venture was funded by the U.S. Public Health Service to provide Fellowships in Medicine, grants for staff and research facilities. I was interviewed in July 1958 by Victor and was offered one of these Fellowships specifically to develop chromosome analysis in patients with the Klinefelter syndrome (KS).

My interest in KS is detailed more fully elsewhere (Ferguson-Smith, 2011) but a brief outline may be appropriate here. I had been a trainee pathologist at Glasgow University and, in 1956–1957 with Bernard Lennox, a high frequency of KS at an infertility clinic was discovered (Ferguson-Smith et al., 1957). In one KS testis biopsy there was a solitary tubule with complete spermatogenesis in which the XY sex bivalent was evident in spermatocytes (Ferguson-Smith & Munro, 1958). KS individuals were thought to be sex reversed females with no Y chromosome and so it was important to find someone willing to check the sex chromosomes in KS. (This was known to be possible from cell culture as the normal human chromosome number had been studied in 1956 and corrected to $2n = 46$.) Our local geneticists were not interested and referred me to Charles Ford who encouraged me to try to do this myself from short-term bone marrow cultures. However, attempts in 1958 on several cases produced only scant numbers of poor metaphases which could not be interpreted. My professor realized that my pathology training schedule gave insufficient time for developing the method and recommended me to Victor in the hope that opportunities would be available at Hopkins.

Victor's early interest in genetics is evident in his third publication on Peutz-Jegher syndrome in 1949 and in his later work on Marfan syndrome which led to his delineation of "heritable disorders of connective tissue" first published in 1954 and then in book form in 1956. The classification of genetic disorders, by lumping and splitting, became a prominent theme in his future work. Victor appreciated that chromosome maps, like those available in Drosophila, maize, and mouse, in which the location of genes on chromosomes was ordered by meiotic recombination studies, would be needed in human genetic research. This is indicated in his masterly review "On the X chromosome of man" (McKusick, 1962) published as a second book in 1964. The linkage of hemophilia and color blindness had been discovered by Bell and Haldane (1937) and Victor with Ian Porter would later add the G6PD gene to the same linkage group (Porter et al., 1962). Victor clearly saw the potential for chromosome research in medical genetics and this most probably explains his enthusiasm for encouraging a would-be human cytogeneticist to join his new division.

As over 60 years have elapsed since my 3 years at Hopkins I have relied on my diary and notes to refresh my memory in the following necessarily very personal account. The dates from the diary may help to illustrate the rapid course of events. I arrived in Baltimore on February 15, 1959. Already, Ford et al. (1958) had published the bone marrow method for analyzing somatic chromosomes and had included the finding of an apparently normal female karyotype in a "sex reversed" KS patient; but there was no Y chromosome. The discovery of trisomy for a small acrocentric in Down syndrome by Lejeune et al. (1959) in January was followed by the report from Jacobs and Strong (1959) of a 47, XXY karyotype in KS (January 31); I was happy to note that this time the Y chromosome was found as expected from the previous observation of the sex bivalent! The discovery of the 47, XXY karyotype in KS was followed by the report (April 4) of the 45, XO karyotype in the Turner syndrome (Ford et al., 1959) showing for the first time that the Y chromosome has a dominant role in mammalian sex determination.

Victor was quick to give his support and soon (March 17) a microscope arrived which enabled me to study my chromosome preparations from Glasgow. A talk on the incidence and pathogenesis of KS at the Endocrine Conference at Hopkins to an audience including Harry Klinefelter, Lawson Wilkins, and Victor (March 18) helped to generate local interest in the potential of chromosome diagnosis. Three weeks later I had the good fortune to meet T. C. Hsu (TC) at the American Tissue Culture Association meeting at Atlantic City (April 9) and was invited to visit his cytology laboratory at the M. D. Anderson Tumor Hospital in Houston to learn chromosome technology. His advice stimulated me to make a new attempt at bone marrow culture (April 19) which again failed to yield adequate mitoses. An invitation to talk on KS at the Jefferson-Davies Hospital in Houston (May 14) enabled me to take up TC's offer of help and I spent 4 days in his lab (May 11–14) learning chromosome technology. It happened that Albert Levan was on sabbatical with TC and so I had the advantage of instruction from two world class cytogeneticists. I was shown their current work on tumor chromosomes and Albert taught me how to draw chromosomes by camera lucida. These 4 days were a turning point and I have remained indebted to them both ever since.

Back in Baltimore, a camera lucida was obtained, and work was started on two samples kindly donated by patients whose bone marrow was being taken for hematological diagnosis (May 21). Amazingly, both samples yielded good mitoses which could be karyotyped by camera lucida. With this encouragement, permission was given to biopsy sternal marrow from two male pseudohermaphrodites (June 3), a patient with Turner syndrome (June 5) and a male patient with Down syndrome (June 9). All samples provided excellent numbers of mitoses with karyotypes showing 46, XY, 45, XO, and 47, XY + 21, respectively. These results were presented (June 16) at the first Genetics Conference held at Colorado Springs and published later in a paper "Cytogenetics in Man" (Ferguson-Smith, 1960). There were less than 50 at this meeting in the Broadmoor Hotel, mostly academics in human genetics, and my diary records that Kurt Hirschhorn, Arthur Steinberg, Arno Motulsky, Lytt Gardner, Barton Childs, Newton Morton, Ted Puck, James Sidbury, and Victor were present. This was an opportunity to meet with the wider human genetic community in the United States and learn about the specialty. It also led to patient and sample referrals to our chromosome diagnostic service at the Moore Clinic.

Some weeks later Victor invited Albert Levan to Hopkins and he was interested to study my chromosome slides from the male Down syndrome patient. Levan used the camera lucida to draw the small acrocentric chromosomes in several mitoses and we became convinced that the extra autosome was the smallest, that is, chromosome 22. Lejeune had claimed that the trisomic chromosome was number 21 and this had been adopted by everyone. As techniques improved in the following years it became clear that Levan's conclusion was correct. However, by then it was already too late to change the nomenclature and the anomaly persists to this day in the standard human karyotype.

Sex chromosome abnormalities were of special research interest in the early days and our main source of referrals came from pediatric endocrinology and from gynecology. Pioneers in these fields were Lawson Wilkins and Howard W. Jones respectively. Wilkins ran a clinic every Saturday morning at the Harriet Lane Home at Hopkins. I was introduced to Wilkins at his clinic (March 7, 1959) and attended the clinic regularly during my time at Hopkins. Children with gonadal disorders and/or sexual ambiguity were sent from all over the States for Wilkins' opinion. His team was one of the two groups that discovered the absence of sex chromatin in the Turner syndrome in 1954 (the group of Polani and Lennox was the other) and he was enthusiastic for my lab to study the chromosomes of his patients.

Victor was keen to provide further resources and enlisted a strong team to cope with the volume of chromosome work. Yvonne Hadja and Bonny Lewis were taken on as research assistants in cytogenetics and they were joined by students Stan Handmaker, Dick Hill, Sandy Miller, and Lynn Ghant. Alan Johnston (Fellow in Medicine from the UK) came to strengthen the clinical side. A nearby restroom and lavatory were converted into a chromosome laboratory and darkroom. Rosemary Wise became our photographer and the camera lucida was abandoned in favor of a single lens reflex camera which was attached to the microscope incorporating an exposure meter in the optical path. By adjusting the light intensity to a constant level an identical exposure was obtained for every metaphase. This proved to be a valuable development as it speeded the chromosome analysis. From then on at least three karyotypes were made from photographs in each patient. Thus, several hundred printed karyotypes were accumulated and used later to improve individual chromosome identification from chromosome measurement and sites of secondary constriction (Ferguson-Smith et al., 1962). When short-term blood cultures replaced bone marrow preparations (Moorehead et al., 1960) the methodology became simpler and the number of mitoses and production of karyotypes increased. For example, at that time it was thought that chromosome pair 21 and either the 13 or 14 pair could be distinguished from the other three acrocentric chromosomes by the presence of satellites at the end of their short arms (nucleolus organizer loci were located proximal to each satellite). Our accumulated photographic karyotypes showed that all five acrocentric

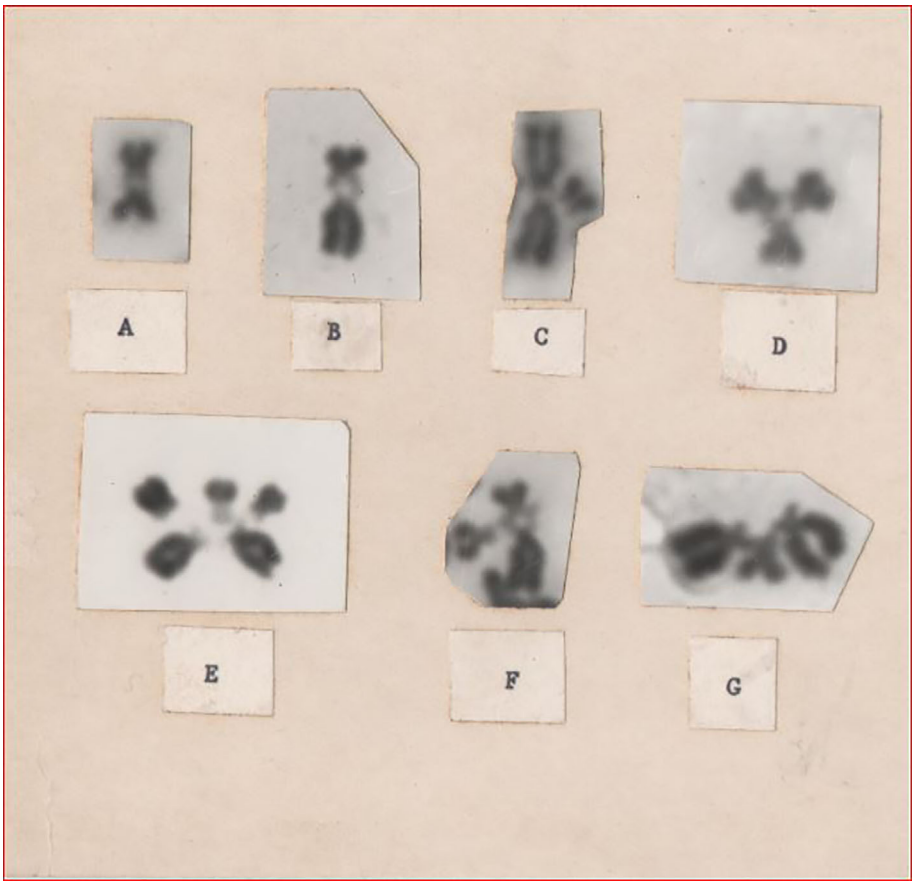

FIGURE 1 Figure showing examples of satellite association at metaphase from Ferguson-Smith and Handmaker (1961) [Color figure can be viewed at wileyonlinelibrary.com]

chromosomes carried satellites and we published a karyotype with clear satellites on 9 of the 10 acrocentrics (Ferguson-Smith & Handmaker, 1961). This report also showed for the first time a phenomenon, termed satellite association, in which the five acrocentric pairs of chromosomes at metaphase tended to adhere to one another by their short arms (see Figure 1). We thought that this was probably due to nucleolar fusion during interphase but soon preferred the explanation of somatic pairing between repetitive DNA. The latter was consistent with the observation that trisomy and translocation between acrocentrics were the most frequent types of autosomal abnormality. It seemed possible that nondisjunction and recombination between homologous regions on non-homologous autosomes might be promoted by illegitimate synapsis during meiosis. In more recent times this mechanism became accepted and is now termed non-homologous allelic recombination. It was shown later that satellited chromosomes tended to associate with heterochromatic regions of other chromosomes that had no nucleolar organizers, especially chromosomes 1, 2, and 9 (Ferguson-Smith & Handmaker, 1963).

During the next few months, 30 female patients with various forms of gonadal dysgenesis and 9 patients with male pseudohermaphroditism were karyotyped, most of whom came from the Wilkins clinic. While all the male pseudohermaphrodites had apparently normal male karyotypes (Alexander & Ferguson-Smith, 1961), those with gonadal dysgenesis had an interesting assortment of X and Y chromosome deletions with or without sex chromosome mosaicism (Ferguson-Smith, Alexander, et al., 1964). The latter study revealed that the short stature and characteristic stigmata in the Turner syndrome occurred when the short arm of the X chromosome was deleted, while cases of gonadal dysgenesis with long arm deletions were of normal stature and without Turner stigmata. This showed that the syndrome was due to haploidization of X-linked genes on the short arm. A novel conclusion was that part of the short arm of both Xs in normal females was genetically active. This idea ran counter to the accepted view based on the X-inactivation hypothesis of Mary Lyon (1961) which affirmed that, in female mice, one of the two Xs was completely inactivated. The apparent conflict led to difficulty in getting the paper accepted for publication. Although the study was completed in 1961, it was not accepted until 1964. When the results were added to cases from the literature, karyotype-phenotype correlations in 307 patients with gonadal dysgenesis became possible (Ferguson-Smith, 1965). This provided evidence that patients with major deletions of the Y chromosome could also have features of the Turner syndrome (and it was obvious that the non-deleted Y chromosome prevented Turner stigmata in normal males). It followed that homologous genes on both the X and Y escaped inactivation in humans and, when present only in single dose, led to the Turner syndrome. In patients with more than two sex chromosomes, such as in XXY, XYY, XXXY, and XXXXY KS, the additional doses of active X or Y genes led to increasingly greater handicap. More than two X chromosomes were associated with additional sex chromatin bodies, two in

XXXY and three in XXXXY patients, indicating that all Xs over one were inactivated; this gave support to the Lyon hypothesis. In patients with X deletions the sex chromatin body was small, and in those with isochromosomes for the long arm of the X, the sex chromatin was larger than normal, indicating that abnormal Xs were preferentially inactivated. The observations in XO and XXY mice had shown that they were phenotypically no different from mice with normal sex chromosome complements and it was this apparent absence of a dosage effect in mice that had caused the confusion between the findings in man and mouse. It took much longer before it was documented that many human X-linked genes escaped inactivation in humans and that there were a smaller number of escapees in the mouse (Carrell & Willard, 2005; Lyon, 2005).

In 1959 a sex chromatin survey of 916 patients was undertaken at the nearby Rosewood Training Centre. Two male patients were found to have a 48, XXXY karyotype and three female patients a 47, XXX karyotype (Ferguson-Smith, Johnston, & Handmaker, 1960; Johnston et al., 1961). Howard W. Jones and Georgeanna Seegar Jones undertook clinical and pathological studies in the XXX cases, and in patients with true hermaphroditism and gonadal dysgenesis (Ferguson-Smith, Johnston, & Weinberg, 1960; Jones et al., 1963, 1965). The true hermaphrodites (with both ovaries and testes, or ovotestes) had apparently normal female karyotypes and this led to a study of rare cases of KS who also had 46, XX karyotypes and no Y chromosome despite male differentiation. In a few of these patients, mapping with the Xg blood group antigen showed that they had failed to receive the XG gene from their father, suggesting that the testis-determining region of the Y had exchanged with part of the short arm of the paternal X containing the XG locus (Ferguson-Smith, 1966). This hypothesis was confirmed by Southern blotting and in situ hybridization (Ferguson-Smith, 1988) and when the sex-determining gene, SRY, was cloned from the X chromosome in a male with XX KS (Sinclair et al., 1990).

Other early cytogenetic contributions from Hopkins included an investigation into the chromosome number of chimpanzees. When the human chromosome number had been corrected from 48 to 46 in 1956, no one seemed to have checked if a similar correction was necessary in the chimp. Bone marrow cultures in several chimps confirmed that 48 was correct (Young et al., 1960). The 46 count in humans was later found to be due to centric fusion between two chimp acrocentrics forming human chromosome 2.

Increased maternal age has long been known to be an etiological factor in Down syndrome and had been noted in KS (Ferguson-Smith, 1960) and especially in KS cases where maternal could be distinguished from paternal nondisjunction (Ferguson-Smith, Mack, et al., 1964). In Turner syndrome, on the other hand, a study (corrected for possible bias) of 63 families showed a mean maternal age of 25 years and that there were no differences in maternal age between patients and their siblings (Boyer et al., 1961). This indicated that paternal nondisjunction during spermatogenesis was probably the main mechanism in Turner syndrome.

The study of human genetic linkage has depended on the availability of polymorphic genes with measurable allelic differences. Victor's work on linkage of X-linked disease (1962) depended on only three polymorphic genes, namely color vision, G6PD variants, and the XG blood group. Apart from hemophilia, no new linkages were found in the many disorders tested. For autosomal linkage, only about 20 blood group, red cell enzyme, and serum protein polymorphisms were available at the time, so it was not surprising that only two single gene linkages were known, namely between the Lutheran and Lewis (including secretor) blood groups (Mohr, 1951) and between the nail-patella syndrome and the ABO blood group locus (Renwick & Lawler, 1955). Victor achieved a notable breakthrough when the first autosomal gene assignment to a human chromosome was announced from the Moore Clinic. Donahue, Bias, Renwick, and Victor (1968) reported linkage of the Duffy blood group locus to chromosome 1 using a familial centromeric heteromorphism. As Duffy had previously been mapped to a familial cataract (Renwick & Lawler, 1963), the latter was added to the linkage group. Mapping genes by linkage to human chromosomes made little further progress until the development of restriction length DNA polymorphisms in 1978.

The journal club was an important weekly event at the Moore Clinic. All Fellows reported on items of genetic interest in the various journals that Victor had assigned to them. Details of each article were submitted on index cards and my diary shows (March 4, 1959) that Victor announced his intention to use these as material for an *Annual Review of Genetics*. These reviews duly appeared in the *Journal of Chronic Diseases* annually from 1959 (covering articles from the previous year) until the sixth in 1964. In 1966, the reviews became incorporated into the first edition of Mendelian Inheritance in Man (MIM). Many of the later editions of MIM included chromosome maps in which gene assignments were added by Victor year on year. An online version of this unique catalog became available in 1987 and has been maintained ever since. It remains a lasting memorial to Victor's genius, his huge productivity, and his early advocacy for the human genome mapping and sequencing project.

The medical genetics teaching program at the Moore Clinic included basic chromosome cytology in addition to biochemical and population genetics. Victor adopted a series of 15 McGraw-Hill black and white films of eminent early genetics pioneers (including Nobel laureates Muller, Lederberg, and Watson) lecturing on their particular topics. This may have prompted Victor to make three color films in 1960–1962 with Milner-Fenwick for the National Foundation. The first one on cytogenetics (1960) included a scene showing a sternal marrow puncture in a Turner patient. Clinical cases were discussed in these films and cartoons of animated chromosomes illustrated mitosis and meiosis. The second film (1961) dealt with biochemical genetics and the third film (1963) was on genes in families and populations. The films were much appreciated at the time but now seem to be forgotten. This is sad as they are of historical importance in view of Victor's unique contributions to teaching in medical genetics.

I returned to Glasgow in November 1961 fully determined to follow a career in medical genetics after an inspiring introduction to the specialty from Victor. Many of his Fellows were similarly inspired and went on to create international centers of excellence. Victor enjoyed visiting these centers, often being invited to open their new

departments. He visited Glasgow in 1981 and opened our Duncan Guthrie Institute in Glasgow as well as taking time to enjoy a short holiday in Scotland. The Moore Clinic grew to be the acknowledged world center for clinical genetics and drew researchers from far afield. His short course in medical genetics held every second year in conjunction with the Jackson Laboratory attracted many students into genetics and I was privileged to give the chromosome talks in the first year (1960) and for several years thereafter. Victor organized a similar European course at Sestri Levante with Giovanni Romeo for many years, so his teaching was continued on an international basis.

The cytogenetics diagnostic service at the Moore Clinic continued under Peter Bowen and Catherine Lee until 1966 when they left for Edmonton, Alberta. Digamber Borgaonkar took over cytogenetics for the next 12 years. Digamber contributed to research on the 47, XYY syndrome and started a valuable database on Chromosome Variation in Man.

When the Division of Medical Genetics was established in 1957, genetics played virtually no part in medical practice. In the intervening period until the present (2021) when we celebrate the centenary of Victor's birth, medicine has been transformed by advances in molecular genetics. Clinical practice in diagnosis, treatment, and prevention of disease are firmly based on genetics. Victor's contributions to this transformation have been outstanding. Thanks to his prescience, human cytogenetics came early to Hopkins. With his strong support and the clinical material from Lawson Wilkins and Howard Jones, my time at the Moore Clinic was a most productive and enjoyable period. It led to an enduring fascination for chromosomes, an appreciation of the importance of a human gene map, and a desire to follow Victor's example and help put genetics more firmly into the practice of medicine. Our specialty rightly regards him as the founding father of Medical Genetics and this is always the way that he will be remembered.

CONFLICT OF INTEREST

The author has no conflict of interest.

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