Having It All*

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When I first learned that I was to give this talk, I looked back at my predecessors to see what they had done. I found basically three prototypes: first, the straightforward scientific talk on the subject of one's work; second, the philosophical talk that tries to either interpret the past or predict the future of genetics; and third, the autobiographical talk that discusses the processes that shaped one's own career. Being bored with the first and not philosophical enough for the second, I have opted for the third. This year marks the 50th anniversary of the first description of the correct human chromosome number.[1] Although I am sure you all think I remember when the number was 48, I have to disappoint you: I actually do not. However, I do remember when we didn't know that Down syndrome was the result of an extra chromosome. Diagnosis of a newborn often involved something called "dermatoglyphics," where one calculated a Bayesian likelihood that the child had what was then called "Mongolism" by scoring a set of finger and palm print patterns. I hope that my talk will both give the younger folk a feeling for how cytogenetics has progressed in successive stages and also be a nostalgic walk along memory lane for the older folks in the audience.

The phrase in my title, "Having It All," is traditionally used as a description of a lifestyle, implicitly by a woman, that tries to combine career and family life without shortchanging either one. The phrase does apply to my life in the usual sense, and I shall return to this at the end of my talk.

However, I chose the phrase because it also seemed to describe my life in human genetics in several other ways. First, cytogenetics has allowed me to combine two seemingly disparate enthusiasms: the part of me that likes to play around in the laboratory with new techniques and the part that likes to sit at my calculator or computer and play around with numbers. Secondly, "Having It All" can also be used as a metaphor for the achievement of the Human Genome Project, which I have also seen come to fruition since attending the first human gene–mapping conference in 1973. Thirdly, I have been able to have it all in another sense, by combining both clinical and research activities during almost 40 years of directing a clinical cytogenetics lab in an academic setting.

My father was a chemist, and I owe him much in giving me an early love of science and the expectation that I could excel in it even though I was female. He bought me chemistry sets and other scientific toys, but he had a strict rule that no chemistry experiments were to be done by me without his presence. I suppose as an attempt to make me cautious, he told me stories about the dangers of each compound in my set, what they should *not* be mixed with, and how they could be used to physically damage either myself or the environment. As a result, he unfortunately instilled in me a fear and dislike of chemistry that persists to this day. I studied biology in college, not only because it was naturally appealing to me because of my love of natural history, but also because it seemed at that time a science fairly free of chemistry. I had discovered I enjoyed mathematics, and part of the appeal of genetics, in which I majored, was that it was a science that dealt in mathematical ratios and experiments that involved counting. I then discovered, under the tutelage of my first mentor, Clarke Fraser at McGill University in Montreal, that there was something called "human genetics" that was even free of experimentation and, at that time, rarely involved labs. This was very attractive to me, and I ended up writing a Ph.D. thesis in human genetics that did not involve ever

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lifting a pipette but instead dealt with statistical and epidemiological analysis of family data.

My problem was that my thesis topic was the role of genetics in spontaneous abortions, and I finished it in 1961, just after the discovery of the first human cytogenetic abnormalities by Lejeune, Jacobs, and others. At that time, we knew nothing about the importance of chromosome abnormalities in embryonic and fetal loss, though, in looking back at the paper published from my thesis, I see that the idea did actually occur to me as a possibility to explain the maternal-age association.

> It is possible that the effect of parental age is due to an increase in chromosomal aberrations, rather than in genic mutations….
>
> [I]n female germ cells…terminalization of chiasmata might increase with maternal age. Terminalization of chiasmata leads to reduced efficiency in pairing of the chromosomes, with subsequent increase in the frequency of nondisjunction. Thus older mothers might have an increased probability of producing gametes with abnormal chromosome complements….[2(p17–18)]

Soon after, Carr in Canada[3] and Szulman in the United States[4] first reported the major role that chromosome abnormalities played in causing miscarriages. If I was to continue in this field, I needed to learn cytogenetics. Although Clarke and I did succeed in making the first human chromosome preparations at McGill in 1960, I was still not convinced that the laboratory was a place where I would ever feel at home.

In 1963, my husband accepted a job at Barnard College in New York City. I was lucky to find a position in the Department of Obstetrics and Gynecology at Columbia University with Orlando J. Miller (known familiarly as "Jack"), who agreed to teach me cytogenetics and let me work on spontaneous abortions if I wished. I was finally working in a lab and discovered that I enjoyed it. Cytogenetics was much more like cooking than chemistry, and I had always enjoyed cooking.

At the time, chromosomes were not banded, and only chromosome groups (A, B, C, D, E, F, and G) could be distinguished reliably. However, it had been discovered that chromosome pairs with similar morphology often replicated asynchronously.[5,6] This could be studied by adding tritiated thymidine to cultured cells at the end of the S phase. Incorporated radioactivity was then detected by dipping metaphase slides in photoemulsion, leaving them for several weeks in the dark, developing the film, and counting silver grains.

So, my passion for numbers was to be satisfied again. Jack, his wife, Sandy, Roy Breg, and I had identified a large number of patients with a deletion of a B-group short arm. We showed that the deleted chromosome in patients with features of cri-du-chat syndrome consistently replicated earlier than the deleted chromosome in patients with the features of Wolf-Hirschhorn syndrome. Furthermore, by measuring chromosomes with a map measurer, we showed that the chromosome that replicated earlier was shorter than the one that replicated later. Thus, cri-du-chat could be defined as due to a deletion of the short arm of chromosome 5, and Wolf-Hirschhorn syndrome was due to a deletion of chromosome 4.[7] It was tedious, and, in the end, futile, but it worked. The same process was used to define the deleted large acrocentric chromosome in two patients with a similar phenotype as chromosome 13.[8]

We also used a statistical approach in what was probably the first example of microdeletion analysis.[9] To settle arguments in the lab about whether certain patients really had small deletions of a B-group short arm, we randomized photos of metaphase spreads from these patients, along with positive and negative controls, and had several observers assess which cells had a B-group chromosome with a short-arm deletion. We then tabulated the data by assessor; table 1 is representative of the interesting results. Whereas scorers varied in the number of normal cells they concluded had deletions, they all agreed on which cases had a larger number of cells with a deletion than did normal controls. This "blind cytogeneticist" approach might still be useful when trying to assess those cases, which still occur, when there is argument in the lab about whether some subtle chromosome rearrangement is really present. Of course, these days, we can usually find other more elegant ways to settle such arguments.

After some years of these kinds of heroic efforts to extract more information from unbanded karyotypes, an end of all scientific interest in human cytogenetics was forecast for the first, but not the last, time. Then banding patterns were discovered, and everything changed.

Quinacrine banding allowed us, for the first time, to identify all individual chromosome pairs and to detect many more rearrangements. This was essential for the first associations of genes and linkage groups with individual chromosomes and was thus the first step in the Human Genome Project. Banding was first described in 1970.[10] By 1973, the first human gene–mapping conference was held at Yale, at which a total of 19 genes were assigned to chromosomes, some of them, as it turned out, incorrectly.[11]

Since, with existing fluorescent microscopic equipment, photographing a Q-banded metaphase might require a 2-min exposure, cytogeneticists all spent a good deal of time sitting in the dark. G banding was thus a major breakthrough. I was fortunate enough to have a super techni-

Table 1. Minute Deletions by Consensus[9]

Sample	No. of Cells	Percentage of Cells Judged to Show a Deletion by Observer			
		O.J.M.	P.W.A.	D.W.	D.A.M.
Normal	84	17	34	11	21
Case 28[a]	70	47	74	33	64
Father of case 28	77	25	32	16	31
Known deletion[a]	18	100	94	94	100

NOTE.—O.J.M. is Orlando J. Miller, P.W.A. is Penny W. Allderdice, D.W. is Dorothy Warburton, and D.A.M. is D. Anne Miller.

[a] Statistically significantly higher than normal control for all observed.

cian, Saundra Villafane, who devised a reliable G-banding method that we quickly adopted in the clinical laboratory. It is now hard to believe, but, at the time, there was an argument among cytogeneticists as to whether Q banding or G banding was better and whether banding needed to be adopted by all labs doing clinical work. Saundra and I were often invited to other labs to demonstrate our banding method. All of you who work in labs (or kitchens) will know that when you perform a technique in someone else's space, it usually doesn't work: this was certainly true for our banding method.

Nevertheless, I was invited to the Paris Conference on Chromosome Nomenclature, where we drew up the initial banding diagrams. Given the preparations we had to work with, it is impressive that these diagrams were so accurate and useful for so long. The meeting was held at a very undistinguished hotel near Orly Airport, where one could not even go out for a walk in pleasant surroundings. The March of Dimes, who financed the meeting, worked us hard from morning to evening. Here I was, relatively young and in Paris for the first time, but I did not actually see the city until 3 days later when the meeting was over. There were many national and personal rivalries involved in coming to any consensus. For example, the French used R banding, and most of the rest of the world used G banding, so a major problem was to decide which bands had priority in the nomenclature system. Luckily, our chairman, John Evans, who was a very strong-minded Welshman with a booming voice, came up with the brilliant idea that there should not be bands with interbands in between but rather that both dark and light bands should be given equal weight in the numbering system.

> A band is…part of a chromosome which is clearly distinguishable from its adjacent segments by appearing darker or lighter…. The chromosomes are visualized as consisting of a continuous series of light and dark bands, so that by definition there are no "interbands."[12(p6)]

Otherwise, it might have been even longer before I saw Paris!

Banding analysis opened up a whole new continent for exploration, as we identified many new kinds of chromosome aberrations in humans that had previously been shown only in experimental organisms. Larry Shapiro and I described the first human insertion[13] and also one of the first human dicentric chromosomes, which we showed had only one centromere that remained as a constriction as metaphase proceeded.[14]

Another technical innovation was the discovery, by Joe Gall and Marylou Pardue,[15,16] that nucleic acid hybridization would occur on chromosomes fixed on a slide, something not at all intuitively obvious. Kim Atwood, Adjie Henderson, and I set out to apply this for the first time to humans. It was not easy. Recombinant DNA technologies had been banned, so that labeled probe had to be produced by growing cells in the presence of tritiated uridine and by extracting the RNA. Because of the low specific activity of the probes that could be produced, only repetitive sequences could be mapped, and exposure times were at least a month. Again, my statistical inclinations were satisfied, as one had to count the silver grains over all chromosomes and perform statistical analysis in order to distinguish real label from background. How different from the practically instant gratification provided by FISH!

In 1972, we published the first localization of human genomic sequences by in situ hybridization,[17] establishing that the 18–28S ribosomal genes were on the short arms of all the acrocentric chromosomes, as had been suggested much earlier by Malcolm Ferguson-Smith based on other evidence.[18] We also showed that the copy number of these sequences could vary a great deal among chromosomes and that this was associated with behavior, such as satellite associations in metaphase.[19] We then set out to compare the localization of rDNA in multiple primate species. Since most of these had not been G banded, we had to work out the karyotypes first. Although we wrote one of the first papers comparing the human and chimpanzee G-banded karyotypes, it was turned down by *Science* because it was "not of general interest."[20] We did succeed in showing that the rDNA regions in primates had evolved in a rather complex pattern, as illustrated in table 2. No two of the great apes were alike. For example, chromosome 15 contained sites only in the human and orangutan, while only the small acrocentrics contained rDNA sites in the two species of gorilla.[21]

Meanwhile, I had not forgotten my interest in miscarriages or epidemiology. In the 1970s, I began a collaboration that would last for many years with Dr. Zena Stein, an epidemiologist interested in Down syndrome. Together with Mervyn Susser, Zena and I had the idea that a search for factors influencing the frequency of trisomy 21 could be done much more efficiently by ascertaining all trisomies from a collection of spontaneous abortions. I learned much from my association with colleagues who did real epidemiology, as opposed to my seat-mof-the-pants approach. This included my first exposure to the notion of statistical power: contrary to intuition, it is easier to detect an increase in an entity that occurs commonly than in

Table 2. rDNA Sites in the Great Apes

Human Homologue	Human	Chimpanzee	Gorilla	Orangutan
2p	−	−	−	+
2q	−	−	−	+
9	−	−	−	+
13	+	+	−	+
14	+	+	−	+
15	+	−	−	+
18	−	+	−	+
21	+	+	+	+
22	+	+	+	+
Total no. of sites	5	5	2	9

NOTE.—A minus sign (−) = no rDNA genes; a plus sign (+) = rDNA genes present. Shaded areas are regions of difference from the human sites.

one that occurs rarely (table 3). To have a 90% chance of observing a doubling of the frequency of trisomy at birth, it would take more than 23,000 births in the exposed and unexposed groups. For the same power, it would take only 893 pregnancies scored as term or miscarriage or 191 karyotyped spontaneous abortions to detect a doubling of the frequency of trisomy at conception. We therefore set out on a 10-year study to examine the role of environmental and other factors in the etiology of aneuploidy and other chromosome aberrations. We ascertained all women having spontaneous abortions in three Manhattan hospitals, karyotyped their fetal tissue, and interviewed women with karyotyped spontaneous abortions, along with an age-matched control of women with live births. To control for recall bias, we used as a secondary control the women with chromosomally normal spontaneous abortions, since women did not know the karyotype of their pregnancy losses at the time of interview. The project director of this study was a graduate student, Jennie Kline, who stayed on at Columbia and has remained my colleague on studies of chromosomes in reproduction ever since.

This study was essentially negative, in that it failed to identify any factors associated with chromosome aberrations at conception.[22–24] The only consistent positive finding was the association of trisomy with maternal age, which was well known for trisomy 21 but which we could establish was true for most other trisomies as well. At the same time we were doing our study, Pat Jacobs and Terry Hassold were carrying out a very similar study in Hawaii. Many of our analyses benefited from either combining or comparing the two studies.[25,26] In spite of very different populations in New York City, which included many African Americans and Hispanics, and Hawaii, which included many people of Asian and Hawaiian descent, the frequencies and distribution of anomalies, as well as the maternal-age curves for individual trisomies, were very similar. Both studies, for example, showed a linear curve relating maternal age to trisomy for chromosome 16 and an exponential curve like that for chromosome 21 for most other trisomies. In both studies, trisomy 16 made up about one-third of all trisomic conceptions, and trisomies for chromosomes 1, 11, 17, and 19 were very rare or absent. This was another indication of the general lack of any genetic or environmental factors, except for maternal age, that were associated with aneuploidy. The high rate of chromosomal anomalies in our species seems to be built into our biology and is not usually the result of accumulation of adverse events.

Later studies with Jennie Kline have concentrated on the maternal-age relationship. In mammals, all oocytes are created in early fetal life, where they are arrested in meiotic prophase. The first meiotic division is completed only at the time of ovulation. The nature of the change that occurs during this long resting period to cause the increase in error rate in older women is still unknown. We carried out two studies to test the hypothesis that the critical factor was correlated with the age-related reduction in the total oocyte pool or the number of antral follicles recruited per cycle. The first tested this indirectly by comparing age at menopause in women with a trisomic conception and controls.[27] The data appear to support the hypothesis. Women with trisomic spontaneous abortions had a mean age at menopause a year younger than controls.

The second study tested the hypothesis more directly by comparing hormonal measures of ovarian age and the number of antral follicles per cycle seen by ultrasound in women with trisomic and chromosomally normal spontaneous abortions. Results were negative with respect to the antral pool size, and there was only a hint, not statistically significant, that the rise in FSH associated with pool size occurred earlier in women with trisomic pregnancies.[28] Currently, we are studying skewed X inactivation in women with karyotyped losses, following up on data from Wendy Robinson and others, and we plan to reexamine the FSH findings in this sample as well.

Meanwhile, on the laboratory front, the Human Genome Project was beginning to take shape. Under one of the first Genome Project grants, my Ph.D. student Steve Gersen and, later, my associate M. T. Yu set out to develop a set of hamster-human hybrids, each of which contained only one selectable human chromosome and was therefore useful for making chromosome-specific libraries and for mapping cloned DNA.[29] We also developed a chromosome 13–deletion hybrid-mapping panel,[30] and I served as the Genome Database Editor for chromosome 13 for many years. Eventually, Columbia became the home of the Genome Center for Chromosome 13, mapping a cosmid library derived from a 13-only hybrid.[31] Unfortunately, this was one of the several blind alleys taken by the

Table 3. Statistical Power in Environmental Monitoring: Detecting a Doubling in the Frequency of Trisomy

	Prevalence of the Outcome in		Sample Size (per Group) Required[a]	
Outcome	Unexposed	Exposed	80% Power	90% Power
Down syndrome in live births	.0014	.0028	18,183	23,874
All trisomies in live births	.0033	.0066	7,693	10,100
Spontaneous abortions in pregnancies	.15	.21	675	893
Trisomies in karyotyped spontaneous abortions	.40	.57	146	191

* At $\alpha = .05$, two-tailed.

Genome Project, since it was later decided that clones derived from hybrids did not make good sequencing material.

Now that we really do "have it all," we are beginning to reap the benefits. Projects that would have taken years now take weeks. I retain my fascination with new technology and have recently begun collaborating with Michael Wigler at the Cold Spring Harbor Laboratory to use genomic microarray analysis to detect small copy-number changes in the genome. Cytogenetics has entered an exciting era of "ultra high-resolution" chromosome analysis via microarray, which is likely to have as big an impact on human genetics as conventional cytogenetics did in the past. It is likely that a significant proportion of unexplained developmental pathology, as well as variation within normal limits, may be due to such submicroscopic changes. We are currently working on a project to examine copy-number changes in children with congenital heart disease, which again marries epidemiology with new technology. I look forward to an exciting next few years.

I will now turn to the third meaning of "Having it All." This is the opportunity that I have had throughout my career to combine both clinical and research activities. I have been as lucky in my clinical life as I have in my research life, in having many long-time associates who are responsible for making things work. I would like, in particular, to mention Judy Yu, who was my clinical laboratory supervisor for 25 years and continues to work in my research laboratory. My assistant Mary Walsh, whom many of you know on the phone, has been the voice of the laboratory to the world, kept me more or less organized, told me when it was time to get my hair done, and always listened to my problems. My long-time clinical collaborator Kwame Anyane-Yeboa is a marvelous dysmorphologist, always interested in research projects that involve his patients. The opportunity to interact directly with patients, physicians, and genetics counselors has given me great personal satisfaction over the years. While one may see the same cytogenetic abnormality again and again, the personalities and the circumstances involved in each family situation are always different.

I have observed the evolution of clinical genetics from a discipline focusing mostly on trying to make the correct diagnosis in order to provide recurrence risks to family members to one where we can offer prenatal and even preimplantation diagnosis for a large number of conditions and effective treatment for a few. I have also seen society change, from a time when children with conditions such as Down syndrome were routinely institutionalized from birth to one that recognizes the importance of maximizing potential for all children with disabilities. A related change has been the emphasis on the protection of human subjects used in research studies, something that did not exist in the early days, when we could go out to the large institutions for the mentally retarded in New York and Connecticut and draw blood from anyone who looked interesting.

Clinical cytogenetic laboratories have also changed a great deal. In my first laboratory, there was just myself, one technician, and no computers. Proficiency testing, guidelines, and certifications were all nonexistent. However, I was introduced relatively early to the concept of proficiency testing, since, under the guidance of Ernest Hook, New York State pioneered in proficiency testing for cytogenetics in 1974. For many years, I participated in the review process and was impressed by the quality improvement brought about by this initiative.

As Pat Jacobs mentioned in her introduction, the clinical laboratory provides a constant source of new material and new phenomena. Often, observations go undeveloped and unexploited, so that I can say when someone else takes it further "Oh yes, I remember seeing that once." However, there are other times when the clinical observations have led to something more. I will briefly mention three of these.

First, more or less by chance, we studied a large number of patients over a 10-year period who had chromosome 13 long-arm deletions and a wide variety of phenotypes. It was striking that some 13 deletions gave very mild phenotypes and others very severe phenotypes, often involving holoprosencephaly. At the cytogenetic level, one could define a region in band 13q32 that seemed to be deleted in only the most severely affected patients. When a new clinical fellow, Stephen Brown, arrived in the mid-'80s, he followed up these observations in more detail, using the molecular methods that were becoming available for comparing chromosomal deletions.[32] Eventually, Steve succeeded in identifying in 13q32 a new gene, *ZIC2,* which is essential for normal brain development and is mutated in some patients with holoprosencephaly.[33] His own lab now tries to decipher the role of *ZIC2* in development in animal models, so this project has evolved all the way from genotype-phenotype correlation to basic developmental biology.

A second example was a fascinating patient of Kwame Yeboa, for whom the original laboratory observations were astonishing. This was a girl with profound mental retardation and microcephaly in whom we found cells with trisomy for virtually every human chromosome in lymphocyte cultures, skin cultures, and bone marrow. When we wrote up this case,[34] we suggested the condition be called "mosaic variegated aneuploidy," and this name seems to have stuck. For many years, I pursued various leads trying to decipher the basic cellular defect in this patient. Recently, some cases of mosaic variegated aneuploidy have been found to have mutations in *BUB1B,* a gene involved in the spindle checkpoint.[35] However, when we tested our first patient, she turned out to have confounded us again, because she has no mutation in this gene. Penny Jeggo's group has shown that there is a defective G2/M checkpoint in the cell line,[36] but mutation screening has been negative for many candidates in this pathway. Someday, I hope to learn the genetic basis for the mitotic error in this patient.

A third example are the patients with marker chromo-

somes now known to contain neocentromeres. These are chromosomes with functional centromeres that do not contain the original centromeric alpha satellite. Although these chromosomes must have been observed for a very long time in cytogenetic laboratories as uncharacterized marker chromosomes, it was not until the availability of alpha-satellite–specific FISH probes that their unique properties could be recognized. Because of my interest in chromosome 13, cells with one of these chromosomes derived from chromosome 13 were originally sent to us by Nancy Carpenter. My son, Peter Warburton, did his graduate and postdoctoral work on centromeres, and so we joined in studying this and other cases that came my way. This led to two publications on which we both appear as authors.[37,38] Peter is now on the faculty at Mt. Sinai, and he and his wife, Alicia, continue to study the fascinating phenomena of neocentromeres.[39]

My clinical involvement also inspired me to do some population-based epidemiological studies to answer difficult questions that arose in counseling.

A recent study was prompted by a recurring clinical question: does a woman with a trisomic spontaneous abortion, particularly at a young age, have a sufficiently increased risk for another trisomy that prenatal diagnosis would be indicated? Our previous data based on spontaneous abortions in the '80s had failed to demonstrate this. However, new data on prenatal diagnoses, collected in collaboration with Louis Dallaire and Maya Thangavelu, both also former students of Clarke Fraser, strongly suggest an increased risk for all trisomies among women with a previous trisomy, whether it be in a pregnancy loss or a prenatal diagnosis.[40]

I was originally asked to collect data on the clinical significance of de novo rearrangements found at prenatal diagnosis, for a symposium at the International Congress of Human Genetics held in Jerusalem in 1980. With the help of a group of dedicated genetics counseling students and the cooperation of many cytogeneticists across the continent, I continued to collect data on follow-up over a 10-year period and finally published the results in 1991.[41] This paper remains one of the few to address this question in a statistically valid way, which I say not as a boast but as a complaint that so few data of this type are being collected by cytogeneticists.

I am concerned that our knowledge of the clinical outcome of cytogenetic changes is unable to keep up with the exciting strides in our ability to detect new abnormalities and to define old ones more precisely. Very few attempts are made to collect the kind of long-term clinical data on outcome that are required for accurate counseling. Even though such things as marker chromosomes may be much better characterized, it often does not help the patient, since there is not enough data to predict the outcome for most specifically defined markers. The situation will only get worse as we explore the submicroscopic lesions defined by microarrays. Since this kind of research is not very high tech, funding is difficult to obtain. I would like to propose that organizations such as the American College of Medical Genetics encourage and even provide support for studies on the outcome of rare cytogenetic anomalies after prenatal diagnosis. This is the only unbiased source for prognostic data, and the ability to pool resources and data on the Internet should make it much easier than when I sent out my little questionnaire by mail.

Lastly, I will turn briefly to the more traditional meaning of "Having It All"—as a woman who tries to combine career and family. I am only the fifth female Allan Award designee out of the total of 44. Does this mean that women are not prominent in our Society? I would say obviously not, both because I know so many distinguished women in our profession and by looking around at this meeting. Does it mean that women have faced problems in being recognized for scientific achievements? I would say that it does. Since the Allan Award is typically given to older members of the society, it is to be hoped that the dearth of female awardees reflects the prejudices of the past and that the future will reflect the more equal opportunities of the present.

Certainly, when I began in science, there were still major barriers for women, regardless of whether they were also facing the problems of trying to raise a family. Columbia had a "nepotism" rule when I joined the faculty, so a man and his wife could not both hold faculty appointments. There was no question which one it would be. Most women in biology at Columbia, including some very eminent ones, were hired on a non–tenure track, as was I. When I finally did come up for tenure, I was turned down. For a variety of reasons, I stayed at Columbia, since I had financial support from both clinical work and grants.

I know from many conversations with younger female colleagues that, while in many ways things are better than when I began my career, women still face problems in obtaining recognition. The recent report of the National Academy of Sciences concludes, for example, that there are still many ways in which the traditional academic system impedes the advancement of women in science, often in very subtle ways.

As was common at the time, I married a fellow student when I was 21 and just beginning graduate school. My husband, Toney, and I had three children before we left Montreal for our first real jobs in New York. Our fourth child was born 4 years later. I wish I could say that this was all well planned and prescient on our part, but it really was not that well thought out. Until the children were grown, I necessarily worked a very regular 8-hour day. We had dinner every night as a family, promptly at 6:30, and take-out and order-in were not the options they are today. Some of my fondest memories are of our traditional '70s family vacations, traveling in the family car and camping. On one memorable trip in 1973, we traveled with four children and my mother across the U.S., from New York to San Francisco and back, in a forerunner of the SUV that we called the "Big Green Machine." This is a part of my life that I treasure, and I wouldn't have had it any other

way. I don't remember feeling constantly exhausted, nor do I think my professional life suffered much from the times the family came first. In retrospect, I believe one of the reasons is that my husband and I had the energy and enthusiasm of youth. The one tragedy of my live was the death of my oldest daughter at the age of 21. The three other children all now live in the New York area, where I am lucky enough to be able to see them and my three terrific grandchildren quite often.

The more common path today is for women to postpone childbearing to a time when they feel they have already become established in their careers, usually after the age of 35. The proportion of all U.S. births to women over 35 has tripled in the last 20 years,[42] and this statistic is much more exaggerated among professional women. Since I have spent a large part of my professional life pondering the association of maternal age with pregnancy loss and trisomy, this change in the pattern of childbearing concerns me.

By the time a woman has reached 35, 30% of her oocytes will have a numerical error, and this figure approaches 50% by the time she is 40. The resulting high rate of apparent infertility and miscarriages, need for prenatal diagnosis, and increased reliance on assisted reproduction not only lead to high anxiety and sometimes despair for couples trying to have a family but also consume healthcare resources. Desperate couples are also easy prey for less-than-scrupulous providers of reproductive technologies that are either not needed or have no proven value. Much of this distress could be avoided if women had their children at a younger age.

Table 4 shows the amazing effect of maternal age on reproductive loss, from two surveys of karyotype in spontaneous abortions, the first in the '70s and '80s, the second more recently. With a 7-year increase in mean maternal age at miscarriage, the proportion of losses with trisomy has doubled, from 23% to 46%.

Our expectancy for productive and healthy life has increased by many years, so that a woman can look forward, if she wishes, to continuing in her chosen career beyond the age of 70. However, at least so far, we have not learned how to reprogram a woman's biological clock, nor to turn off her desire to nurture her children. I believe we need to rethink the current path for women wishing to have both children and a career in science or elsewhere. First, young women should be better educated concerning the very real problems they may face if they delay childbearing, so that they can at least weigh the options with an understanding of the facts. Second, it may be possible for the career paths of men and women to be different but equal. It could become the norm for women who wish to have children to take time between finishing their education and working full time, when they can slow down their career paths for a while. True, men at the same age would be further ahead, but this would not matter if women could routinely rejoin the same path with the expectation of continuing longer. A tax structure that provided relief for young families would be an incentive, as would hiring practices that encouraged women who chose this path to stay in touch with their fields during the hiatus.

I hope I have been able to convey what great fun it has been to be a part of the remarkable journey of human genetics over the past 45 years. An important part of that trip has been my participation in the activities of the American Society of Human Genetics and the extraordinary people that I can count as my friends and associates. I think I have attended every meeting since my first in 1964, with the exception of 1967, when I was about to deliver my last child, and 2005, when I was about to deliver my last grant proposal. In 1980, when the meetings were still being organized by a local committee at the meeting site rather than by professional meeting planners, Arthur Bloom offered to host the meeting in New York City. I discovered that this meant I was expected to run the nonscientific parts of the meeting. I was in charge of all the arrangements, including booking the hotel and setting and collecting the registration fee. This was $65 for members and included the traditional banquet and dance on the night the Allan Award was presented. The dance, at least, is something I am sorry to see has now disappeared from the schedule. I still remember the sinking sensation when, as we sat at the head banquet table, the maitre d' of the Hilton brought me the check for the banquet for 1,000 people. It was bigger than what I had paid for my house some 10 years before! I took a deep breath and signed my name at the bottom. Then, having

Table 4. Consecutive Karyotyped Spontaneous Abortions from Two Time Periods

Finding	New York City 1975–1986	Ridgewood, NJ 2003–2005
No. karyotyped	2,821	479
Percentage chromosomally abnormal	44.8	68.3
Percentage trisomic[a]	26.1	43.8
Percentage of single trisomies:		
Trisomy 16	30.1	28.1
Trisomies of acrocentric chromosomes	33.8	47.4
Double and triple trisomies	3.5	6.2
Mean maternal age at last menstrual period (years)	28.1	34.7

* Includes mosaics, sex-chromosome trisomies, and multiple trisomies.

discovered that we were going to have a surplus of funds due to an unexpectedly large turnout, I ordered an open bar for the dance. Many people have told me that they remember that meeting as one of the best!

Because of my long association with the society and its members, I am very touched and enormously grateful for this award from my peers. Thank you so much for making this one of the best moments of my life.

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