2002 WILLIAM ALLAN AWARD ADDRESS
Introductory Speech for Albert de la Chapelle*

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It is with great personal pleasure that I present this year's recipient of the William Allan Award, Albert de la Chapelle. This prize is the major award of our society and is granted yearly to a scientist for substantial contributions to human and medical genetics that have been carried out over a lifetime of scientific and scholarly inquiry.

Albert de la Chapelle received his M.D. in 1957 at the University of Helsinki; he then began his clinical training, becoming board certified in internal medicine in 1965. His career has been almost exclusively devoted to research in human genetics. He earned a Ph.D. in human genetics at the University of Helsinki in 1962, received postdoctoral training with Paul Marks in biochemistry at Columbia University in 1966–1968, and training in biochemical genetics at the MRC Biochemical Genetics Unit in London in 1974. He was one of four scientists who founded the subspecialty of medical genetics in Finland. He was the first professor of medical genetics in Finland and was chairman of the Department of Medical Genetics at the University of Helsinki, beginning in 1974. Since 1997, Dr. de la Chapelle has been the Charlotte and Leonard Immke Chair of Cancer Genetics at the Ohio State University, where he directs the Human Cancer Genetics Program.

The cytogenetics of human sex determination and differentiation was the focus of his doctoral thesis. He showed that a high proportion of patients with Turner syndrome were mosaics and that these cases displayed milder and somewhat atypical clinical features compared with the standard 45,X cases. In 1964, he described the first example of a human male with an entirely normal-appearing female karyotype 46,XX (de la Chapelle et al. 1964). In a series of papers over the next 20 years, he defined the epidemiology, cytogenetics, genealogy, and clinical features of XX males. The etiology of maleness began to be clarified when he presented the first concrete evidence of an interchange between the X and Y chromosomes (de la Chapelle et al. 1984). This was followed by the detection of Y-specific sequences in some XX males (Page et al. 1985) and the description of the pseudoautosomal region near the end of the short arms of the X and Y chromosomes (Simmler et al. 1985). Finally, he showed that the Y-specific sequences present in XX males were indeed located near the telomeric end of the short arm of one X chromosome (Andersson et al. 1986) and occurred as a result of exchange during paternal meiosis (Page et al. 1987). These findings provided the groundwork for the subsequent cloning of the testis-determining factor, *SRY,* by others.

I have known Albert for more than 30 years. I first met him at the International Congress of Human Genetics in Mexico City in 1976. We both had published papers on chromosome abnormalities in human leukemia at a time when there were very few cytogeneticists interested in this area of research. He described trisomy for a group "C" chromosome in leukemia (de la Chapelle et al. 1970); showed that the extra chromosome was number 8 (de la Chapelle et al. 1972); and used this information to map a gene, glutathione reductase, to this chromosome (de la Chapelle et al. 1976). It was later shown that trisomy for chromosome 8 is the most common numerical abnormality in acute myeloid leukemia (AML) and confers a poor prognosis. Albert and I decided that enough information was available to consider having an international workshop on the types of chromosome abnormalities seen in human leukemia and to investigate some of their clinical implications. He was chairman of the 6th International Chromosome Conference, first organized by Professor Darlington in Oxford, and the meeting was to be held in Helsinki in 1977. It seemed appropriate, then, for this conference to be the occasion for inviting individuals from around the world who had published on the chromosome pattern in human leukemia. The workshop was held in the fall of 1977; it was the first of a series of workshops on chromosomes in leukemia that each developed important information about the frequency and clinical implications of chromosome abnormalities in various subtypes of leukemia and lymphoma (First International

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Workshop on Chromosomes in Leukaemia 1978). The conferences were held in Europe and Japan, as well as the United States. These workshops have served as models of international collaboration by providing state-of-the-art correlations between cytogenetic findings and clinical parameters, such as prognosis in human leukemia and lymphoma. Many of these studies have had a significant impact, not only on the diagnosis and classification of leukemia and lymphoma but also on the treatment selected for patients. They have provided a model for many subsequent workshops focusing on a particular relatively rare disease.

Dr. de la Chapelle's career has been characterized by his uncanny ability to be involved in a scientific problem at the right time and right place, but most importantly, to have acquired the requisite skills to pursue groundbreaking research. In the early 1980s, his interest began to shift to human disease genes. What better place to study rare diseases and discover new genes than Finland? The Finnish population is a typical founder population that displays important special features. In these populations, enrichment of random alleles typically occurs as a result of founder effect, population bottlenecks, and genetic drift (de la Chapelle 1993). In Finland, this has resulted in the accumulation of approximately 34 hereditary disorders, mostly autosomal recessive (de la Chapelle and Wright 1998). In the 1980s, not a single one of these disorders had been genetically characterized. Mapping, cloning, and characterizing the genes for these disorders became the main focus of the de la Chapelle laboratory. Today most of these diseases have been molecularly characterized, to some degree at least, including the mapping and cloning of the gene and detection of its mutations (reviewed in de la Chapelle and Wright 1998). It is noteworthy that among the disorders characterized so far, approximately half have been elucidated by the de la Chapelle group. Highlights include the first mapping by genomewide search for linkage of one of the "Finnish" recessive disorders, diastrophic dysplasia, in 1990. The gene product, DTDST, turned out to be a sulfate transporter affecting the growth of cartilage (Hästbacka et al. 1994). Other highlights are the description of and gene detection in two previously unrecognized, novel "Finnish" disorders, hereditary hypogonadotropic gonadal failure caused by mutations in the follicle-stimulating hormone-receptor gene (Aittomäki et al. 1995) and progressive epilepsy with mental retardation caused by mutations in the *CLN8* gene (Ranta et al. 1999). More recent discoveries include the fact that cartilage hair hypoplasia was due to mutations in an untranslated gene, *RMRP*, encoding the RNA component of a ribonuclease MRP, active both in the nucleolus and in the mitochondria (Ridanpää et al. 2001). This intriguing finding is being followed up by mouse modeling in the de la Chapelle laboratory. Further, in Usher syndrome type 3, a previously unknown gene with two transmembrane domains was found to be mutated (Joensuu et al. 2001). This gene appears to bear no relationship to the five previously characterized genes for other forms of Usher syndrome; thus, in all likelihood, it will eventually broaden our understanding of signaling mechanisms in the retina and cochlea. In his studies of these "Finnish" disorders, Dr. de la Chapelle has been one of the pioneers in utilizing linkage-disequilibrium analysis in the positional cloning of genes (de la Chapelle 1993; de la Chapelle and Wright 1998). This method is now one of the cornerstones of gene detection worldwide, not only in Mendelian disorders but also in multifactorial disease, including cancer. The mapping, cloning, and characterization of these disease genes by Dr. de la Chapelle and his former students have already had major clinical consequences. First, their work allows precise molecular diagnosis, often with prognostic implications. Second, it allows carrier detection and risk assessment in affected families. Third, it is an entrée to our understanding of disease mechanisms, which, in turn, is a prerequisite for devising effective therapeutic strategies.

One of the most recent and far-reaching examples of his "nose" for innovative research is his work in colon cancer. The painstaking work of Henry Lynch, who gathered pedigrees of families with cancer, raised intriguing questions. In the 1980s, the existence of major hereditary forms of the common cancers was controversial. De la Chapelle's breakthrough findings in hereditary nonpolyposis colon cancer (HNPCC) initiated a new era in hereditary cancer research preceding similar discoveries in, for example, breast and prostate cancer (Aaltonen et al. 1993). Because this research is the focus of Dr. de la Chapelle's lecture, I will not summarize the results here.

This quick review points out just a few of Albert's most remarkable accomplishments. They are notable for their innovative qualities and for their breadth. Albert is truly an international human geneticist! In addition to being a regular attendee at ASHG meetings, he is also a member of the European Society of Human Genetics, of which he was president in 1993–1994. Albert has long worked for closer interactions between the American and European societies on a number of scientific, political, and ethical issues.

As you would expect, he has received numerous honors and awards in Finland and elsewhere in recognition of his research accomplishments. In Finland, he is a member and honorary member of its senior Academy of Sciences and Letters. He also is a fellow ("1 of 12") of the Academy of Finland. He was the first M.D. ever to receive this highest scientific honor of the country. He holds an honorary doctorate at the University of Oulu and the University of Uppsala. Among his other awards

are the Anders Jahre Prize for Medicine (University of Oslo) and the Phoenix-Anni Verdi Award for Genetic Research (Italy). He is a foreign member of the Royal Swedish Academy of Sciences and of the National Academy of Sciences, U.S.A.

It is my great pleasure to introduce Dr. de la Chapelle, who certainly follows in the footsteps of Dr. William Allan, acknowledged as the first physician who was involved in extensive genetic research in the United States. The title of his lecture is, "Inherited Human Diseases: Challenges, Victories, Disappointments."

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